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Practical and Scalable Synthesis of (*Z*)-9-Tricosene, the Housefly Sex Pheromone

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Abstract: A practical and scalable synthesis of (*Z*)-9-tricosene, the sex pheromone of the housefly, has been achieved by the addition of one-carbon unit from the readily available (*Z*)-erucic acid. The synthesis is composed of three consecutive steps, lithium aluminium hydride reduction of erucic acid, tosylation of the resulting alcohol, and copper-catalyzed Kumada-type cross-coupling of the tosylate with methylmagnesium bromide as the key step. This approach is *quite straightforward* and *capable of scale-up synthesis.*

Keywords: (*Z*)-9-Tricosene, biochemical pesticide, erucic acid, housefly, kumada cross-coupling, sex pheromone.

INTRODUCTION

Biochemical pesticides are naturally occurring substances that control pests by non-toxic mechanisms and can substantially decrease the use of conventional pesticides. The biochemical pesticides such as insect sex pheromones are effective against only the target pest and closely related organisms in very small quantities, thereby resulting in lower exposures and largely avoiding the pollution problems caused by the conventional pesticides [1].

was identified as (*Z*)-9-tricosene [2]. Later several sex-related pheromones in the housefly were also identified and the structures are depicted in Fig. (**1**). A number of studies have figured out that (*Z*)-9-tricosene **1** serves as a major component in the sex pheromones, and it can be modified to the corresponding oxygenated congeners (**2** and **3**) and homologated to the chain isomers (**4** and **5**) during hydrocarbon biosynthesis [3]. In addition, field evaluations have proved that (*Z*)-9-tricosene is the most active component [4]. The attractant (*Z*)-9-tricosene, commonly called muscalure, is

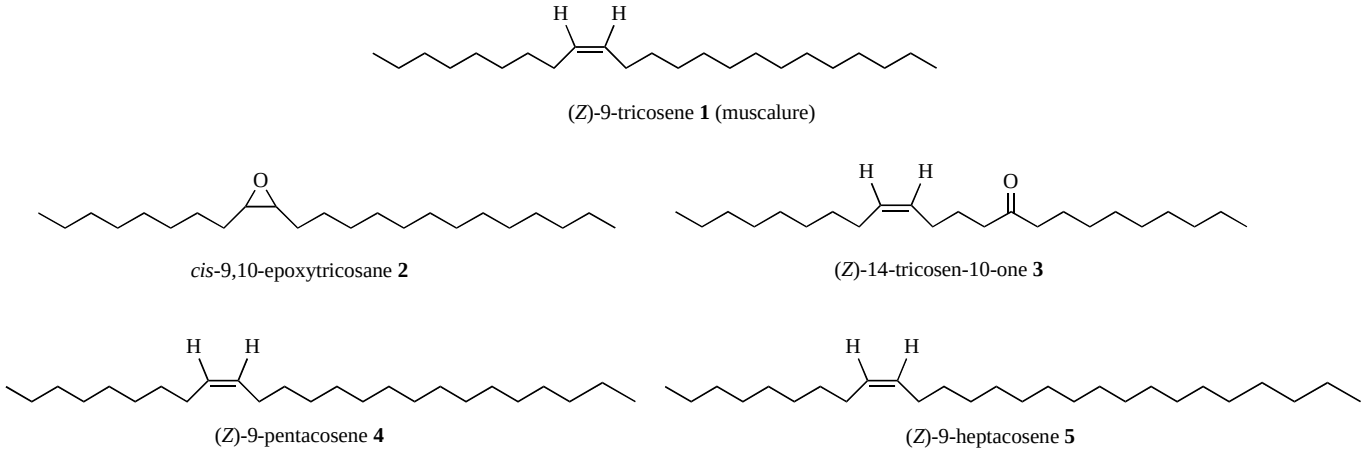

Fig. (1). Common female housefly sex pheromones.

The hydrocarbon sex pheromone of the female housefly *Musca domestica* was isolated by Carlson *et al.* in 1971 and currently registered as a biochemical pest control agent for use to get rid of houseflies, stable flies, eye gnats, and horse flies [5]. Owing to the substantial importance of muscalure in ecology-based pest management, an adequate supply from an economical synthesis is desirable.

The synthesis of (*Z*)-9-tricosene as a mixture of 85% of (*Z*)- and 15% of (*E*)-isomer was firstly reported by Carlson,

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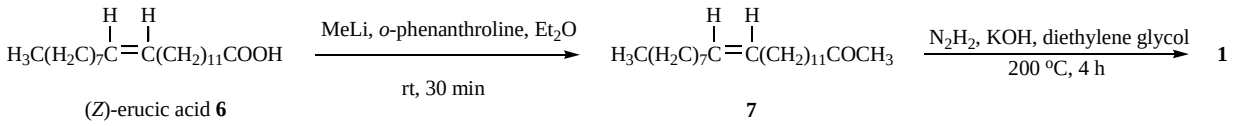
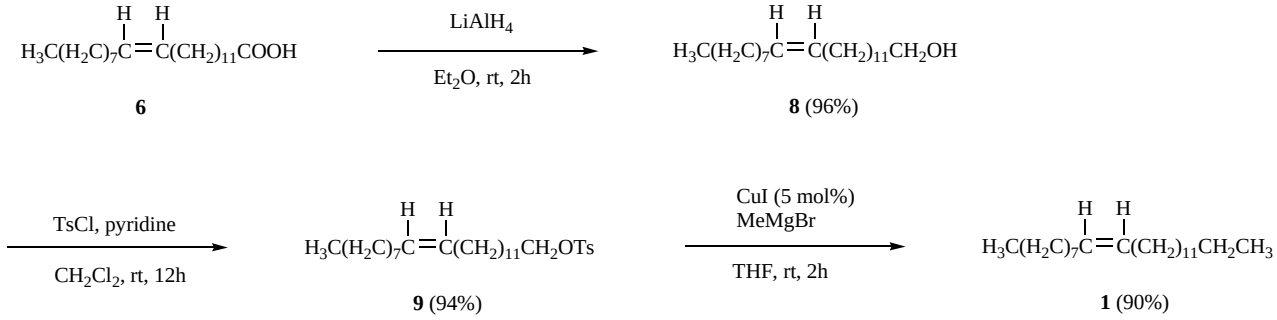


Scheme 1. Previous synthesis of (*Z*)-9-tricosene from (*Z*)-erucic acid *via* Wolf-Kishner reduction of ketone **7** [11a].



Scheme 2. Synthesis of (*Z*)-9-tricosene **1**.

utilizing a Wittig reaction of 1-bromotetradecane and nonanal [2a]. Until now, several efficient methods have been published for the stereoselective synthesis of the pheromone. These mainly include Wittig-type olefination of aldehydes and phosphorane derivatives [2a, 6], alkylation of alkynes followed by partial hydrogenation [7], and metathesis of olefins [8]. However, the methods are not likely to be scalable because they use expensive materials, require a more sophisticated reaction control, and sometimes suffer from *E*/*Z*-selectivity. In turn, there have been reports on the synthesis through utilization of biologically available materials such as jojoba wax [9], oleic acid derivatives [10], and erucic acid [11].

In order to secure a substantial amount, we need a greener, cheaper, and more reliable method for the synthesis of muscalure. Herein we report a practical and scalable synthesis of (*Z*)-9-tricosene from the bio-origin material (*Z*)-erucic acid as a greener way.

RESULTS AND DISCUSSION

Previously, Cargill *et al*. reported a very efficient synthesis of (*Z*)-9-tricosene [11a], where (Z)-erucic acid **6** was converted into ketone **7** by the treatment of 2 equiv of methyllithium followed by Wolf-Kishner reduction [10a] using 85% hydrazine hydrate with potassium hydroxide in diethylene glycol (200 °C, 4 h) to give **1** in 82% overall yield (Scheme **1**). The (*Z*)-erucic acid is produced naturally across a great range of green plants [12] and is available commercially at low prices [13]. Thus, the choice of the acid made the synthesis simple and ***straightforward***, because it already possesses a *Z*-geometry in the appropriate position. Keeping in mind the above view, we adopted the second sequence since it is easy in handling and manipulation. Indeed, many pheromonal hydrocarbons [9, 10b, 11b, 14] have been frequently synthesized by way of Grignard addition into the appropriate alkyl halides in the presence of Li_2CuCl_4 as the catalyst [15]. We thus ambitioned that copper-catalyzed coupling of halide or tosylate with one-carbon unit would offer the most reliable synthetic route to **1** as depicted in Scheme **2**, without the use of any dangerous material.

Reduction of (*Z*)-erucic acid **6** with lithium aluminium hydride in diethyl ether at room temperature gave erucyl alcohol in 96% yield. Then, alcohol **8** was smoothly converted to erucyl *p*-toluenesulfonate **9** in 94% yield, by the treatment with tosyl chloride and pyridine in methylene chloride at ambient temperature. The final installation could be efficiently achieved *via* copper-catalyzed Kumada-type cross-coupling reaction of the tosylate with methyl Grignard [16]. After considerable experimentation, we found that copper(I) iodide is the catalyst of choice and 5 mol% of the catalyst is sufficient for the coupling reaction of **9** with methylmagnesium bromide to afford (*Z*)-9-tricosene **1** in 90% yield (Scheme **2**). The whole synthesis was double checked and the spectroscopic data were exactly matched with those of an authentic sample in all regards.

In conclusion, we have developed a convenient and practical synthesis of the sex pheromone of the female housefly, (*Z*)-9-tricosene with quite a straightforward way. The synthesis is based on chain-elongation of (*Z*)-erucic acid by the one-carbon addition, employing copper-catalyzed Kumada-type cross coupling reaction of erucyl tosylate with methylmagnesium bromide. The use of bio-origin and the one-carbon strategy renders our approach green and competitive. Thus, this approach should obviously be adaptable to a large scale preparation.

EXPERIMENTAL SECTION

(*Z*)-Erucic acid (99+% for GC) was obtained from a commercial supplier. All analytic grade chemicals and anhydrous solvents were purchased and used without further purification. The reactions were monitored by TLC with Merck silica gel 60 F_{254} TLC glass plates. All reactions were conducted under argon atmosphere. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Jeol Eclipse FT 300 MHz Spectrometer in $CDCl_3$ as solvent using TMS as internal standard and chemical shifts are expressed as δ ppm. Mass spectra were ***detected by electronic impact* (*EI*)** and obtained on an Agilent 1100 Series VLL or JEOL the MStation JMS 700 mass Spectrometer. The E/Z ratio was determined by GC analysis using HP 5890

equipped with a FID detector on a 50 m × 0.2 mm ID, BP-20 capillary column.

Synthesis of (*Z*)-docos-13-en-1-ol (8)

To a suspension of $LiAlH_4$ (1.68 g, 44.3 mmol) in diethyl ether (20 mL) was added (*Z*)-erucic acid **6** (10.0 g, 29.5 mmol) in diethyl ether (80 mL) dropwise for 15 min at 0 ^{0}C under argon atmosphere. The reaction mixture was stirred vigorously for 2 h at room temperature. Then, the reaction was quenched with ethyl acetate (40 mL) at 0 ^{0}C and 0.1N HCl (60 mL). The reaction mass was filtered through a pad of Celite and washed with ethyl acetate (2 x 20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with brine (2 x 30 mL) and dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give **8** as an oil (9.21 g, 96.2%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (t, J = 4.8 Hz, 2H), 3.63 (t, J = 6.6 Hz, 2H), 2.02 (t, J = 7.4 Hz, 5H), 1.68-1.45 (m, 3H), 1.26 (m, 29H), 0.88 (t, J = 5.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.50, 130.10, 64.89, 63.25, 33.0, 32.11, 29.98, 29.90, 29.85, 29.82, 29.77, 29.73, 29.65, 29.52, 29.47, 29.38, 28.80, 27.41, 26.1, 25.95, 22.88, 14.30; EI-HRMS calcd for $C_{22}H_{44}O$: 324.3392, found: 324.3389.

Synthesis of (*Z*)-docos-13-enyl 4-methylbenzenesulfonate (9)

To a solution of **8** (9.20 g, 28.3 mmol) in dichloromethane (120 mL) was added pyridine (6.15 mL, 29.5 mmol) at 0 ^{0}C under argon atmosphere. To this solution was added TsCl (8.26g, 43.3 mmol) in dichloromethane (70 mL) at 0 ^{0}C and the resulting mixture was allowed to stir vigorously for 12 h at room temperature. To this mixture was introduced 6N HCl (120 mL) at 0 ^{0}C. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 30 mL). The combined organic layer was washed with water (2 x 30 mL) and dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to afford **9** as oil (12.8 g, 94.5%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.7 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 5.35 (t, J = 5.2 Hz, 2H), 4.01 (t, J = 6.4 Hz, 2H), 2.45 (s, 3H), 2.01 (m, 4H), 1.68-1.57 (m, 4H), 1.39-1.14 (m, 28H), 0.93-0.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.81, 133.46, 130.42, 130.12, 130.08, 129.99, 128.09, 70.91, 32.11, 29.98, 29.82, 29.80, 29.76, 29.73, 29.71, 29.59, 29.52, 29.14, 29.02, 27.41, 25.53, 22.89, 21.83, 14.32; EI-HRMS calcd for $C_{29}H_{50}O_3S$: 478.3481, found: 478.3480.

Synthesis of (*Z*)-tricos-9-ene (1)

In a 250 mL flame-dried flask, copper(I) iodide (0.23 g, 1.20 mmol) was activated by flame under argon atmosphere. The resulting solid was dissolved in THF (30 mL) at 0 ^{0}C. To this cooled solution, 3M MeMgBr in diethyl ether (33.4 mL, 100.2 mmol) was added dropwise over 10 min. During the addition, the yellow color of the solution changed to colorless. After 10 min, **9** (12.0 g, 25.0 mmol) in THF (80 mL) was added to the solution at 0 ^{0}C. The reaction mixture was stirred for 2 h at room temperature. Then, the reaction mixture was quenched with 5% aqueous solution of sodium bicarbonate (20 mL) at 0 ^{0}C. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give crude residue. The residue was purified by passing through a pad of silica gel with hexane to afford **1** as a colorless oil (7.26 g, 90.0%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (t, J = 5.7 Hz, 2H), 2.01 (d, J = 4.9 Hz, 4H), 1.58 (d, J = 1.9 Hz, 2H), 1.39-1.14 (m, 32H), 0.93-0.81 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.05, 32.10, 32.08, 29.95, 29.87, 29.83, 29.74, 29.70, 29.54, 29.50, 27.37, 22.86, 14.26; EI-HRMS calcd for $C_{23}H_{46}$: 322.3600, found: 322.3596. Anal. Calcd for $C_{23}H_{46}$: C, 85.63; H, 14.37. Found: C, 85.55; H, 14.79.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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