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Opinion

Hydrogen/Deuterium Exchange in Ambrox Could Improve the Long-Term Scent and Shelf Life of Perfumes

Antonio Rosales Martínez [1,*] and Ignacio Rodríguez-García [2]

[1] Department of Chemical Engineering, Escuela Politécnica Superior, University of Sevilla, 41011 Sevilla, Spain
[2] Organic Chemistry, CIAIMBITAL, University of Almería, 04120 Almería, Spain; irodrigu@ual.es
* Correspondence: arosales@us.es

Abstract: Ambrox is a marine natural compound with a delicious ambergris-type scent widely used in fine perfumery. The increase in the long-term scent and shelf life of perfumes has become a paramount endeavor in the fragrance industry. To the best of our knowledge, the exchange of hydrogen by deuterium to decrease the volatility of the constituents of a perfume has not yet been investigated. In this article, we propose this new use of deuteration to synthesize deuterated ambrox in order to decrease its volatility and improve the long-term scent and extend the shelf-life of perfumes.

Keywords: ambrox; deuteration; perfumes

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1. Introduction

The deuteration of organic compounds has been viewed by synthetic organic chemists as a method to expand their horizons due to the plethora of applications attributed to deuterated organic compounds which have emerged in recent years. Deuteration has been widely used in the study of reaction mechanisms [1–7] mainly by the measurement of kinetic isotope effects, that is, the change in the speed of a chemical reaction when hydrogen is replaced by deuterium. Deuteration also plays a critical role in the analysis of organic compounds by spectroscopic techniques such as IR, NMR, and mass spectroscopy [8–10]. In mass spectroscopy, deuterated analogues are excellent internal standards as they have a chemical behavior nearly identical to that of their undeuterated counterparts. The deuterated internal standards must have a significant mass increment in order to move their signals outside of the zone where the natural mass distribution of the undeuterated analyte appears. This goal can be easily achieved by perdeuteration [11,12]. More recently, deuteration has also shown to be a powerful tool in pharmaceutical chemistry [13–15]. In this context, the most attractive technique is the incorporation of deuterium at those strategic positions of the drug where its metabolism may be affected by the kinetic isotope effect, making the deuterium–carbon bonds stronger than the hydrogen–carbon bonds. This could allow for an increase in the half-life of the drug, which can be translated into a lower dose with an identical pharmacological effect. The first deuterated drug approved by the Food and Drug Administration was deutetrabenazine for the treatment of Huntington's disease [16].

Deuterium-labeled compounds can be prepared using the base- or acid-catalyzed exchange of enolizable protons for deuteration [17], the use of transition metals and organometallic catalysis [18] such as palladium [19], ruthenium [20], or iridium complexes [21,22], and single-electron transfer systems such as Cp_2TiCl/D_2O [23,24], SmI_2/D_2O [25], and titanocene(III) complexes [26]. However, despite the multiple applications and synthetic developments carried out, to the best of our knowledge, the deuteration of organic compounds has not been used as a tool to reduce the volatility of organic compounds as a consequence of the increase in molecular weight observed when hydrogen atoms are replaced by deuterium. This new application can be very useful for the chemical and perfume industries. It is known that the three main constituents of a perfume are fixatives, fragrant oils, and solvents.

A fixative is an indispensable component in the production of perfumes, providing long-term scent, helping to mix with the other constituents, and extending the shelf-life of perfumes [27].

A commonly used fixative is ambergris, which is a waxy excretion product from sperm whales (*Physeter macrocephalus*) used since the ninth century as a valuable component of fine fragrances [28,29]. The chemical constituents within marine ambergris include a substituted homosesquiterpenoid known as ambrox (**1**) (trade name of Firmenich, the world's largest company in the flavor and fragrance business), amberlyn (trade name of Quest), and ambroxan (trade name of Henkel) [30]. The chemical structure of **1** is shown in Figure 1.

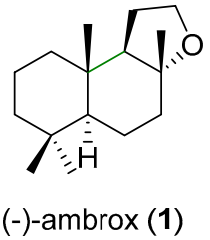


Figure 1. Chemical structure of natural (-)-ambrox (**1**).

The pleasantness of the smell and scents of fragrances depends on the volatility of their constituents. Volatile organic compounds are characterized by their low molecular weights, which allows for efficient evaporation [31–34]. Although volatility is a requirement to enjoy the pleasant aroma of fragrances, this property could also be an inconvenience, as too high volatilities will decrease the long-term scent and shelf life of perfumes. In this context, different research groups have dedicated significant efforts to the development of selective and effective delivery systems, which could increase the long-term scent and shelf life of perfumes. To achieve this aim, two approaches are being investigated: One is to embed the fragrance substances in polymeric matrices or microcapsules [35]. However, this approach presents as its main drawbacks low material stabilities and low perfume encapsulation capacities [36–39]. The other approach is the design of profragrances, which are nonvolatile derivatives of fragrances. These derivatives should allow for the controlled and slow release of extremely volatile compounds as a result of a selective bond cleavage initiated by an external stimulus [40,41]. However, the complexity and cost involved in the design of functional interlocked compounds programmed to release the active molecule in response to an external signal make this second proposal impractical from an industrial point of view.

Continuing our research in perfume chemistry [42], we believe that the deuteration of volatile organic compounds such as ambrox (**1**) may give rise to a new fixative of greater interest in the perfume industry. In this way, the decrease in the volatility of deuterated ambrox as its molecular weight increases should impart a greater long-term scent and improve the shelf life of perfume. To the best of our knowledge, this is the first time that the deuteration of ambrox (**1**) has been proposed to improve its fixative properties since although deuterium-labeled ambrox has been synthesized, it has only been used as an internal standard for quantification purposes in gas chromatography/mass spectrometry [43]. However, despite its simplicity, we consider that this new approach proposed in this article, aimed to improve the long-term scent and shelf life of perfumes, requires optimization of the number of hydrogen atoms exchanged for deuterium. The main reason is that a high substitution (above 50%) could modify the smell of the perfume [44] and affect the efficiency of its evaporation by increasing the molecular weight, shortening the persistence of the odor [31–34].

This manuscript is an opinion-type article which reflects the author's viewpoint on a novel application of the deuteration of volatile organic compounds. In concrete, the low deuteration of ambrox (**1**) could improve its power as a fixative in fine perfumery and is

not intended to be a comprehensive review of the synthesis of ambrox (**1**). The synthesis of deuterated ambrox should proceed as shown below.

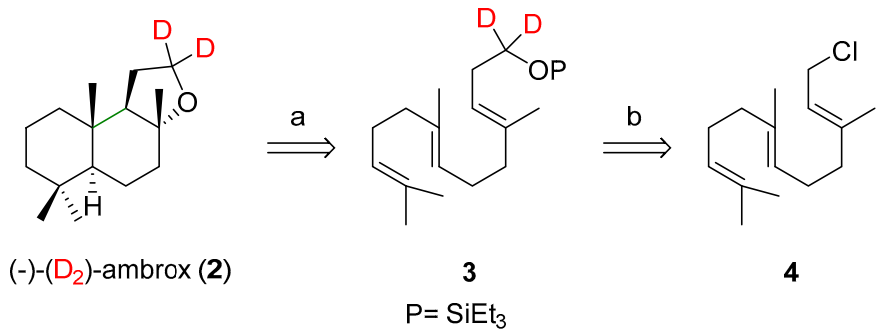
2. Future Perspectives: Synthesis Proposals for the Deuteration of Ambrox (1)

Due to its high price, various synthetic methodologies for ambrox (**1**) have been reported [45]. However, due to the presence of four chiral centers in the molecule, the most efficient synthetic routes to prepare ambrox (**1**) use enantiopure natural products as starting materials (monoterpenes, sesquiterpenoids, and diterpenes) or are based on biogenetic-type cyclizations of farnesol, farnesoic acid, monocyclofarnesoic acid, and their derivatives [45].

The main purpose of this section is to propose efficient and sustainable potential syntheses of deuterated derivatives of ambrox (**1**) with a low incorporation of deuterium. Previously described synthetic routes towards this compound could be easily modified to allow for the incorporation of deuterium into the ambrox carbon skeleton. Sclareol [46] has traditionally been the main natural chiral synthon used in the preparation of ambrox (**1**) due to its reasonable price and commercial availability as a product present in the extract of *Salvia sclarea* L. [47]. However, this compound cannot be used for the synthesis of deuterated derivatives because the described procedures are based on the oxidative degradation of the side chain present in sclareol. For that reason, we consider that four of the most viable and efficient routes to produce deuteroambrox (**2**) could be the cyclization of deuterated polyprenoids induced by chiral Brönsted acid; the manganese-catalyzed deuteration of natural sclareolide (**6**); $LiAlD_4$ reduction of sclareolide (**6**); and the reduction of a cyanide derived from albicanol (**7**) with the same reagent. It is important to mention that Chapuis and coworkers [43] have already reported the preparation of D_4-ambrox by the treatment of sclareolide (**6**) with MeONa in refluxing MeOD, subsequent reduction of the formed dideuterated sclareolide with $LiAlD_4$, and a final cyclization of the diol using tosyl chloride and pyridine.

3. Modified Yamamoto's Synthesis of Ambrox (1)

This retrosynthetic proposal of (D_2)-ambrox (**2**) by the cyclization of polyprenoids induced by chiral Brönsted acid is based on research previously developed by Yamamoto and coworkers [48] (Scheme 1). There are two key steps: (A) chiral Brönsted-acid-induced enantioselective cyclization of (D_2)-(*E*,*E*)-homofarnesyl trialkyl silylether (**3**, P = $SiEt_3$) to produce a chiral decalinic intermediate which, after diastereoselective cyclization, could form (D_2)-ambrox (**2**). (B) The homologation of commercially available (*E*,*E*)-farnesyl chloride (**4**) to generate **3**. This transformation can be accomplished by the preparation of the barium derivative of **4**; in situ treatment of this organometallic species—(*E*,*E*)-homofarnesylbarium(II) chloride—with excess of CO_2 to yield (*E*,*E*)-homofarnesylic acid; reduction of this acid with $LiAlD_4$; and final silylation of the primary alcohol formed to produce the desired deuterated compound **3**.

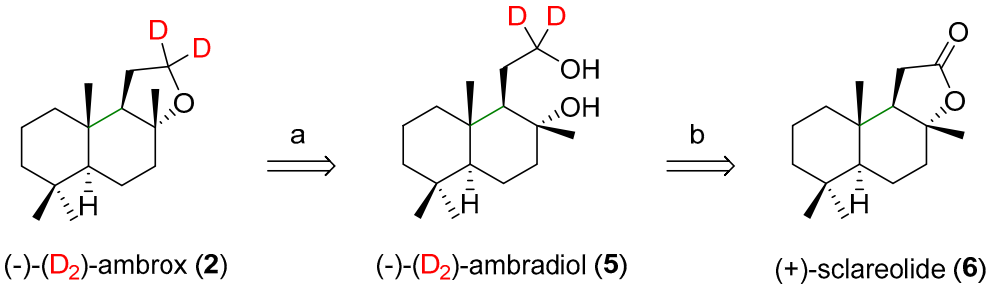


Scheme 1. Retrosynthesis of (-)-(D_2)-ambrox (**2**) through cyclization of a polyprenoid derivative. (a) Chiral cyclization of (D_2)-(*E*,*E*)-homofarnesyl trialkyl silylether (**3**, P = $SiEt_3$); (b) Homologation of (*E*,*E*)-farnesyl chloride (**4**).

This non-enzymatic enantioselective polyene cyclization of deuterated compound **3** is an attractive alternative to other multistep synthesis which use chiral natural products as starting materials. The cyclization of compound **3** should be enantioselective because it has been reported that a chiral Brönsted acid can induce the enantioselective cyclization of polyprenoids [48].

4. Modified Schaub's Synthesis of Ambrox (1)

The retrosynthetic scheme for this approach is depicted in Scheme 2. The synthesis of (D_2)-ambrox (**2**) is based on a manganese-pincer-complex-catalyzed deuteration of (+)-sclareolide (**6**) with D_2 gas to yield (D_2)-ambradiol (**5**), a procedure inspired on recent research carried out by Schaub and coworkers [49] (Scheme 2b). Subsequently, (D_2)-ambrox (**2**) could be obtained by an acid-catalyzed cyclization of (D_2)-ambradiol (**5**) (Scheme 2a).

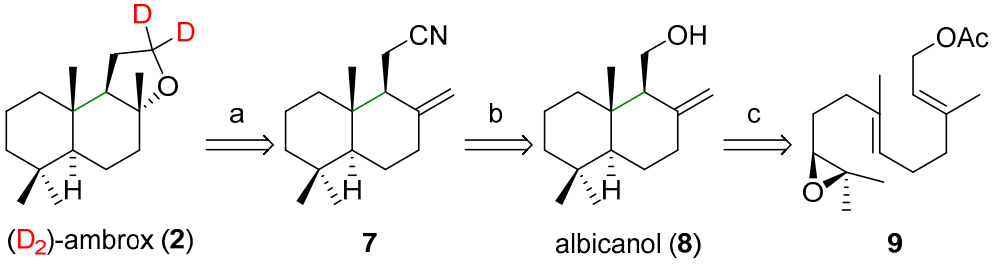


Scheme 2. Retrosynthesis of (-)-(D_2)-ambrox (**2**) through manganese-pincer-complex-catalyzed deuteration of (+)-sclareolide (**6**). (a) Acid-catalyzed cyclization of (D_2)-ambradiol (**5**); (b) Deuteration of (+)-sclareolide (**6**) with D_2 gas.

This retrosynthetic route represents a methodology in tune with the principles of green chemistry since the desired (D_2)-ambradiol (**5**) could be obtained using substoichiometric amounts of catalyst, and an almost quantitative yield is expected.

5. Modified Rosales Martínez's Synthesis of Ambrox (1)

The retrosynthetic route of (D_2)-ambrox (**2**) by the Cp_2TiCl-catalyzed radical tandem cyclization of a farnesol derivative is based on the research carried out by our research group [42] (Scheme 3). This approach comprises three retrosynthetic operations: (a) The incorporation of deuterium was achieved by reduction of nitrile **7** with $LiAlD_4$, a process that would give as intermediate (D_2)-homoalbicanol. Subsequently, this deuterated intermediate can be converted into (D_2)-ambrox (**2**) by acid-mediated cyclization. (b) The second retrosynthetic operation is the homologation of albicanol (**8**) with NaCN to form the nitrile derivative **7**. (c) Finally, albicanol (**8**) can be enantioselectively prepared by the Cp_2TiCl-catalyzed radical cyclization of enantiomerically pure epoxyfarnesyl acetate (**9**). The required epoxide **9** can be obtained from commercially available (*E*,*E*)-farnesol following the procedure reported by Spinella and coworkers [50], followed by the deoxygenation of the hydroxyl group at C3 using the Barton–McCombie deoxygenation protocol.



Scheme 3. Retrosynthesis of enantiomeric (D_2)-ambrox (**2**). (a) Reduction of nitrile **7** with $LiAlD_4$, and subsequently acid-mediated cyclization; (b) Homologation of albicanol (**8**); (c) Cp_2TiCl-catalyzed radical cyclization of epoxyfarnesyl acetate (**9**).

The key step of this retrosynthetic route is a highly diastereoselective Cp_2TiCl-catalyzed radical tandem cyclization of epoxide **9**.

In summary, this article intends to be a proposal for the use of deuteration as a powerful tool to decrease the volatility of deuterated derivative compounds compared to their non-deuterated analogues. This new application could be used to obtain deuterated ambrox in order to reduce its volatility and improve the long-term scent and the shelf life of perfumes. For this purpose, different retrosynthetic approaches have been proposed. We believe that this new way of preparing ambrox with a low exchange of hydrogen by deuterium may be highly attractive for the perfume industry and analytical chemistry since the deuterated ambrox derivatives can also be used as internal standards for the determination of low concentrations of ambrox (**1**) in water after biodegradability test [31].

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