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Synthesis of the sex pheromone of the obscure mealybug, the first example of a new class of monoterpenoids

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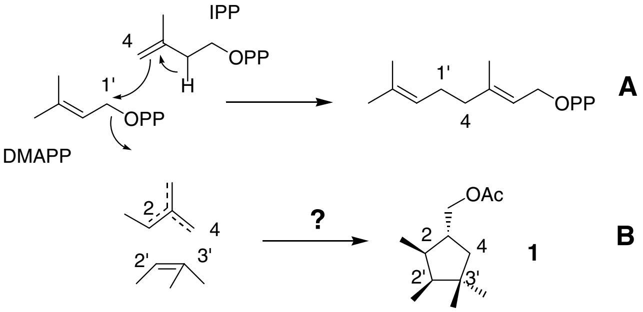
Abstract—A diastereoselective synthesis of (1*R**,2*R**,3*S**)-1-acetoxymethyl-2,3,4,4-tetramethylcyclopentane, the sex pheromone of the obscure mealybug *Pseudococcus viburni*, is described. Key steps included the polyphosphoric acid-catalyzed cyclization of isobutyl methacrylate to form the core five-membered ring, and diastereoselective quenching of an enolate intermediate to give the thermodynamically less favored cis orientation of vicinal methyl groups in a cyclopentanone intermediate.

We recently identified (1*R**,2*R**,3*S**)-1-acetoxymethyl-2,3,4,4-tetramethylcyclopentane **1** as the female-produced sex pheromone of the obscure mealybug, *Pseudococcus viburni* (Homoptera: Pseudococcidae),[1] a widely distributed pest of ornamental plants, crop plants, and grape vines.[2] This compound, with its 1-hydroxymethyl-2,3,4,4-tetramethylcyclopentane skeleton, represents the first example of a new structural class of monoterpenoids, in which the 1′-4, head-to-tail connections that link the dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) units that make up the 10-carbon skeleton of a typical monoterpene (Scheme 1A) appear to have been replaced with unprecedented 2′-2 and 3′-4 linkages (Scheme 1B).



Scheme 1. (A) Typical biosynthesis of monoterpenes by head-to-tail connection of DMAPP and IPP; (B) Connection of the two isoprene units forming the carbon skeleton of the obscure mealybug sex pheromone.

During the identification of this compound, the relative stereochemistry of the insect-produced compound was difficult to determine because of the very small amounts that were isolated from the insects. Thus, to verify the structure a nonstereoselective synthesis was developed,[1] aimed at producing a mixture of all four possible diastereomers (as pairs of enantiomers), from which the correct diastereomer was separated chromatographically, conclusively identified, and unambiguously matched with the postulated structure for the insect pheromone. However, the low overall yield of the biologically active isomer and its purification in very limited quantities from the mixture of isomers by preparative gas chromatography rendered this synthesis unsatisfactory for larger scale production of the pheromone for field trials. We report here a diastereoselective synthesis of this highly irregular terpenoid from readily available starting materials (Scheme 2).

Treatment of isobutyl methacrylate **2** with polyphosphoric acid at 100 °C as described by Conia and Leriverend[3] and modified by Mori and Sasaki[4] produced 2,4,4-cyclopent-2-en-1-one **3** in moderate yield. As expected, Michael addition of Me_2CuLi to **3**, followed

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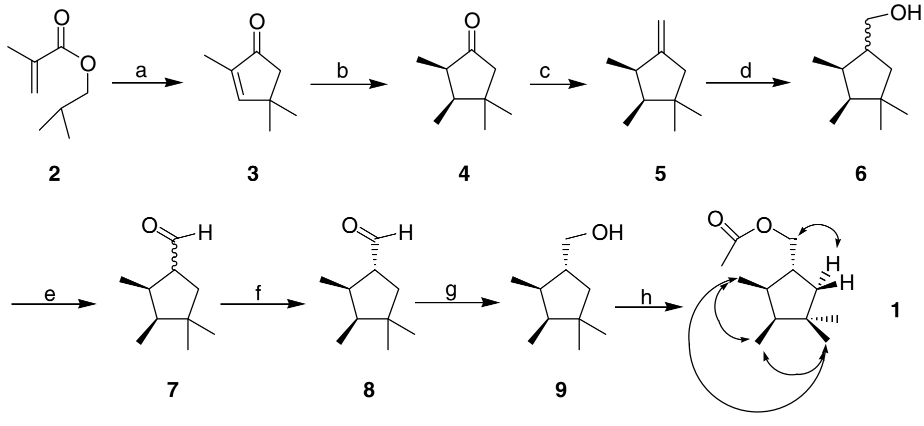
by quenching in the usual fashion produced a preponderance of the *trans*-2,3,4,4-tetramethylcyclopentanone mixed with the desired cis-diastereomer (ratio 82:18), due to preferential protonation of the intermediate enolate to form the thermodynamically more stable trans-diastereomer. However, the selectivity could be reversed by using a chelating proton donor during the quenching of the enolate.[5] Thus, ketone **3** was added dropwise to a solution of Me_2CuLi in ether at <−50 °C, the mixture was warmed to −40 °C, and stirred at −40 °C until GC analysis indicated that the starting material had been consumed. The reaction mixture then was cooled to −60 °C, and the resulting slurry was transferred by canula into a precooled solution (−78 °C) of 4 equiv of ethyl salicylate in ether. After warming to room temperature and workup, 2,3,4,4-tetramethyl cyclopentanones **4** were obtained in 89% yield as a 72:28 mixture of the cis and trans-diastereomers.

Reaction of the mixture of diastereomers with methylenetriphenylphosphorane under typical Wittig reaction conditions was not successful due to competing enolization of the sterically hindered ketone. However, the ketone was cleanly converted to methylene tetramethylcyclopentene **5** by treatment with the $Zn–CH_2Br_2–TiCl_4$ reagent.[6] Hydroboration with oxidative workup gave alcohols **6**, with the wrong configuration at carbon 1. This center was readily inverted by the straightforward sequence of oxidation to aldehydes **7** with pyridinium dichromate, and epimerization of the purified aldehyde by brief treatment with catalytic NaOMe in MeOH, giving **8**.[7] Purification of the aldehyde before epimerization proved to be crucial, because attempted base-catalyzed epimerization of the crude aldehyde did not proceed to completion. Reduction of epimerized **8** with $NaBH_4$ produced alcohol **9** with the desired relative configuration. The synthesis was completed by acetylation with acetyl chloride and pyridine in ether. Spectra of product **9** were identical to those of the insect-produced compound.[1]

The unique terpenoid skeleton of this compound suggests several implications. First, the obscure mealybug has a broad host range that includes such important and widely studied crop plants as grapes, apples, and pears.[2] These and other known host plants have not been reported to contain terpenoids with a 1-hydroxymethyl-2,3,4,4-tetramethylcyclopentane skeleton, suggesting that the mealybug is not simply producing the pheromone by modification of a closely related precursor from the host plants. Second, most monoterpenes are generated from cyclizations of geranyl pyrophosphate followed by subsequent Wagner–Meerwein rearrangements that generate the diversity of known terpenoid structures.[8] However, we have been unable to discern any relatively short and reasonable biosynthetic route to the 1-hydroxymethyl-2,3,4,4-tetramethylcyclopentane skeleton from a geranyl precursor. Third, the production of the pheromone is clearly under tight control, because the insects only produce one of the eight possible stereoisomers.[1] Taken together, these points suggest that obscure mealybugs are producing these compounds de novo by a clearly defined biosynthetic pathway. They further suggest that these small insects may have developed terpenoid biosynthetic pathways that are distinctly different from the typical terpenoid pathways found in other organisms. In fact, the production of irregular terpenoids appears to be a common trait in mealybugs and the related armoured scale insects.[9,10] For the six mealybug species for which pheromones have been reported,[10,11] all consist of irregular terpenoids, with all except that of the obscure mealybug having a 1′-2 linkage. Overall, the irregular terpenoid pheromones produced by mealybugs and scales suggests that these insects represent a rich and untapped source of enzymes capable of catalyzing novel cyclizations and rearrangements.

The fact that all of the irregular terpenoid pheromones identified from mealybugs and scales are unique structures is also worth noting from a biological standpoint. In many other insect families, species-specific pheromone signals are typically created from different subsets and ratios of a small group of compounds that are shared by some or all members of the group. In contrast, from the examples reported to date, scales and mealy-



Scheme 2. Reagents and conditions: (a) Polyphosphoric acid, 100 °C, 34%; (b) Me_2CuLi; ethyl salicylate quench, −78 °C, 89%; (c) $Zn–CH_2Br_2–TiCl_4$; (d) $BH_3·DMS$, THF, 0 °C; aq NaOH, H_2O_2, 75% from **5**; (e) PDC, CH_2Cl_2, 81%; (f) NaOMe, MeOH; (g) $NaBH_4$, EtOH; 93% from **7**; (h) AcCl, pyridine, ether; 81%. Curved arrows on structure **1** indicate NOE correlations used to assign the relative stereochemistry.

bugs may make much greater use of species-specific chemicals to create unique communication channels. Production of a unique olfactory signal would limit the possibility of interference with or competition for a pheromone channel. This lack of competition may explain why these insects often appear to be less sensitive to stereoisomers or other analogs of their pheromones (pink hibiscus mealybug represents the only published exception to date).[11] This stands in distinct contrast to insect families such as the Lepidoptera and Coleoptera, in which individuals are frequently acutely sensitive to even traces of isomers or other structural analogs of their pheromone components.

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Supplementary data

Supplementary data includes experimental procedures, and tables of the mass, ^{1}H NMR, and ^{13}C NMR data of the isomers of alcohols **9** and acetates **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.169.

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