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A Simplified Synthesis of HNDB (Albiducin A) and Calidiol A

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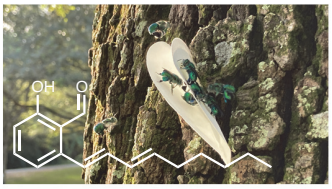

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Abstract A short, gram-scale synthesis of 2-hydroxy-6-nona-1,3-dienylbenzaldehyde (HNDB, albiducin B) starting from 3-hydroxyphthalic anhydride is reported that also allows access to the fungal metabolite calidiol A. HNDB is needed to understand the ecology of certain euglossine bees that actively search for this compound for uptake. The original source of HNDB is unknown.

Key words phenols, aromatic aldehydes, Wittig reaction, diol protection, natural products, solitary bees, pheromones, bee perfume

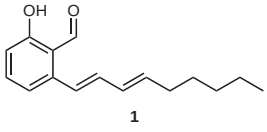

Figure 1 Structure of HNDB (**1**), also known as albiducin B, and calidiol A (**2**)

Euglossa orchid bees collect volatile compounds from the environment to form a complex blend of compounds, a so-called perfume, for use as a pheromone in mating sites.[2] In the green orchid bee, *Euglossa dilemma* (previously referred to as *Euglossa* cf. *viridissima*), 2-hydroxy-6-nona-1,3-dienylbenzaldehyde (HNDB, **1**, Figure 1) is a dominant component of the male perfume.[2] The *E*,*E*-isomer prevails, but minor amounts of other isomers also occur. The source of HNDB is unknown, but it must be widespread throughout the range of the bees, including Central America and even in Florida and the Caribbean. HNDB has also been isolated from the ash-tree-associated saprotrophic fungus *Hymenoscyphus albidus*, and showed moderate antibacterial and cytotoxic activity.[3] In the aforementioned isolation, HNDB was named albiducin B.

A synthesis of HNDB has been reported, starting from (2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-5-yl)methanol, but no experimental details or yields were described.[2] Some details can be found in a related PhD thesis that reported a total yield of 1.7% and low conversion in the last benzyl alcohol oxidation step using PDC.[4] For further evaluation of the chemical ecology of euglossine bees, including a study of their behavior, a reliable synthesis of HNDB is required, which we report here. The synthesis also allows access to calidiol A (**2**), an aromatic alcohol of the fungus *Aspergillus californicus* with moderate antibacterial activity against methicillin-resistant *Staphylococcus aureus*.[5]

A convenient starting material was 3-hydroxyphthalic anhydride (**3**), which was reduced with excess $LiAlH_4$ to give triol **4** (Scheme 1).[6] The phenolic and vicinal benzylic alcohols were then protected as a siladioxy moiety, exploiting the propensity for six- vs. seven-membered ring formation to give **5** in high yield. Oxidation of the remaining benzylic alcohol under Parihk–Doering conditions yielded **6**, which was combined with the ylide of (*E*)-oct-2-enyltriphenylphosphonium bromide in a Wittig reaction to yield a mixture of inseparable geometric isomers. The phosphonium salt was generated from the corresponding (*E*)-2-octen-1-ol through bromination[7] and treatment with triphenylphosphine. A 1:0.6 mixture of **7** and **8** was obtained, with preference for the *Z*-configured product. Fortunately, following the deprotection of the silyl protecting group under standard TBAF conditions, the two geometric isomers **9** and **2** could be separated by column chromatography. During this process, the proportion of the products shifted slightly towards the desired *E*,*E*-diastereomer **2**. HNDB (**2**) was ob-

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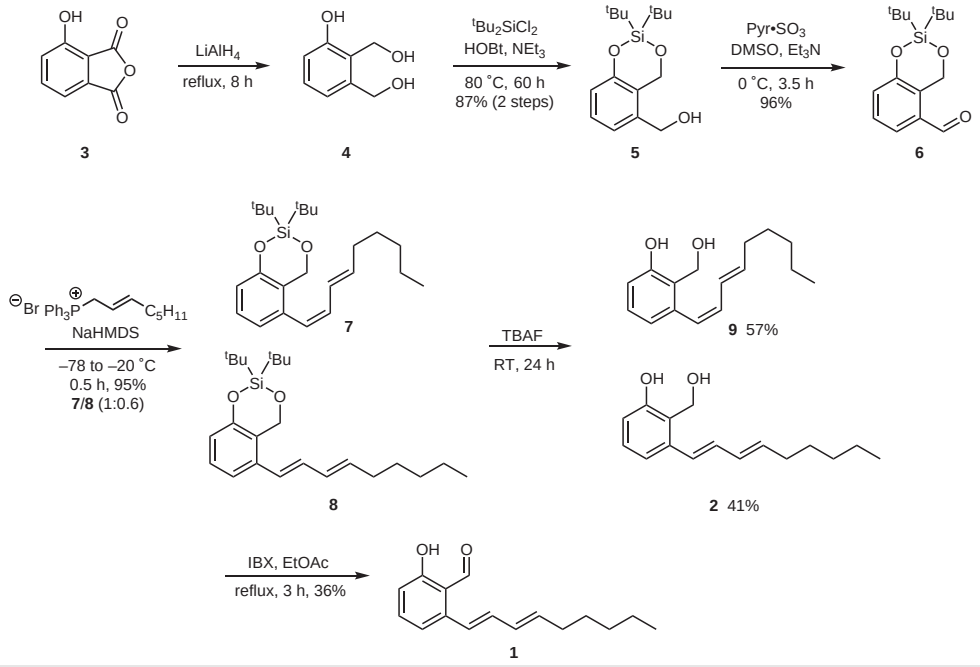

Scheme 1 Synthesis of HNDB (**1**) starting from 3-hydroxyphthalic anhydride (**3**)

tained in 41% yield as a pure compound, while **9** contained up to 10% of **2**, depending on the isolated fraction. Finally, the remaining benzyl alcohol group was oxidized with 2-iodoxybenzoic acid (IBX) to aldehyde **1**, which gave better yields than with PDC (15%).

Prior to starting in-depth testing, we wanted to establish whether the synthesized compounds can attract euglossine bees. In a bioassay, male bees were attracted to an area with the known attractant 1,3-dimethoxybenzene.[2] After confining this odor source in a car, filter paper with a mixture of HNDB isomers in hexane was attached to a tree trunk. Eight bees arrived at the filter paper where they collected the material for 3–5 minutes. As documentation, a video of this approach is presented in the Supporting Information.

In conclusion, the described synthesis allows access to both **1** and **2** on a gram scale. The overall yield from **3** is 11.7% for **1** and 32.5% for **2**. The most significant challenge is the last oxidation step for which IBX gave the best results.

The source of HNDB was previously suggested to be fungal, due to the presence of structurally similar compounds in fungi and fungus-infected substrates.[2] The independent isolation of HNDB itself from fungi is further supporting evidence for this hypothesis. The synthesis of HNDB will facilitate more in-depth studies of these fascinating insect pollinators and their perfume-collecting behavior.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0043-1773535.

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