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Stereospecific synthesis of the sex pheromone of the passionvine mealybug, *Planococcus minor*

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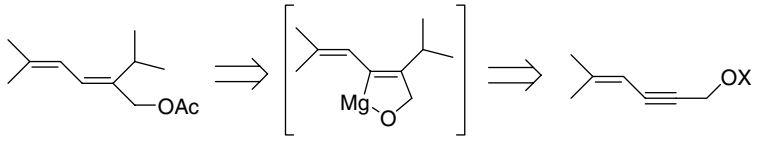
Abstract—A short and completely stereospecific synthesis of (*E*)-2-isopropyl-5-methyl-2,4-hexadienyl acetate, the very recently identified sex pheromone of the passionvine mealybug *Planococcus minor*, is described. In the key step, CuI-catalyzed anti-addition of a Grignard reagent to a propargyllic alcohol intermediate gave the required trisubstituted alkene with 100% regio- and stereospecificity. The stereochemical purity of the pheromone is critically important because the (*Z*)-isomer is a powerful behavioral antagonist.

The passionvine mealybug, *Planococcus minor* (Maskell), is a significant pest of more than 250 host plants, including major agricultural crops as diverse as citrus, corn, grapes, and tree fruits. It currently has a broad geographical distribution which includes many of the tropical and temperate areas of the world.[1] However, it has not yet become established in the continental United States,[1] and the economic consequences of its introduction and establishment in the US have been estimated to be severe.[1] Until very recently, there was no easy way to detect this invasive pest. However, the sex pheromone of this insect has now been identified as the non-head-to-tail monoterpenoid (*E*)-2-isopropyl-5-methyl-2,4-hexadienyl acetate **1**,[2] and preliminary tests showed that small doses of the pheromone were highly attractive to male mealybugs,[2] indicating that pheromone-baited traps would provide a highly sensitive and effective method of detecting even small populations of this pest. However, the preliminary bioassays also demonstrated that attraction of male mealybugs to the pheromone was strongly antagonized by the (*Z*)-isomer of the pheromone.[2] Thus, the initial, non-stereoselective synthesis of the pheromone that was used to produce both isomers for verification of the structure and stereochemistry of the pheromone is not suitable for large scale production of the pheromone for practical use; the two isomers can only be separated with difficulty in milligram amounts.[2] To overcome this obstacle to the development of applications for this pheromone, a three-step, stereospecific synthesis of the pheromone is reported here (Scheme 1).

Retrosynthetic analysis of the structure of **1** suggested that the conjugated diene structure might be accessible through enyne structure **3**, if **3** could subsequently be converted stereospecifically to the required trisubstituted alkene skeleton. In particular, the substitution pattern of the trisubstituted alkene seemed ideally set up for copper-catalyzed, regio- and stereospecific anti-addition of isopropylmagnesium bromide to the propargyllic alcohol precursor **3**.[3] The stereospecificity of the reaction has been reported to be the result of the



Scheme 1. Retrosynthetic analysis of pheromone structure **1**.

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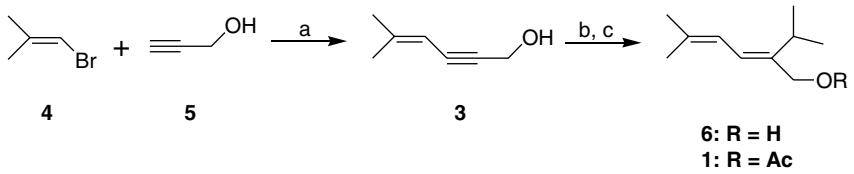

Scheme 2. Synthesis of pheromone structure (1) Reagents and conditions: (a) CuI, $(Ph_3P)_2PdCl_2$, pyrolidine (40%); (b) isopropylMgBr, THF, CuI (64%, or 94% based on recovered starting material); (c) AcCl, pyridine, ether (97%).

formation of cyclic intermediate **2**,[3] and the stereochemistry is completely retained during subsequent quenching of the intermediate. In the event, this short and stereospecific synthesis was readily realized (Scheme 2).

Thus, 1-bromo-2-methyl-1-propene **4** (30 mmol; Aldrich Chemical Co.) was added dropwise to a stirred solution of propargyl alcohol **5** (36 mmol), bis(triphenylphosphine) palladium II chloride (1.4 mmol), and CuI (2.6 mmol) in 30 ml dry pyrolidine at 0 °C under argon, and the mixture was warmed to room temperature and stirred overnight. The resulting dark brown slurry was poured into ice-cold 3 M HCl and extracted three times with ether. After drying and concentration, the brown oil was purified by vacuum flash chromatography on silica gel (20% ether in pentane). The purified product was Kugelrohr distilled (oven temp 40–60 °C, 1 mm Hg), yielding known enynol **3**[4] as a pale yellow oil (40%).

Slow addition under argon of isopropylmagnesium bromide (2 M in THF, 15 mmol; foams!) to a slurry of alcohol **3** (5 mmol) and CuI (1 mmol) in 2 ml THF at ~−10 °C in an ice-salt bath, followed by warming to room temp and stirring for 24 h gave a 68:32 mixture of the desired product with unreacted starting material. Warming to 40 °C for 3 h increased the proportions to 78:22, but additional stirring at this temperature resulted in no further change in the ratio of product to starting material. Thus, the reaction mixture was diluted with ether, cooled to 0 °C, and quenched by slow addition of saturated aqueous NH_4Cl (foams!). After separation of the layers, the aqueous phase was extracted twice more with ether. The combined ether phases were dried, concentrated, and purified by flash chromatography on silica gel (15% EtOAc in hexanes). The product eluted first, and was cleanly resolved from unreacted alcohol **3**. After Kugelrohr distillation (oven temp 80–90 °C, 1.9 mm Hg), alcohol **6** was obtained in 64% overall yield (94% based on recovered starting material), in >99% chemical and isomeric purity. Running the reaction in ether[3] resulted in a lower overall conversion rate (67:33 ratio of product to starting material) and yield.

The synthesis was completed by acetylation of **6** with excess acetyl chloride and pyridine in ether at 0 °C to room temperature overnight. After workup, concentration and Kugelrohr distillation (oven temp 85–100 °C, 2.3 mm) gave the pheromone **1** in 97% yield and >99% chemical purity, with no detectable amounts of the undesired (*Z*)-isomer by GC–MS analysis. Overall, this short, efficient, and stereospecific synthesis of the pheromone should allow the rapid development of the pheromone for detection and management of passionvine mealybug.

The structure of this pheromone continues the developing motif of irregular terpenoids being used as pheromones by mealybug and scale species.[5–7] In particular, this compound has the same unusual 1′–2 connection of two isoprene units that now has been found in the pheromones of five other mealybug species.[5,6] It is also interesting to note that for all of the scale and mealybug pheromones identified so far, each species produces unique pheromone chemicals, eliminating the possibility of competition for or interference with a particular pheromone channel. Furthermore, the fact that passionvine mealybug is strongly inhibited by the (*Z*)-stereoisomer of its pheromone suggests that this compound may be the pheromone of a related, sympatric species. This remains to be determined by field testing of the two isomers.

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Supplementary data

Supplementary data includes the EI mass spectra and ^1H and ^{13}C NMR spectra of compounds **1**, **3**, and **6**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.045.

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