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# Synthesis of Methyl Diantilis, a Commercially Important Fragrance

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Multistep synthetic sequences introduce organic students to the art and science of organic synthesis (1, 2). Synthetic sequences in the undergraduate organic chemistry laboratory illustrate important synthetic strategies, reagents, or experimental techniques, oftentimes resulting in the synthesis of commercially important compounds. Fragrances are a common synthetic target, since the utility of the final product is readily ascertained by simply (and carefully) smelling it (3). The fragrance industry is a relatively mature industry, and synthetic organic chemists remain at the heart of the research leading to new products (4). Givaudan, the Swiss-based fragrance and flavors company, has recently introduced Methyl Diantilis (3-ethoxy-4-hydroxybenzyl methyl ether), a fragrance with a “spicy, carnation, sweet, vanilla” olfactive note. Named after carnations (*Dianthus caryophyllus*), Methyl Diantilis is a replacement for isoeugenol and has found use in shampoos and fine fragrances. The U.S. patent describing the synthesis and olfactory properties of several 3-ethoxy-4-hydroxybenzyl alkyl ethers (including Methyl Diantilis) and their corresponding esters was issued in 1987 (5). The patent claims that this series of compounds are stronger and better odorants than the corresponding vanillyl ethers (3-methoxy-4-hydroxybenzyl alkyl ethers), covered by an earlier Japanese patent. Methyl Diantilis was a Givaudan “captive” (i.e., used but not sold by Givaudan) for many years until Givaudan recently began to offer samples of Methyl Diantilis to its customers.

## Experiment

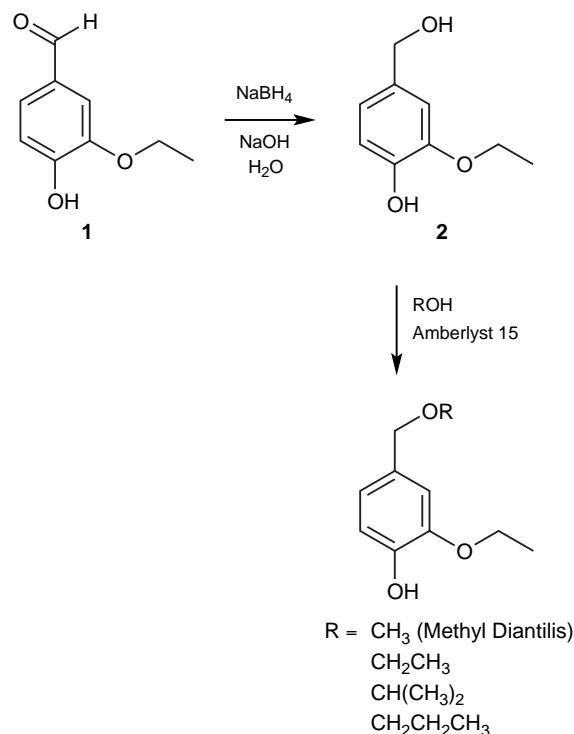
### Synthesis

With minor modifications, the two-step industrial synthesis of Methyl Diantilis (Scheme I) begins with ethyl vanillin, **1** (3-ethoxy-4-hydroxybenzaldehyde), a fragrance in its own right. Ethyl vanillin is hydrogenated to give ethyl vanillyl alcohol, **2** (3-ethoxy-4-hydroxybenzyl alcohol), which is reacted with methanol under  $\text{NaHSO}_4$  catalysis to give Methyl Diantilis. With minor modifications, this synthetic sequence was readily adapted for the undergraduate organic laboratory. Although hydrogen is by far the cheapest reducing reagent available, the substitution of  $\text{NaBH}_4$  is preferable in the undergraduate laboratory. The previously reported  $\text{NaBH}_4$  reduction of vanillin to vanillin alcohol (6) was adapted for the reduction of **1** to **2**. Typical student yields were in the range of 70–95%. In our hands the reaction of **2** with methanol using  $\text{NaHSO}_4$  catalysis gave Methyl Diantilis contaminated with impurities that could only be removed by distillation or column chromatography. Rather than using the patent procedure and developing an appropriate purification procedure, we investigated some other Lewis acid catalysts for the reaction. The reaction of **2** with methanol catalyzed by *p*-toluenesulfonic acid gave better yields and much cleaner product than the  $\text{NaHSO}_4$ -catalyzed reaction. The yield and ease of isolation of Methyl Diantilis was fur-

ther improved using Amberlyst-15 (a highly acidic polystyrene resin) as the catalyst (3c). Methyl Diantilis was produced in excellent yield with little or no need for purification. Using ethanol, 1-propanol, or 2-propanol instead of methanol, the students could prepare related 3-ethoxy-4-hydroxy alkyl ethers, which also were described in the original patent.

### Product Identification

The products of this two-step sequence were readily identified by IR and  $^1\text{H}$  NMR. Ethyl vanillyl alcohol, **2**, differs dramatically from the starting material, ethyl vanillin, **1**. In the IR, the successful reduction is evidenced by the absence of the  $\text{C}=\text{O}$  and aldehyde  $\text{C}-\text{H}$  stretches, and the appearance of a more complex pattern of bands in the  $\text{O}-\text{H}$  region. The absence of the aldehyde proton and the appearance of a two-proton doublet at  $\delta$  4.58 and a one proton triplet at  $\delta$  1.56 in the  $^1\text{H}$  NMR complemented the IR information. For the etherification products, the  $\text{O}-\text{H}$  region simplified to a single broad band in the IR. In the  $^1\text{H}$  NMR, there was an upfield shift of the methylene protons (now a singlet) and the appearance of new peaks associated with the type of ether (methyl, ethyl, *n*-propyl, or *iso*-propyl) prepared by the student. The aromatic region of all of the products was especially instructive owing to the well-resolved peak(s) illustrating long-range coupling in aromatic compounds. The



Scheme I. Two-step synthesis of Methyl Diantilis.

aromatic protons were in close proximity to one another ( $\delta$  6.78–6.88) and sometimes overlapping, but were assignable based on the multiplicity and magnitude of the coupling constants. In all cases, the hydrogen of C-6 was observed as a doublet of doublets with a small  $J_{\text{meta}}$  and a large  $J_{\text{ortho}}$ .

## Hazards

This experiment should be conducted in a well-ventilated room with eye and hand protection. Ethyl vanillin and Amberlyst-15 are irritants. Sodium borohydride is a flammable solid and corrosive. Methanol, ethanol, 1-propanol, and 2-propanol are flammable. Aqueous solutions of sodium hydroxide and hydrochloric acid are corrosive and will cause serious burns.

## Discussion

Since our synthesis is based on the patent procedure, this experiment served as an excellent introduction to intellectual property laws (7), particularly the role of patent protection in the chemical industry. The United States Patent and Trademark Office Web site provides ready access to all U.S. patents. The patents issued in 1976 to the present are searchable by keyword, inventor name, assignee name, and several other criteria. The patents issued before 1976, however, are only searchable by patent number and current classification. With the appropriate plug-in for the Internet browser, the full original patent with all of the drawings is available for viewing. There are further links to other patents within a particular patent, so that students can do a thorough search of a type of process or chemical. Although searching the patent literature stands as a worthy exercise without the need for an experimental tie-in, the students derived a certain satisfaction in finding their compound in Givaudan's patent with its associated olefactive attributes.

The synthesis of Methyl Diantilis and related fragrances was run early in the second semester of organic chemistry. The two reactions in the sequence, the reduction of aldehydes and the acid-catalyzed etherification of alcohols, were covered earlier in the lecture portion of the second semester of organic chemistry, so the students were familiar with both reactions. In addition to serving as an illustration for these reactions, the etherification reaction posed interesting mechanistic questions for the students. The chemoselectivity observed in the etherification reaction (phenolic OH versus benzylic OH) and the much milder conditions of this reaction compared to the synthesis of diethyl ether (covered in most, if not all, organic textbooks) is easily explained based on a mechanism involving highly stable benzylic carbocation. The introduction of Amberlyst-15 was our students' first look at the world of solid-phase chemistry (8), which has become increasingly important in chemistry owing to the continuing role of combinatorial chemistry (9) in the pharmaceutical industry and organic chemistry. Although we allude to the role of solid-phase chemistry at this point, we save our full discussion of combinatorial chemistry and Merrifield's synthesis until later in the semester when we cover proteins.

## Summary

In his recent review article on odorants (4), Kraft (using a quote from Eshenmosher; ref 10) makes an excellent point

that the "synthesis of properties" is the primary goal of organic synthesis. Although many syntheses in the undergraduate organic laboratory are good vehicles for introducing laboratory techniques as well as superbly illustrating concepts in the lecture, they often fail to produce end products that connect the academic laboratory to the "real" world. The synthesis of fragrances, especially ones that have obtained commercial success and are described in the patent literature, conveys that connection to the student in a direct and pleasing manner. Our students have enjoyed this experiment, with many noting it as their favorite in the evaluations for the course. The diverse range of topics that we can introduce in the context of this synthesis has made it one of our favorites, too.

## Acknowledgment

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## Supplemental Material

Instructions for the students and notes for the instructor are available in this issue of *JCE Online*.

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