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# 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-methyloctanoic 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-methyloctanoate (**2**) is the aggregation pheromone of the tropical *Oryctes rhinoceros* (*1*, *2*) and of *Oryctes monoceros* (*6*−*8*), whereas 4-methyloctanoic 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-methyloctanoic 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.

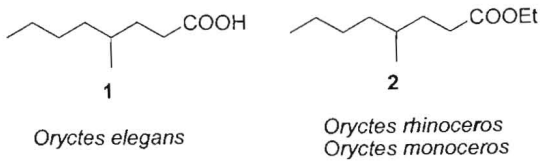


**Figure 1.** Aggregation pheromones of rhinoceros beetles.

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-methyloctanoic 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 bithienyl carboxylic acids (*13*); (c) methylation of *N*-*tert*-butylimine derivative of hexanal, condensation with malonic acid, and hydrogenation (*14*); (d) conjugate addition of organocuprates to ethyl acrylate (*1*, *6*) or Ni-catalyzed coupling of alkyliodides with ethyl acrylate (*7*); and, finally, (e) chain elongation of 2-methylhexanoic acid via malonic ester synthesis (*15*) or via reduction and elongation of the chain by the Wittig reaction (*16*). Concerning the optically active 4-methyloctanoic 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. Resolution of the racemic acid

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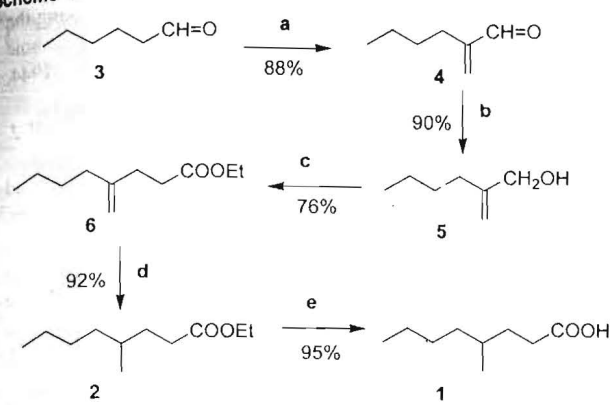
**Scheme 1**[a]




[a] Reagents and conditions: (a) $(CH_3)_2NH{\cdot}HCl$, 37% aqueous formaldehyde, 70 °C, 24 h; (b) $NaBH_4$, 5% $NaHCO_3$, MeOH, 5 °C, 1 h; (c) $CH_3C(OC_2H_5)_3$, $CH_3CH_2COOH$, 138 °C, 5 h; (d) $H_2$, 10% Pd/C, EtOH, 3 h; (e) KOH/EtOH/$H_2O$, reflux 2.5 h.

by a lipase-mediated enantioselective esterification has also been described (*18*–*20*).

The above presented methods involve not readily available substrates (*13*, *14*), starting materials already lacking the methyl group (*15*, *16*), or the use of organometallic syntheses (*1*, *6*, *7*, *12*) unsuitable for large-scale preparations.

Addressing the drawbacks of the existing methods, we were looking for an alternative synthesis of racemic 4-methyloctanoic acid (**1**), which should be simple, low cost, and workable on large scale. The proposed synthetic route is outlined in **Scheme 1**.

## 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 $CCl_4$ solutions (5%) on a Perkin-Elmer 247 spectrophotometer. $^1H$ NMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 200 MHz spectrometer, with TMS as an internal standard. Gas chromatography–mass sprectrometry analyses were carried out with a GC-MS Hewlett-Packard 5890-5970 system, equipped with a 30 m × 0.25 mm i.d. SPB-1 fused silica capillary column: carrier gas, helium, 1 mL/min; injector temperature, 230 °C; oven temperature, 50 °C (5 min isothermal) raised at 4 °C/min to 250 °C; ion source temperature, 220 °C; interface temperature, 250 °C; mass range, 40–500 amu; EI, 70 eV.

**2-Methylenehexanal (4).** A mixture of hexanal **3** (10.00 g, 0.10 mol), dimethylamine hydrochloride (9.85 g, 0.12 mol), and 37% aqueous formaldehyde (9.73 g, 0.12mol) was stirred at 70 °C for 24 h. The aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with anhydrous $Na_2SO_4$, and the solvent was evaporated under reduced pressure. The product was purified by distillation to afford pure **4** (9.87 g, 88%; purity by GC = 95%) as a colorless oil: bp 60–64 °C/40 mmHg [lit. (*21*) 46–48 °C/15 mmHg]; IR, $cm^{-1}$ 1696, 1627; $^1H$ NMR $\delta$ 0.91 (t, 3H, $J$ = 7.2 Hz), 1.22–1.51 (m, 4H), 2.25 (t, 2H, $J$ = 7.2 Hz), 5.98 (s, 1H), 6.24 (s, 1H), 9.54 (s, 1H); $^{13}C$ NMR $\delta$ 13.73, 22.3, 27.4, 29.83, 133.75, 150.41, 194.65; IR and $^1H$ NMR values are in accordance with the literature data (*21*, *22*).

**2-Methylenehexanol (5).** To a cold (5 °C) suspension of $NaBH_4$ (2.75 g, 0.072 mol) in $H_2O$ (20 mL) and 5% $NaHCO_3$ (6.8 mL) was added a cold solution of aldehyde **4** (8.00 g, 0.072 mol) in methanol (100 mL). The final solution was stirred for 1 h at 5 °C. The reaction mixture was then poured into ice water (220 mL), followed by the addition of 10% HCl (35 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL); the combined organic layers were washed with brine, dried with anhydrous $Na_2SO_4$, and concentrated under reduced pressure to leave a clear oily product. The product was purified by column chromatography on silica gel (1:1 petroleum ether/diethyl ether) to give the allyl alcohol **5** (7.35 g, 90%; purity by GC = 97%) as a colorless oil: IR, $cm^{-1}$ 3624; $^1H$ NMR $\delta$ 0.88 (t, 3H, $J$ = 7.2 Hz), 1.14–1.49 (m, 4H), 2.03 (t, 2H, $J$ = 7.2 Hz), 2.37 (s, 1H), 4.04 (s, 2H), 4.82–4.85 (m, 1H), 4.97–4.98 (m, 1H); $^{13}C$ NMR $\delta$ 13.87, 22.43, 29.89, 32.63, 65.77, 108.85, 149.17; $^1H$ NMR and $^{13}C$ NMR values are in accordance with the literature data (*22*).

**Ethyl 4-Methyleneoctanoate (6).** A mixture of the 2-methylenehexanol **5** (6.50 g, 0.057 mol), triethyl orthoacetate (55 mL, 0.29 mol), and a catalytic amount of propionic acid (4 drops) was heated at 138 °C for 5 h with continuous removal of the ethanol formed during the reaction. The reaction mixture was cooled to room temperature, poured into ice water (150 mL) containing $NaHCO_3$ (1.0 g), and extracted with diethyl ether (3 × 50 mL). The organic phase was washed with water, dried with $Na_2SO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (8:1 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 $\delta$ 0.80–0.91 (m, 3H), 1.19–1.26 (t, 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); $^{13}C$ NMR $\delta$ 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), 69 (100), 41 (98), 55 (97) Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.54; H, 10.85.

**Ethyl 4-Methyloctanoate (2).** A mixture of pure ethyl 4-methyleneoctanoate **6** (3.00 g, 16.3 mmol) in ethanol (15 mL) and 10% Pd/C (10 mg) was stirred under $H_2$ 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 almost pure **2** (2.78 g, 92%; purity by GC = 97%) as a colorless oil: IR, $cm^{-1}$ 1735; $^1H$ NMR $\delta$ 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); $^{13}C$ NMR $\delta$ 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 by the addition of 10% HCl (5 mL) and was extracted with diethyl ether (3 × 20 mL). The organic phase was washed with water, dried with anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give pure acid **1** (2.14 g, 95%; purity by GC = 98%) as a colorless oil: IR, $cm^{-1}$ 1710; $^1H$ NMR $\delta$ 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); $^{13}C$ NMR $\delta$ 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-methylenehexanal (**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 heating alcohol **5** with triethyl orthoacetate in 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


(1) Hallett, R. H.; Perez, A. R.; Gries, G.; Gries, R.; Pierce, H. D., Jr.; Yue, J.; Oehlschlager, A. C.; Gonzalez, L. M.; Borden, J. H. Aggregation pheromone of coconut rhinoceros beetle, *Oryctes rhinoceros* (L.) (Coleoptera: Scarabaeidae). *J. Chem. Ecol.* **1995**, *21*, 1549−1570 and references cited therein.

(2) Morin, J. P.; Rochat, D.; Malosse, C.; Lettere, M.; Desmier de Chenon, R.; Wibowo, H.; Descoins, C. Ethyl 4-methyloctanoate, major component of *Oryctes rhinoceros* (L.) (Coleoptera: Dynastidae) pheromone. *C. R. Acad. Sci. Paris, Life Sci.* **1996**, *319*, 595−602.

(3) Rochat, D.; Mohammadpoor, K.; Malosse, C.; Avand-Faghih, A.; Lettere, M.; Beauhaire, J.; Morin, J. P.; Pezier, A.; Renou, M.; Abdollahi, G. A. Male aggregation pheromone of date palm fruit stalk borer *Oryctes elegans*. *J. Chem. Ecol.* **2004**, *30*, 387−407 and references cited therein.

(4) Chung, G. F.; Sim, S. S.; Tan, M. W. Chemical control of rhinoceros beetles in the nursery and immature oil palms. In *Proceedings of the PORIM International Palm Oil Conference—Progress, Prospects and Challenges towards the 21st Century, Module I, Agriculture*; Basiron, Y., Sukaimi, J., Chang, K. C., Cheah, S. C., Henson, I. E., Norman, K., Paranjothy, K., Rajanaidu, N., Dolmat, H. T., Darus, A., Eds.; Kaula Lumpur, Malaysia, 1991; pp 380−395.

(5) Julia, J. F.; Mariau, D. Piegeage olfactif a l'aide du chrysanthemate d'ethyle. Recherches sur *Oryctes monoceros* (Olivier) en Cote d'Ivoire. *Oleagineux* **1976**, *31*, 263−276.

(6) Gries, G.; Gries, R.; Perez, A. L.; Oehlschager, A. C.; Gonzalez, L. M.; Pierce, H. D., Jr.; Zebeyou, M.; Kouame, B. Aggregation pheromone of the African rhinoceros beetles *Oryctes monoceros* (Olivier) (Coleoptera: Dynastidae). *Z. Naturforsch.* **1994**, *49C*, 363−366.

(7) Sim, T. B.; Choi, J.; Yoon, N. M. A new coupling reaction of alkyliodides with α,β-unsaturated esters using $Ni_2$(cat.)-BER in methanol. *Tetrahedron Lett.* **1996**, *37*, 3137−3140.

(8) Allou, K.; Morin, J. P.; Kouassi, P.; Hala N'Klo, F.; Rochat, D. *Oryctes monoceros* trapping with synthetic pheromone and palm material in Ivory Coast. *J. Chem. Ecol.* **2006**, *32*, 1743−1754 and references cited therein.

(9) Wong, E.; Nixon, L. N.; Johnson, C. B. Volatile medium chain fatty acids and mutton flavor. *J. Agric. Food Chem.* **1975**, *23*, 495−498.

(10) Karl, V.; Gutser, J.; Dietrich, A.; Maas, B.; Mosandl, A. Stereoisomeric flavour compounds LXVIII. 2-, 3-, and 4-alkylbranched acids, part 2: chirospecific analysis and sensory evaluation. *Chirality* **1994**, *6*, 427−434.

(11) Kim, G. Y.; Lee, J. H.; Min, D. B. Study of light-induced volatile compounds in goat's milk cheese. *J. Agric. Food Chem.* **2003**, *51*, 1405−1409.

(12) Cason, J.; Adams, C. E.; Bennett, L. L., Jr.; Register, U. D. Branched-chain fatty acids. III. New method of introducing the branching methyl group. Synthesis of 15-methyloctadecanoic acid and 14-methyltetracosanoic acid. *J. Am. Chem. Soc.* **1944**, *66*, 1764−1767.

(13) Wynberg, H.; Bantjes, A. The chemistry of polythienyls. II *J. Am. Chem. Soc.* **1960**, *82*, 1447−1450.

(14) Sonnet, P. E.; Baillargeon, M. W. Synthesis and lipase catalysed hydrolysis of thiolesters of 2-, 3-, and 4-methyloctanoic acids. *Lipids* **1989**, *24*, 434−437.

(15) Hedenstrom, E.; Nguyen, B. V.; Silks, L. A.; III. Do enzymes recognise remotely located stereocentres? Highly enantioselective *Candida rugosa* lipase-catalysed esterification of the 2- to 8-methyldecanoic acids. *Tetrahedron: Asymmetry* **2002**, *13*, 835−844.

(16) Sonnet, P. E.; Cazzillo, J. Asymmetric synthesis of 2-, 3-, and 4-methyloctanoic acids. *Org. Prep. Proced. Int.* **1990**, *22*, 203−208.

(17) Karl, V.; Kaunzinger, A.; Gutser, J.; Steuer, P.; Angles-Angel, J.; Mosandl, A. Stereoisomeric flavour compounds LXVII. 2-, 3-, and 4-alkylbranched acids, part 1: general approach to the synthesis of the enantiopure acids. *Chirality* **1994**, *6*, 420−426.

(18) Heinsman, N. W. J. T.; Valente, A. M.; Smienk, H. G. F.; van der Padt, A.; Franssen, M. C. R.; de Groot, A.; van't Riet, K. The effect of ethanol on the kinetics of lipase mediated enantioselective esterification of 4-methyloctanoic acid and the hydrolysis of its ethyl ester. *Biotechnol. Bioeng.* **2001**, *76*, 193−199.

(19) Heinsman, N. W. J. T.; Schroen, C. G. P. H.; van der Padt, A.; Franssen, M. C. R.; Boom, R. M.; van't Riet, K. Substrate sorption into the polymer matrix of Nonozym 435 and its effect on the enantiomeric ratio determination. *Tetrahedron: Asymmetry* **2003**, *14*, 2699−2704.

(20) Litjens, M. J. J.; Straathof, A. J. J.; Jongejan, J. A.; Heijnen, J. J. Exploration of lipase-catalysed direct amidation of free carboxylic acids with ammonia in organic solvents. *Tetrahedron* **1999**, *55*, 12411−12418.

(21) Alexakis, A.; Commerçon, A.; Coulentianos, C.; Normant, J. F. Alkenyl copper reagents-18. Carbocupration of acetylenic acetals and ketals. Synthesis of manicone, geranial and 2,4-(*E,Z*)-dienals. *Tetrahedron* **1984**, *40*, 715−731.

(22) Aronica, L. A.; Raffa, P.; Caporusso, A. M.; Salvadori, P. Fluoride-promoted rearrangement of organosilicon compounds; a new synthesis of 2-(arylmethyl)aldehydes from 1-alkynes. *J. Org. Chem.* **2003**, *68*, 9292−9298.

(23) Menicagli, R.; Wis, M. L. Efficient conversion of aldehyde acetals into α-alkylacrylaldehydes. *J. Chem. Res. (S)* **1978**, 262−263.

(24) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. A simple stereoselective version of the Claisen rearrangement leading to trans-trisubstituted olefinic bonds. Synthesis of squalene. *J. Am. Chem. Soc.* **1970**, *92*, 741−743.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