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Enantioselective synthesis of (*S*)-3,7-dimethyl-2-oxo-6-octene-1,3-diol: a Colorado potato beetle pheromone

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ABSTRACT

The recent identification of a male-produced aggregation pheromone [(*S*)-3,7-dimethyl-2-oxo-6-octene-1,3-diol, (*S*)-CPB] offers a new tool for Colorado potato beetle (CPB) management. We developed a novel synthetic approach to produce CPB pheromone in seven steps and 46.54% overall yield. Grignard reaction, oxidation, and stereoselective methylation using organometallic reagent are the key steps in the commercially viable total synthesis, generating CPB pheromone in 98.6% enantiomeric purity and gram quantity.

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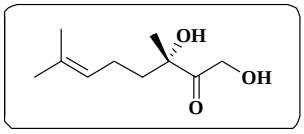
The Colorado potato beetle[1] (CPB); (*Leptinotarsa decemlineata*), is a worldwide pest causing billions of dollars damage annually. Control of the CPB has relied primarily on insecticides; however, the beetle has evolved resistance to virtually every pesticide ever used against it, and is now showing resistance to new insecticide classes such as the neonicotinoids.[1c] At present, there are limited alternatives to the use of synthetic pesticides. Insecticide resistance management and environmental stewardship promote management using CPB pheromone as a desirable alternative. For many insect pests, cost of synthesis of chiral pheromones is prohibitively expensive, limiting their commercial production and general acceptance. Because of the complexity and stereospecificity of pheromones, it is often productive to pursue novel approaches using natural reactants in order to develop high-yielding economic production.



(*S*)-3,7-Dimethyl-2-oxo-6-octene-1,3-diol
CPB-Pheromone

Earlier, a male-produced aggregation pheromone was identified by USDA scientist in our laboratory.[1a] The formal synthesis was carried out to reveal the absolute configuration of the pheromone.[2a] The first field evaluation of formulations comprising synthetic CPB-pheromone revealed practical utility in pest management and organic farming.[3]

Growing awareness of an environmental friendly crop protection as well as some disadvantages in earlier synthetic approaches[2] prompted us to develop novel, efficient, and enantioselective synthesis of (*S*)-CPB pheromone. Our synthetic route includes mannitol, a commercially available natural sugar, as an economical starting material (Scheme 1). Eliminating chiral/enzymatic resolution as one of the cost limiting factors, we are able to produce CPB pheromone in high purity and gram quantity for commercial production.

Grignard reaction of aldehyde **1** (prepared from mannitol diacetonide[4]) with (4-methylpent-3-enyl)-magnesium bromide (generated from Mg and 5-bromo-2-methyl-2-pentene) in dry tetrahydrofuran at 0 °C afforded the secondary alcohol **2** in 91% yield. Oxidation of compound **2** was achieved by using PCC and 4 Å molecular sieves in dichloromethane to form the ketone **3** in 93% yield. Formation of the tertiary alcohol **4** was the key intermediate, necessary for attaining the high enantiomeric purity of the pheromone. The stereochemistry of addition reaction onto glyceraldehyde acetonide has been well explored and highly stereoselective protocols have been developed generating either *syn* or *anti* products.[5] Conversely, the stereochemistry of the organometallic addition reaction onto ketone (**3**) remains unexplored.

First we treated the ketone **3** with MeLi in dry THF at −78 °C, which afforded tertiary alcohol with 20:80 (*syn*:*anti*) diastereoselectivity, which was not suitable as >80% enantiomeric excess

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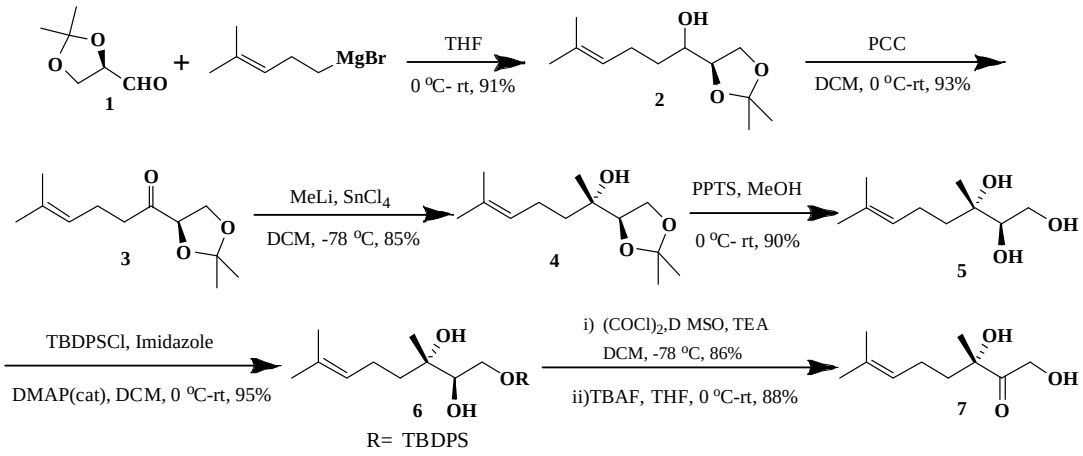

Scheme 1.

of *S*-CPB pheromone is required for optimum bioactivity.[3] Then we examined the reaction of ketone with combination of MeLi and Lewis acids ($BF_3{\cdot}Et_2O$, $TiCl_4$, and $SnCl_4$). Interestingly, the optimized combination of MeLi and $SnCl_4$ in dichloromethane at −78 °C was found to provide the *anti*-isomer of tertiary alcohol **4** as single product in 85% yield.[6] The isomeric purity was determined by the chiral GC analysis.[7] Exposure of **4** to PPTS in methanol cleaved the acetonide protection (**5**), and then selective protection of primary hydroxyl group with tertiarybutyldiphenyl silylchloride in the presence of imidazole and catalytic amount of DMAP provided the product **6**, which set the stage for the oxidation at C-2. Swern oxidation on **6** gave the ketone, which was treated with TBAF to furnish the pure (*S*)-CPB pheromone in 88% yield.[8]

Our synthetic approach not only produces this pheromone in higher enantiomeric purity, but also allows for flexibility in production of analogues while leaving the active site intact. Unchanged GC-EAD response of female CPB antenna to (*S*)-3,7-dimethyl-2-oxo-6-octane-1,3-diol, a saturated derivative of **7**, led us to explore structure–activity relationships. We synthesized some of the analogues of (*S*)-CPB pheromone containing oxygenated part (C1–C3) intact. Using the appropriate Grignard reagent in the first step of Scheme 1, we succeeded in modifying the tail portion, C4–C8. This offers us a rare opportunity of exploiting bio-activity while possibly improving on the physiochemical properties of the original pheromone structure in terms of volatility and persistence under field conditions.

In summary, we demonstrated a facile and versatile method for the synthesis of Colorado potato beetle pheromone. The synthetic method we developed not only produces (*S*)-CPB economically, but it can be used to derive novel analogues for structure–activity research. Our ultimate goal is to optimize efficacy and utility of semiochemicals in the integrated pest management of CPB.

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6. Procedure for the preparation of tertiary alcohol **4**: An oven-dried two-necked flask equipped with magnetic stir bar, nitrogen inlet, and septum was charged with dichloromethane solution (20 mL) of ketone (**3**) (7.0 mmol, 1.5 g) and cooled to −78 °C, then $SnCl_4$ (7.0 mmol, 0.82 mL) was added and stirred under a nitrogen atmosphere for 10 min. MeLi (1.6 M in diethyl ether, 14.0 mmol) was added dropwise to the solution at the same temperature and stirred for 2 h. The mixture was allowed to warmed to 0 °C over 1 h, then treated with saturated ammonium chloride, and extracted with dichloromethane (2 × 30 mL). The combined organic phases were washed with water, brine solution, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation to give a crude oil which was purified by column chromatography (hexanes–ethylacetate 7:1) to give **4** as colourless oil (1.37 g, 85% yield).
7. The absolute configuration at C-3 of **4** was determined as (*S*), by comparing the retention times (GC analysis) of the known compounds (**6** and **7**). GC method was used for the analysis of compounds: 30 m × 0.25 mm Chiraldex™ (Advanced Separation Technologies, Inc.) B-DM, H2 carrier, 100 °C (2) min then programmed at 2 °C/min to 200 °C and held at that temperature.
8. All the spectral properties were matched with the reported values (Ref. 2).