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Pheromone synthesis. Part 260: Synthesis of (±)-(*anti*-1,2-dimethyl-3-methylenecyclopentyl)acetaldehyde, the racemate of the female-produced sex pheromone of the pineapple mealybug (*Dysmicoccus brevipes*), and its *syn*-isomer☆

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ABSTRACT

(±)-(*anti*-1,2-Dimethyl-3-methylenecyclopentyl)acetaldehyde, the racemate of the female-produced sex pheromone of the pineapple mealybug, was synthesized in four different ways. Ireland–Claisen rearrangement or conjugate addition was employed for the construction of the quaternary carbon center, while ring-closing olefin metathesis or cationic cyclization was used for the construction of the five-membered carbocycle.

1. Introduction

Recent studies by Millar and co-workers culminated in the identifications of three monoterpenes **A**, **B** and **C** (Fig. 1) with a five-membered carbocycle as the sex pheromones of the mealybugs.[2] In 2005, **A** was identified as the pheromone of the obscure mealybug (*Pseudococcus viburni*).[3] Then in 2007, the pheromone of the grape mealybug (*Pseudococcus maritimus*) was shown to be **B**.[4] Finally in 2009, **C** was proved to be the pheromone of the longtailed mealybug (*Pseudococcus longispinus*).[5] Their unique structures including stereochemistry were all confirmed by syntheses.[2]

In Japan, Tabata et al. are working on the identification of the female produced sex pheromone of the pineapple mealybug [*Dysmicoccus brevipes* (Cockerell), Homoptera: Pseudococcidae], which is a pest infesting pineapples in Okinawa.[6] Dr. Tabata asked me to synthesize samples with the proposed structure **1** of the pheromone (Tabata, J. personal communication). My synthesis provided both (±)-*anti*- and *syn*-**1**. Their NMR and GC–MS comparisons with the natural pheromone as well as their bioassay established the structure of the pheromone as *anti*-**1**, although its absolute configuration still remains unknown.[7]

This paper describes in detail the synthesis of (±)-*anti*- and *syn*-**1** as achieved by several different approaches.

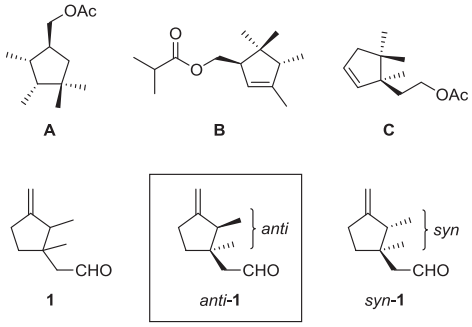

Fig. 1. Structures of the mealybug pheromones. **A**: the obscure mealybug (*Pseudococcus viburni*); **B**: the grape mealybug (*Pseudococcus maritimus*); **C**: the longtailed mealybug (*Pseudococcus longispinus*); **1**: the pineapple mealybug (*Dysmicoccus brevipes*). The structures depicted for *anti*- and *syn*-**1** show relative configuration.

☆ For Part 259, see Ref. 1. This work was orally reported by K.M. as a part of his lecture at International Chemical Ecology Conference 2016 (July 5, 2016) in Iguassu Falls, Brazil.

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2. Results and discussion

2.1. Retrosynthetic analyses of 1

Fig. 2 shows the retrosynthetic analyses of **1**, all of which could be realized later to give (±)-**1**. The most direct route to **1** is route (a), making the ring first and then generating the quaternary carbon center. Conjugate addition of allylsilane[8] is employed as the key step for conversion of the known **E** to **1** via **D**. This route was examined first, and gave both (±)-*anti*- and *syn*-**1** used for the identification of the natural pheromone.[7]

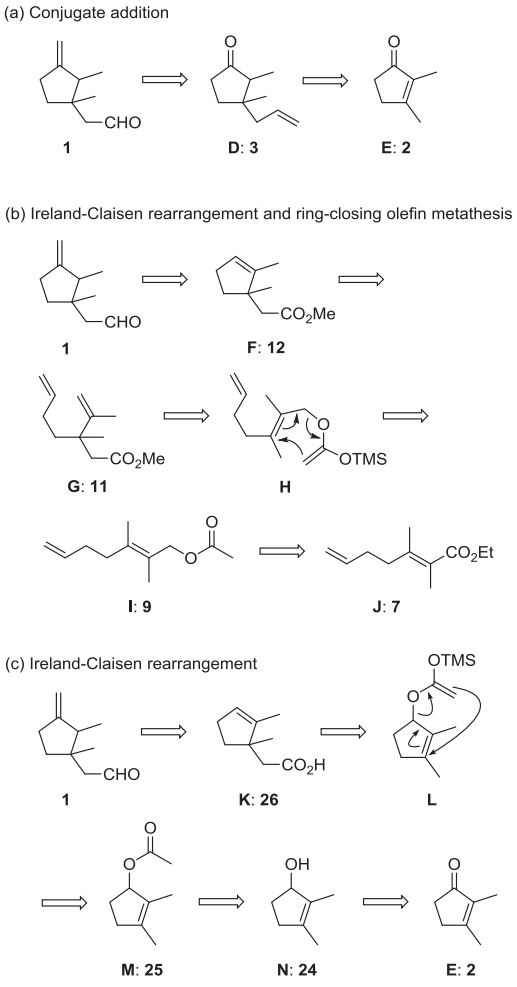


Fig. 2. Retrosynthetic analyses of **1**.

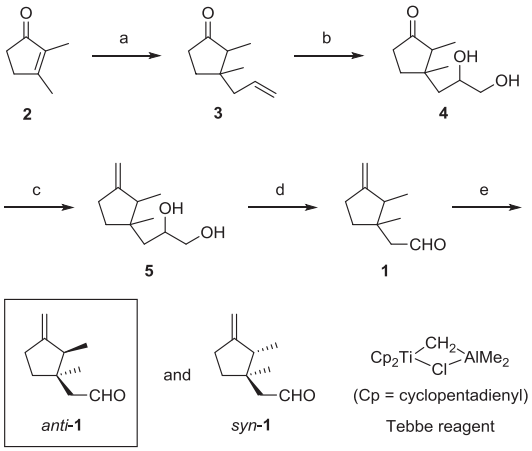
Practical difficulties encountered in the course of the realization of route (a) forced me to adopt route (b) as the more reliable one. Ireland's ester-enolate Claisen rearrangement[9] and Grubbs's ring-closing olefin metathesis[10,11] serve as the two key reactions. The five-membered ring is to be closed by olefin metathesis (**G**→**F**), and the quaternary carbon center is to be constructed by Ireland–Claisen rearrangement (**I**→**H**→**G**). Ester **J** will give **I** in two steps.

In future it will be necessary to prepare both the enantiomers of *anti*-**1** so as to determine the absolute configuration of the natural pheromone. Route (c) can be used for that purpose, because the resolution of **N** may be feasible to give the enantiomers of **N**. The Ireland–Claisen rearrangement of acetate **M** via **L** gives **K**, which is structurally equivalent to **F** in route (b). Accordingly, **K** can readily be converted to **1**. It must be mentioned that the construction of the quaternary center in cyclopentanoids by means of route (c) was first reported by Jäger and co-workers in their polycyclopentanoid synthesis,[12] and then Zou and Millar in their synthesis of the pheromone **C**.[13]

The rest of the present paper details the realization of these three retrosynthetic analyses to achieve three different syntheses of **1** as well as a formal synthesis of **1** via **K**.

2.2. First synthesis of the pheromone 1

The first synthesis of **1** was accomplished as shown in Scheme 1. Synthesis of the starting material, 2,3-dimethyl-2-cyclopenten-1-one (**2**) have been reported repeatedly.[14–18] Polyphosphoric acid (PPA)-mediated cyclization of 4-methyl-4-hexenoic acid was most reliable to give over 10 g of **2**.[12,14] Methylation of the enol phosphate of 2-methyl-1,3-cyclopentanedione with Me_2CuLi was also a good method to prepare **2**.[15] Isopropylmagnesium chloride-promoted unilateral addition of MeMgBr to 2-methyl-1,3-cyclopentanedione according to Yuan et al.[19] afforded **2**, but in a low yield of 14% after distillation.



Scheme 1. First synthesis of (±)-*anti*-**1**. Reagents: (a) CH_2=$CHCH_2TMS$, $TiCl_4$, CH_2Cl_2, −78 to −30 °C; then SiO_2 chromatography (12%); (b) OsO_4, NMO, *t*-BuOH, Me_2CO,H_2O (58%); (c) Tebbe reagent, toluene, THF; (d) $NaIO_4$, THF, H_2O; then SiO_2 chromatography (18%, two steps); (e) $AgNO_3/SiO_2$ chromatography.

Conjugate addition of allyltrimethylsilane to **2** was achieved according to Hosomi and Sakurai,[8] employing $TiCl_4$ as the catalyst. The desired allylated ketone **3** (diastereomer ratio=ca. 1:1) was obtained in 12% yield after SiO_2 chromatography. Although the yield was quite unsatisfactory, **3** could be obtained repeatedly, confirming the reproducibility of the reaction. An attempt was made to increase the yield by employing $InCl_3$ as the catalyst,[20] which unfortunately did not work at all. Additional unsuccessful attempts were made to construct the quaternary carbon center by means of copper(I)-catalyzed conjugate addition to **2** of allyl Grignard reagent in the presence of conventional CuI or CuBr/Me_2S, LiCl and TMSCl.[21] Conjugate addition of dimethyl malonate to **2** in the presence of NaOMe in MeOH was not fruitful, either.

Dihydroxylation of the allylated ketone **3** with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO)[22] yielded dihydroxy ketone **4**, which was treated with excess Tebbe reagent[23] to give methylenated diol **5**. Finally, cleavage of the glycol system of **5** with $NaIO_4$ afforded a crude oil (540 mg), which was purified by SiO_2 chromatography to give 132 mg of **1** (44.4% GC purity) as a stereoisomeric mixture. The overall yield of **1** was 0.6% based on **2** (four steps).

The mixture could be further purified by $AgNO_3/SiO_2$ chromatography[24] to separate (±)-*anti*-**1** from its *syn*-isomer. After the separation, the ^1H NMR spectra of the two isomers were compared, and the relative configuration of the two methyl groups was