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Synthesis of the Pheromone of the Longtailed Mealybug, a Sterically Congested, Irregular Monoterpenoid

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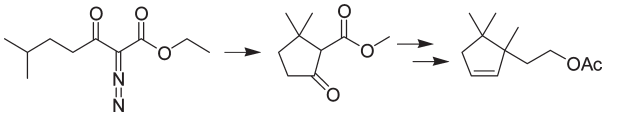
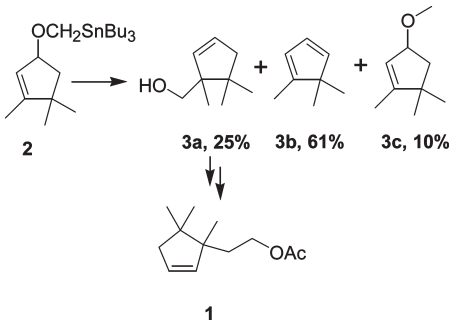


A straightforward and scaleable synthesis of the sterically congested pheromone of the longtailed mealybug, with two adjacent quarternary carbons in a cyclopentene ring, was accomplished in 13.5% overall yield. Key steps included regiospecific cyclization of an α-diazo-β-ketoester to build the cyclopentane ring, followed by reduction of the enol triflate of the ketone to place the double bond.

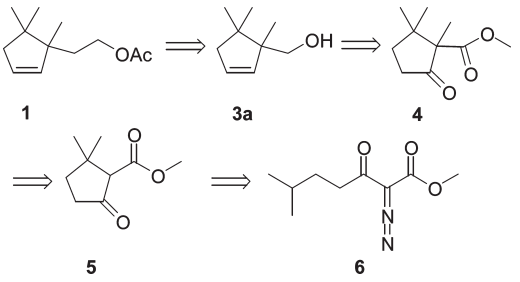
The longtailed mealybug, *Pseudococcus longispinus*, is a widely distributed pest of numerous agricultural and ornamental crops.[1] In addition to direct feeding damage and indirect damage caused by the growth of sooty mold on honeydew excreted by the insects, the insect is rapidly increasing in importance because of its role in transmission of plant viruses, particularly to high-value wine grapes.[2] As part of a program to develop improved methods of detection and sampling populations of mealybug species in vineyards, we recently identified the sex pheromone produced by female longtailed mealybugs to attract the fragile and ephemeral males for mating as acetate **1**.[3] This sterically congested monoterpenoid, with two adjacent quaternary carbons in a cyclopentene ring, is the first example of a new structural class of monoterpenoids. 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.

The racemic pheromone initially was synthesized by an unequivocal route as final proof of the structure identification,

SCHEME 1. 2,3-Wittig Reaction To Create Adjacent Quaternary Centers



SCHEME 2. Retrosynthetic Analysis of Acetate 1



but the published synthesis is not suitable for scale-up to provide commercially useful quantities of the pheromone. Specifically, a key step in the synthesis that used a 2,3-Wittig rearrangement of allylic stannane **2** to alcohol **3a** (Scheme 1) to place the two adjacent quaternary centers and the endocylic double bond simultaneously proceeded in only 25% yield, with major side products resulting from elimination to conjugated cyclopentadiene **3b** and reduction to methyl ether **3c**. This key step defied all efforts at improvement. Attempts to assemble the tetrasubstituted cyclopentene skeleton by Claisen rearrangement of analogues of **2** also failed, producing only diene **3b**.

To circumvent this limitation, we developed an alternate synthesis of **1** with the following goals in mind. First, we wanted as many steps as possible to be uncomplicated, high-yielding, and requiring minimal use of expensive reagents so that the synthesis could provide multigram quantities of the pheromone at an affordable cost. Second, we wanted to use steps that yielded products requiring only rapid, if any, chromatographic purification (e.g., vacuum flash chromatography), to minimize time, labor, and materials costs.

In a retrosynthetic analysis (Scheme 2), we reasoned that a route proceeding through alcohol **3a** might still be useful, if **3a** could be made more efficiently. This appeared to be feasible via β-ketoester **5**, whereby the ketone represented a latent endocyclic alkene in the correct position, via reduction of the corresponding enol triflate of the ketone. Furthermore, the ketone would serve as a second activating group to direct methylation regiospecifically to the sterically hindered carbon between the two carbonyl groups in ketoester **5**. The cyclic β-ketoester **5** was in turn available by rhodium-catalyzed

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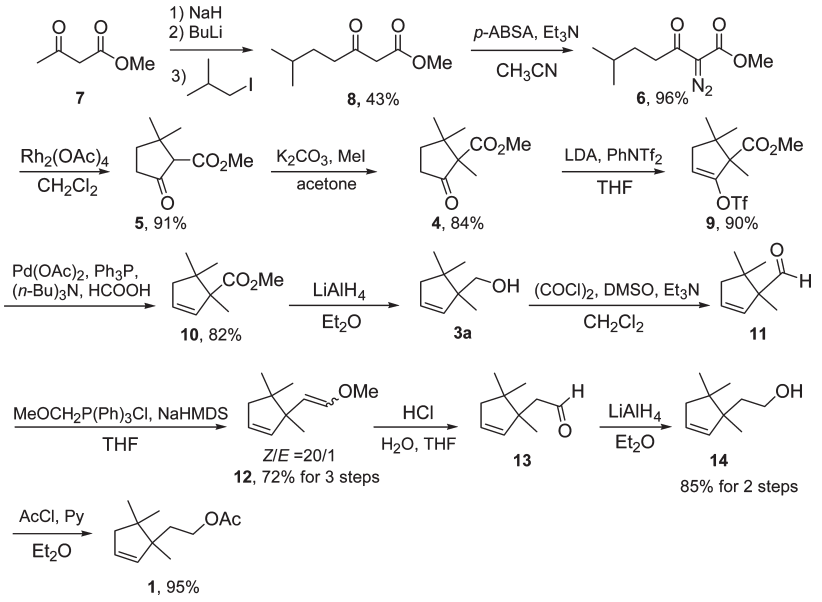
SCHEME 3. Synthesis of the Longtailed Mealybug Pheromone



intramolecular cyclization of α-diazo-β-ketoester **6**.[4,5] In particular, the cyclization favors insertion into a methine C−H bond and formation of five-membered rings,[5] both factors working in our favor.

Thus, alkylation of the dianion of methyl acetoacetate **7** with isobutyl iodide (Scheme 3) gave β-keto ester **8** in moderate 43% purified yield, as previously reported.[6] Use of either an excess of isobutyl iodide or the dianion resulted in no improvement in yield, probably because of steric hindrance from the adjacent methyl groups hampering S_N2 displacement of the iodide. An alternate procedure involving nucleophilic acyl substitution of dimethylcarbonate with the enolate of 5-methylhexan-2-one[5] gave a better yield (65%), but the desired product was contaminated with 8% of the product from alkylation of the thermodynamic enolate, and the mixture was not separable on a multigram scale. Use of reported variations of the reaction conditions (e.g., diethyl ether or toluene as solvent) resulted in similar yields and regioselectivities.[7]

Diazotization of β-ketoester **8** with *p*-acetamidobenzenesulfonyl azide[8] afforded α-diazo-β-ketoester **6** cleanly, in almost quantitative yield. The crucial Rh-catalyzed intramolecular C−H insertion reaction to create cyclopentane **5** proceeded smoothly in excellent (91% isolated) yield. Regiospecific methylation of the resulting cyclic β-ketoester **5** with methyl iodide and potassium carbonate[9,10] gave ketoester **4** (84%).

With the two adjacent quaternary carbons in place, we then addressed the insertion of the endocyclic double bond. Conversion of the ketone in **4** to its enolate by treatment with LDA in THF at −78 °C and trapping the enolate with $PhNTf_2$[11] gave enol triflate **9** (90%). Palladium-catalyzed reduction with formic acid as a hydrogen source[12] then afforded the key intermediate **10** in 82% yield, with the double bond placed in the desired position.

The remainder of the synthesis required only one-carbon chain extension of the side chain and functional group manipulation. After $LiAlH_4$ reduction of ester **10** to give alcohol **3a**, Swern oxidation of **3a** to aldehyde **11** proved superior to oxidation with PCC in CH_2Cl_2. In the subsequent Wittig reaction of aldehyde **11**, deprotonation of methoxymethyltriphenylphosphonium chloride with the nonnucleophilic NaHMDS resulted in better yields of the methyl vinyl ether products **12** (72% over 3 steps) than deprotonation with BuLi, which was complicated by production of significant amounts of side products. Acid-catalyzed hydrolysis of the methyl vinyl ethers **12** gave aldehyde **13**, which was immediately reduced to alcohol **14** with $LiAlH_4$ in ether. This reagent and solvent combination proved superior to $NaBH_4$ in EtOH due to a simpler workup and better overall yield (85% vs. 71% isolated yield over 2 steps).[3] The synthesis was completed by acetylation of alcohol **14** with acetyl chloride and pyridine, giving acetate **1** in 13.5% overall yield, versus the 4.2% yield obtained in the previous synthesis. Overall, this straightforward synthesis provided > 5 g of the pheromone, sufficient for > 200 000 pheromone lures at the effective dose of 25 μg per lure.

Experimental Section

2-Diazo-6-methyl-3-oxo-heptanoic Acid Methyl Ester (6). A solution of **8** (4.31 g, 25 mmol) and *p*-acetamidobenzenesulfonyl azide (6.01 g, 25 mmol) in CH_3CN (125 mL) was cooled to 0 °C,

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then Et_3N (10.5 mL, 75 mmol) was added in one portion. The reaction mixture was warmed to room temperature overnight with stirring. The solvent was removed under reduced pressure, and the residue was triturated with a 1:1 mixture of ether/pentane, filtering through Celite to remove the sulfonamide byproduct, and the filtrate was concentrated. The crude product was purified by vacuum flash chromatography (VFC) (hexanes/Et_2O = 4/1) to give 4.77 g (96%) of **6** as a yellow oil. ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 1.48−1.64 (m, 3H), 0.89 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 193.3, 161.9, 75.8, 52.2, 38.4, 33.3, 27.9, 22.4; IR (film) 2958, 2872, 2135, 1726, 1659, 1438, 1312, 1213, 1045, 746 cm^{-1}; HRMS (ESI/APCI) calcd for $[C_9H_{14}N_2O_3 + H]^+$ 199.1077, found 199.1081.

2,2-Dimethyl-5-oxo-cyclopentanecarboxylic Acid Methyl Ester (5). A slurry of $Rh_2(OAc)_4$ (125 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (75 mL) under Ar was cooled to 0 °C. A solution of **6** (5.59 g, 28.2 mmol) in anhydrous CH_2Cl_2 (20 mL) was added, and the reaction mixture was stirred for 4 h while warming to room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by VFC (hexanes/EtOAc = 95/5) to give 4.35 g (91%) of **5** as a light yellow oil. ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H), 2.90 (s, 1H), 2.31−2.51 (m, 2H), 1.95−2.04 (m, 1H), 1.70−1.79 (m, 1H), 1.20 (s, 3H), 1.08 (s, 3H). The ^1H NMR spectrum was in agreement with that previously reported.[4]

1,2,2-Trimethyl-5-oxo-cyclopentanecarboxylic Acid Methyl Ester (4). Anhydrous K_2CO_3 (2.09 g, 15.12 mmol) and iodomethane (1.0 mL, 16.50 mmol) were added sequentially to a solution of **5** (2.34 g, 13.75 mmol) in dry acetone (50 mL) under Ar, and the reaction mixture was stirred overnight. After concentration under reduced pressure, a 1:1 mixture of ether/pentane was added to the residue. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc = 95/5) to give 2.13 g (84%) of **4** as a colorless oil. ^1H NMR ($CDCl_3$) δ 3.66 (s, 3H), 2.55 (ddd, J = 19.6, 9.2, 3.2 Hz, 1H), 2.28 (dt, J = 19.6, 9.2 Hz, 1H), 2.01 (dt, J = 12.8, 9.2 Hz, 1H), 1.72 (ddd, J = 12.8, 9.2, 3.2 Hz, 1H), 1.14 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 217.0, 172.3, 63.0, 52.0, 42.9, 36.1, 34.5, 25.1, 24.7, 14.2; IR (film) 2958, 2875, 1752, 1732, 1456, 1265, 1202, 1117, 1057 cm^{-1}; MS (m/z, rel abundance) 41 (77), 43 (17), 53 (13), 55 (45), 59 (14), 67 (12), 69 (52), 73 (25), 83 (33), 97 (100), 109 (10), 115 (16), 129 (20), 141 (24), 156 (38), 184 (M^+, 4); HRMS (ESI/APCI) calcd for $[C_{10}H_{16}O_3 + H]^+$ 185.1172, found 185.1175.

1,5,5-Trimethyl-2-trifluoromethanesulfonyloxycyclopent-2-enecarboxylic Acid Methyl Ester (9). A solution of diisopropylamine (6.8 mL, 48 mmol) in anhydrous THF (40 mL) under Ar was cooled to 0 °C, *n*-BuLi (2.63 M in hexane, 16.7 mL, 44 mmol) was added, and the solution was stirred at 0 °C for 15 min, and then cooled to −78 °C. A solution of **4** (7.37 g, 40 mmol) in anhydrous THF (40 mL) was added and the mixture was stirred at −78 °C for 2 h. A solution of $PhNTf_2$ (15.72 g, 44 mmol) in anhydrous THF (80 mL) was added, and the mixture was warmed to 0 °C and stirred overnight. The mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were washed with water and brine, dried, and concentrated. The crude product was purified by VFC (hexanes/Et_2O = 95/5) to give 11.40 g (90%) of **9** as a colorless oil. ^1H NMR ($CDCl_3$) δ 5.73 (t, J = 2.8 Hz, 1H), 3.69 (s, 3H), 2.30 (dd, J = 15.6, 2.4 Hz, 1H), 2.17 (dd, J = 15.6, 2.4 Hz, 1H), 1.26 (s, 3H), 1.09 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.8 (C), 149.6 (C), 116.5 (CH), 59.5 (C), 52.0 (CH_3), 44.3 (C), 42.1 (CH_2), 25.7 (CH_3), 24.9 (CH_3), 16.1 (CH_3) (CF_3 not observed); ^{19}F NMR ($CDCl_3$) δ 126.56 (s) ($CFCl_3$ in acetone-d_6 at 0 ppm); IR (film) 3099, 2971, 2878, 1739, 1660, 1423, 1211, 1143, 1056, 892, 829, 633 cm^{-1}; MS (m/z, rel intensity): 41 (100), 43 (30), 53 (26), 55 (71), 59 (25), 67 (33), 69 (85), 79 (34), 81 (20), 91 (30), 95 (52), 107 (81), 109 (23), 123 (71), 151 (80), 183 (23), 257 (18), 301 (2); HRMS (ESI/APCI) calcd for $[C_{11}H_{15}F_3O_5S + H]^+$ 317.0665, found 317.0669.

1,5,5-Trimethylcyclopent-2-enecarboxylic Acid Methyl Ester (10). A 3-neck round-bottomed flask with a reflux condenser was charged with **9** (12.65 g, 40 mmol), tributylamine (28.6 mL, 120 mmol), palladium acetate (0.18 g, 0.8 mmol), triphenylphosphine (0.42 g, 1.6 mmol), and DMF (80 mL). The mixture was flushed with Ar for 1−2 min, and then formic acid (3.0 mL, 80 mmol) was added dropwise. The resulting mixture was heated to 60 °C for 1 h, during which the mixture became black. The reaction mixture was poured into 2 M HCl and extracted with pentane. The combined organic layer was washed with water and brine, dried, and concentrated. The crude product was purified by Kugelrohr distillation (8 Torr, 70 °C) to give 5.52 g (82%) of **10** as a colorless oil. ^1H NMR ($CDCl_3$) δ 5.73−5.76 (m, 1H), 5.67−5.70 (m, 1H), 3.65 (s, 3H), 2.24 (dt, J = 16.0, 2.4 Hz, 1H), 2.10 (ddd, J = 16.0, 2.8, 1.2 Hz, 1H), 1,13 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.5 (C), 135.9 (CH), 129.4 (CH), 60.1 (C), 51.4 (CH_3), 46.8 (CH_2), 44.2 (C), 26.4 (CH_3), 23.4 (CH_3), 20.4 (CH_3); IR (film) 3058, 2965, 2875, 2844, 1732, 1461, 1370, 1269, 1229, 1131, 1114, 722 cm^{-1}; MS (m/z, rel abundance) 41 (33), 43 (20), 55 (14), 67 (40), 77 (15), 79 (12), 81 (12), 93 (25), 109 (100), 125 (26), 153 (4), 168 (M^+, 6); HRMS (ESI/APCI) calcd for $[C_{10}H_{16}O_2 + H]^+$ 169.1223, found 169.1223.

(1,5,5-Trimethylcyclopent-2-enyl)methanol (3a). A suspension of $LiAlH_4$ (1.67 g, 44 mmol) in anhydrous Et_2O (40 mL) under Ar was cooled to 0 °C and a solution of **10** (6.73 g, 40 mmol) in Et_2O (40 mL) was added. The mixture was stirred for 2 h while warming to room temperature, then cooled to 0 °C and quenched by sequential addition of water (1.67 mL), 15% aqueous NaOH (1.67 mL), and water (5.0 mL). After being stirred for 10 min, the mixture was filtered through Celite to remove the granular precipitate and the filtrate was dried and concentrated. The crude product **3a** was used in the next step without further purification. A pure sample was obtained by Kugelrohr distillation (0.5 Torr, 70 °C) as a white solid, mp 74−75 °C. ^1H NMR ($CDCl_3$) δ 5.75 (dt, J = 5.6, 2.4 Hz, 1H), 5.34 (dt, J = 5.6, 1.6 Hz, 1H), 3.45 (d, J = 10.8 Hz, 1H), 3.28 (d, J = 10.8 Hz, 1H), 2.22 (dt, J = 16.0, 2.0 Hz, 1H), 1.99 (dt, J = 16.0, 2.0 Hz, 1H), 0.98 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H). The ^1H NMR spectrum was in agreement with that previously reported.[3]

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all new compounds and improved procedures for the preparation of **8**, **11**−**14**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.