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Development of a Two-Step 'Green' Process for (-) Ambrafuran Production

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Abstract : Ambergris, and more specifically its oxidation product (–)-ambrafuran, is a scarce, valuable, and sought-after perfumery ingredient. The material is used as a fixative agent to stabilise perfumes in formulations by reducing the evaporation rate of volatile substances. Ambergris is a metabolic product of the sperm whale (Physeter macrocephatus L.), resulting from intestinal irritation. Chemically, (–)-ambrafuran is produced from the natural product sclareol in eight synthetic steps – in the process using harsh and often toxic chemicals to do so. An overall yield of no more than 76% can be achieved in some routes, but generally, this is lower. A new 'green' route has been developed in our laboratory in which sclareol, extracted from the Clary sage plant, is converted to (–)-ambrafuran in two steps with an overall yield in excess of 80%. The first step uses a microorganism, Hyphozyma roseoniger, to bioconvert sclareol to an intermediate diol using substrate concentrations up to 50g/L. The yield varies between 90 and 67% depending on the substrate concentration used. The purity of the diol product is 95%, and the diol is used without further purification in the next step. The intermediate diol is then cyclodehydrated to the final product (–)-ambrafuran using a zeolite, which is not harmful to the environment and is readily recycled. The yield of the product is 96%, and following a single recrystallization, the purity of the product is > 99.5%. A preliminary LC-MS study of the bioconversion identified several intermediates produced in the fermentation broth under oxygen-restricted conditions. Initially, a short-lived ketone is produced in equilibrium with a more stable pyranol, a key intermediate in the process. The latter is oxidised under Norrish type I cleavage conditions to yield an acetate, which is hydrolysed either chemically or under lipase action to afford the primary fermentation product, an intermediate diol. All the intermediates identified point to the likely CYP450 action as the key enzyme(s) in the mechanism. This invention is an exceptional example of how the power of biocatalysis, combined with a mild, benign chemical step, can be deployed to replace a total chemical synthesis of a specific chiral antipode of a commercially relevant material.

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