# Improved Synthesis of the Pheromone of the Longtailed Mealybug

Yunfan Zou,* Jocelyn G. Millar

Department of Entomology, University of California, Riverside, CA 92521, USA
Fax +1(951)8273086; E-mail: yunfanz@ucr.edu

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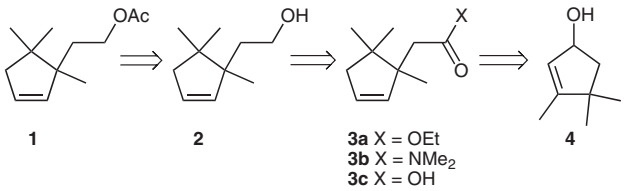
**Abstract:** A short and efficient synthesis of the longtailed mealybug pheromone featuring an Ireland–Claisen rearrangement as the key step is described.

**Key words:** pheromone, monoterpenoid, allylic cyclopentenol, Ireland–Claisen rearrangement

We recently identified the sex pheromone of the longtailed mealybug *Pseudococcus longispinus* as the novel monoterpenoid derivative **1**, with two adjacent quaternary carbons in a cyclopentene ring.[1] The mealybug is a widely distributed pest of vineyards and glasshouse crops, and it has recently gained additional importance because of its role as a vector of leafroll viruses in high value wine grapes.[2,3] In field tests, the pheromone proved to have extraordinary biological activity, with lures loaded with 25 μg of the racemic pheromone remaining highly attractive to male mealybugs for more than three months. Two syntheses of the pheromone have now been reported, but both have significant drawbacks, particularly in terms of scale-up syntheses for commercialization of the pheromone. In our first synthesis of **1**, developed primarily to verify the structure of the pheromone, a key step that used a 2,3-Wittig rearrangement of an allylic stannane intermediate proceeded in only 25% yield.[1] In a follow-up synthesis, the core cyclopentane ring structure was constructed by regiospecific cyclization of an α-diazo-β-ketoester.[4] This synthesis resulted in a higher overall yield and provided >5 g of the pheromone, but the reaction sequence was still unacceptably long (12 consecutive steps).

Retrosynthetic analyses had indicated that the desired pheromone **1** might be readily obtainable from reduction of a γ,δ-unsaturated carbonyl compound **3**, which in turn might be accessible from a Claisen-type rearrangement of cyclopentenol **4** (Scheme 1). However, preliminary studies testing different Claisen rearrangement conditions did not look promising,[4] and so the routes described above were used to provide material for ongoing field trials. With material in hand to work with, we then did a more thorough literature search and determined that there were several precedents for allylic cyclopentenols to undergo Johnson–Claisen,[5] Eschenmoser–Claisen,[5d,6] or Ireland–Claisen rearrangements.[5e,7] Encouraged by those results, we decided to revisit this general route, particularly because of its potential to provide much shorter and more easily scalable syntheses.




**Scheme 1**

To begin the synthesis, known cyclopentenone **5**, prepared in one step on multigram scale from cheap isobutyl 2-butenoate by treatment with hot polyphosphoric acid,[8,9] was reduced with $LiAlH_4$ to give the key allylic alcohol intermediate **4**.[1] Several sets of reaction conditions were then tested, beginning with the Johnson–Claisen rearrangement by heating alcohol **4** with excess triethyl orthoacetate in the presence of an acid catalyst. In our earlier, failed attempts with this reaction,[4] a carboxylic acid was used as catalyst and resulted only in production of 1,5,5-trimethylcyclopentadiene from elimination of the alcohol. Thus, we tried the weaker acid catalyst hydroquinone in the hope that elimination would be suppressed in favor of esterification and rearrangement. In the event, a complicated mixture was obtained, containing only trace amounts of the desired rearrangement product **3a** along with unreacted starting material, the previously obtained elimination product, and several unidentified side products.

We then tried the Eschenmoser–Claisen rearrangement conditions, expecting that they might give better results because the reaction is carried out under essentially neutral conditions. Refluxing alcohol **4** with dimethylacetamide dimethyl acetal resulted in a low yield (18%) of the desired γ,δ-unsaturated tertiary amide **3b**. Whereas this was readily reduced to alcohol **2** with lithium triethylborohydride, the yield in the rearrangement step was still unacceptably low.

Finally, we tried the Ireland–Claisen conditions in two steps. First, alcohol **4** was esterified with $Ac_2O$,[10] DMAP, and pyridine to give acetate **6**.[11] Then reaction of **6** with LDA and *tert*-butyldimethylsilyl chloride[12] in THF followed by thermolysis of the resultant silyl ketene acetal generated the desired *tert*-butyldimethylsilyl ester, which was hydrolyzed with aqueous NaOH to give γ,δ-unsaturated acid **3c** in 50% isolated yield. The remaining synthesis required only straightforward reduction of acid **3c** with $LiAlH_4$ and acetylation of alcohol **2** with acetyl chloride

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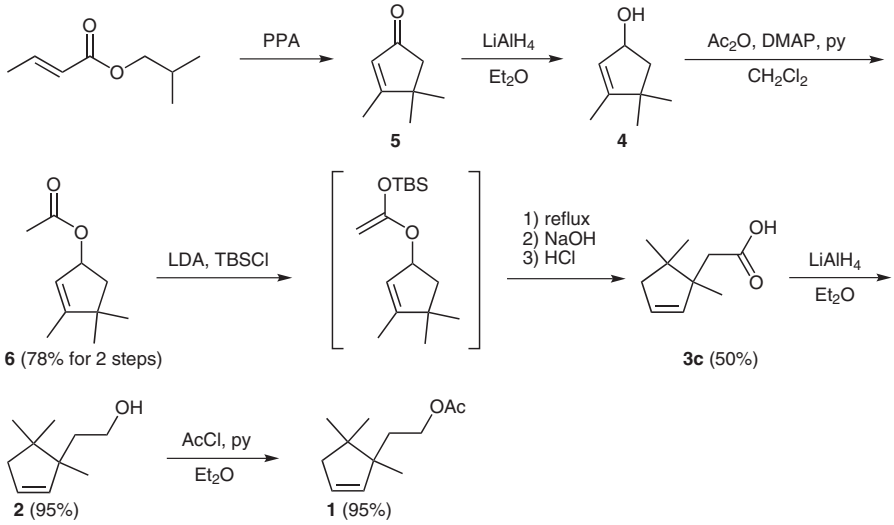


**Scheme 2**

and pyridine, giving acetate **1** in 35% yield from **5** in five steps (Scheme 2). This relatively short and efficient synthesis of the pheromone will expedite its commercial development for detection, monitoring, and control of longtailed mealybugs and the leafroll viruses that they vector.

**(1,5,5-Trimethylcyclopent-2-enyl)acetic Acid (3c)**

A solution of DIPA (0.51 mL, 3.6 mmol) in anhyd THF (5 mL) under Ar was cooled to 0 °C, *n*-BuLi (2.1 M in hexane, 1.6 mL, 3.3 mmol) was added, and the solution was stirred at 0 °C for 15 min, then cooled to –78 °C. A solution of ester **6** (0.50 g, 3.0 mmol) in anhyd THF (5 mL) was added dropwise, and the mixture was stirred at –78 °C for 30 min. A solution of *tert*-butyldimethylsilyl chloride (0.47 g, 3.15 mmol) in anhyd THF (2 mL) was then slowly added. After 30 min, the cold bath was removed, the mixture was warmed and stirred at r.t. for 2 h, and then refluxed for 1 d. The mixture then was cooled to r.t. and treated with 2 M aq NaOH (6 mL). The mixture was stirred 1 h at r.t., then extracted with hexanes (3×) to remove nonacidic side products. The aqueous layer was acidified with 6 M HCl to pH 1.0 and extracted with $Et_2O$ (3×). The combined ether extracts were washed with brine, dried, and concentrated, and the crude product was purified by Kugelrohr distillation ($1.33 \cdot 10^{-3}$ bar, 90 °C) to give 0.25 g (50%) of **3c** as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.81 (dt, *J* = 6.0, 2.0 Hz, 1 H), 5.66 (dt, *J* = 6.0, 2.0 Hz, 1 H), 2.38 (d, *J* = 13.6 Hz, 1 H), 2.24 (d, *J* = 13.6 Hz, 1 H), 2.19 (dt, *J* = 16.0, 2.0 Hz, 1 H), 2.12 (dt, *J* = 16.0, 2.0 Hz, 1 H), 1.03 (s, 3 H), 0.98 (s, 3 H), 0.95 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 179.9 (C), 138.6 (CH), 128.3 (CH), 49.9 (C), 46.8 ($CH_2$), 44.3 (C), 40.8 ($CH_2$), 24.6 ($CH_3$), 24.2 ($CH_3$), 19.8 ($CH_3$). IR (film): 3300–2500 (br), 1707, 1450, 1409, 1295, 1235, 1137, 954, 716 $cm^{-1}$. MS: *m/z* (rel. abundance) = 41 (66), 43 (35), 53 (18), 55 (13), 67 (40), 69 (12), 77 (20), 79 (22), 81 (23), 91 (27), 93 (45), 107 (40), 108 (57), 109 (100), 153 (13), 168 (4) [$M^+$]. ESI-HRMS (APCI): *m/z* calcd for $[C_{10}H_{16}O_2 + H]^+$: 169.1223; found: 169.1226.

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(9) In ref. 8c and 8d, the α,β-unsaturated ester was reacted with hot polyphosphoric acid for 10 min and 3 min, respectively, before the reaction was stopped. However, in our hands, only starting material was recovered with such short reaction times. We found the reaction to be complete after ca. 5 h, which is more consistent with ref. 8a and 8b.
(10) When AcCl was used instead of $Ac_2O$, the yield was lower (65%).

(11) **Data for Acetic Acid 3,4,4-Trimethyl-cyclopent-2-enyl Ester (6)**
$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.50 (m, 1 H), 5.33 (m, 1 H), 2.13 (dd, *J* = 14.0, 7.2 Hz, 1 H), 1.99 (s, 3 H), 1.69 (dd, *J* = 14.0, 2.8 Hz, 1 H), 1.66 (t, *J* = 1.6 Hz, 3 H), 1.08 (s, 3 H), 1.01 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.3, 155.8, 122.1, 78.4, 46.9, 45.4, 27.9, 27.4, 21.6, 12.4. IR (film): 3055, 2959, 2869, 1734, 1654, 1438, 1373, 1242, 1019, 970 $cm^{-1}$. MS: *m/z* (rel. abundance) = 41 (34), 43 (85), 55 (18), 67 (21), 77 (22), 91 (24), 93 (100), 108 (15), 109 (36), 111 (24), 126 (17), 153 (2), 168 (7) [$M^+$]. HRMS (CI/$CH_4$ on GC-MS): *m/z* calcd for $[C_{10}H_{16}O_2]^+$: 168.1150; found: 168.1151.

(12) When 1.3 equiv of *tert*-butyldimethylsilyl chloride was used, a silicon-containing acidic byproduct was formed, which was difficult to separate from **3c**. With 1.05 equiv, this byproduct was not observed.

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