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Scalable Synthesis of the Amber Odorant 9-*epi*-Ambrox through a Biomimetic Cationic Cyclization/Nucleophilic Bromination Reaction

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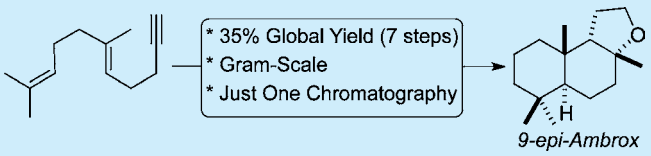
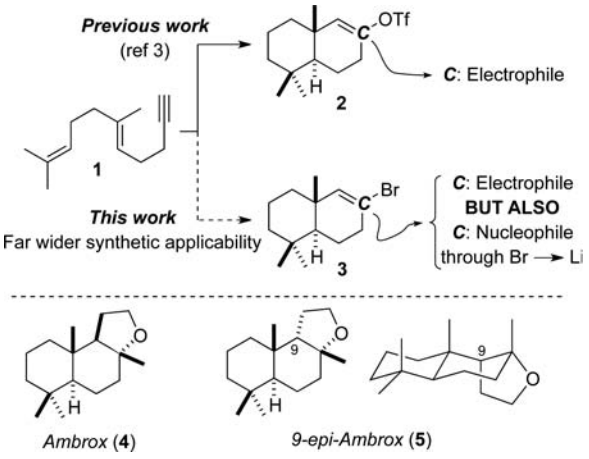
Supporting Information

ABSTRACT: A novel biomimetic nucleophilic bromocyclization reaction is used in the key step of a new and straightforward synthesis of 9-*epi*-Ambrox, an organic compound of high interest and value in the context of fragrances. This strategic reaction allows access to 9-*epi*-Ambrox on a gram scale from a dienyne derivative, easily available from geraniol, following a sequence of seven steps (35% global yield) with just one purification process. Both enantiomers of the molecule were obtained by a challenging enzymatic resolution.



Terpenes constitute the largest and most varied class of natural products with tens of thousands of members.[1] They have found wide application in the pharmaceutical, agrochemical, food, and cosmetic industries. The way the enzymatic machinery transforms simple starting materials into intricate terpenes in Nature has always fascinated synthetic chemists and has served as an inspiration for the development of beautiful biomimetic cyclization processes.[2] In this context, we have recently reported a new method for the synthesis of (poly)cyclic alkenyl triflates from simple acyclic precursors.[3] For example, from the dienyne derivative **1**, we have constructed the decaline-derived triflate **2**, a versatile reagent for the synthesis of terpenes (Scheme 1).[3] Thus, triflate **2** is an ideal substrate for subsequent well-documented cross-coupling reactions where the carbon of the C−OTf bond is an electrophilic position. However, it would be much more interesting to have at our disposal a reagent similar to **2** that could behave not only as an electrophilic partner but also as a nucleophile. Alkenyl bromide **3** fulfills these prerequisites as it is also an appropriate reagent for conventional cross-coupling reactions but could be easily converted into a nucleophile through a simple bromine−lithium interchange. Herein, we report not only a biomimetic synthesis of alkenyl bromide **3** but also its application in the context of terpene synthesis. In particular, a scalable synthesis of the powerful odorant 9-*epi*-Ambrox is presented.

Scheme 1. Our Proposal and Previous Work



Within the field of perfumery, an important family of perfumes are the ambergris fragrances.[4] In particular, Ambrox (**4**; Scheme 1) is typically used as base note of perfume compositions, and the list of commercial products containing this compound is very long.[5,6] Interestingly, studies of structure−odor relationships undertaken on different amber-type compounds showed that the 9-*epi* isomer **5** is more powerful than Ambrox (Scheme 1).[7] In fact, (−)-9-*epi*-Ambrox (**5**) possesses the strongest scent and lowest threshold concentration (0.15 ppb) of all the tested molecules. In spite of that, and surprisingly, this compound hardly earned any synthetic interest.[8] For all these reasons, 9-*epi*-Ambrox is an interesting synthetic target not only from an academic but also from an industrial point of view.

Our synthetic plan to 9-*epi*-Ambrox (**5**) is shown in Scheme 2. First, we considered that the target molecule **5** could be available through a simple acid-catalyzed cyclization of the exocyclic alkenol derivative **6**. Probably, the most important challenge in the synthesis of this molecule is the generation of the stereogenic center at C9 with the appropriate configuration. In this context, we thought that compound **6** could be derived from the enol ether **7** through a Claisen rearrangement. The presence of the axial-methyl group at the bridge carbon atom (C8) in **7** should force the Claisen rearrangement to occur through the opposite face to deliver the desired alkyl chain at

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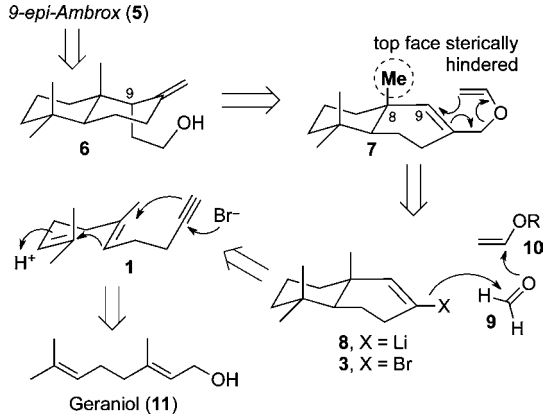
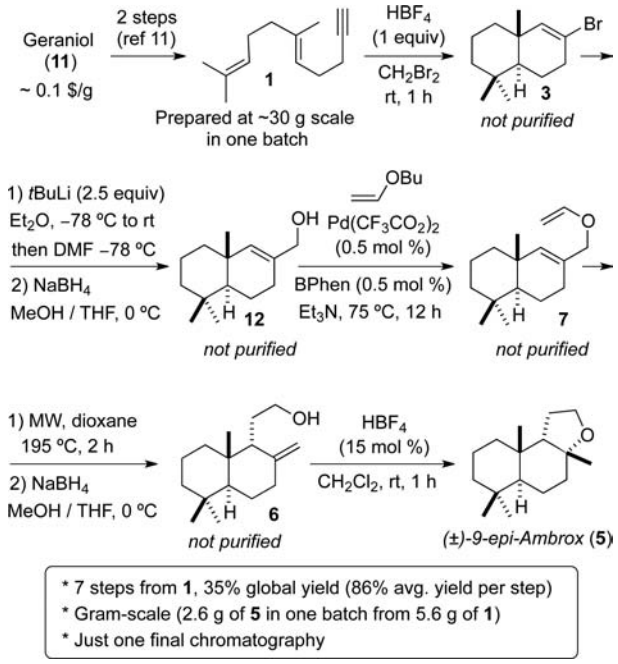
Scheme 2. Retrosynthetic Analysis



Scheme 3. Scalable Synthesis of 9-*epi*-Ambrox



C9 with appropriate configuration.[9] Enol ether **7** could be easily available through the reaction of the alkenyl lithium derivative **8** with formaldehyde **9** (or a related reagent) followed by a formal alkoxy-group exchange reaction with enol ether **10**. Organolithium derivative **8** would be derived from the alkenyl bromide **3**. For the synthesis of this bromine-containing decalin **3**, we devised an unprecedented biomimetic cationic cyclization/nucleophilic bromination reaction of the dienyne **1**, easily available from geraniol (**11**). Thus, we considered that an acid (H^+) would promote a stereoselective cationic bicyclization reaction to deliver an alkenyl cation derivative that should be trapped by a bromide ion (Br^-) present in the reaction media. Our recent studies on the synthesis of alkenyl triflates support the viability of the proposed cationic cyclization reaction of dienyne **1**.[3] At this point, a work published by Johnson and coworkers more than 40 years ago should also be mentioned.[10] In this interesting work, an alkenyl cation generated through a biomimetic cyclization reaction is trapped by a chloride ion coming from the solvent of the reaction (dichloromethane). Although just a single example is reported, the synthetic potential of this reaction seems very high. Surprisingly, this remarkable transformation seems to have passed somewhat unnoticed by the synthetic organic community through the years. However, we believed that this initial finding by Johnson could be further exploited to get interesting alkenyl bromides such as **3** with potential application in the synthesis of terpenes and particularly in the context of the synthesis of 9-*epi*-Ambrox.

As shown in Scheme 3, our synthesis of 9-*epi*-Ambrox commenced with the multigram scale preparation of the dienyne derivative **1** from inexpensive (~0.1 $/gram) and easily available geraniol **11** through a known method.[11] With starting dienyne derivative **1** in hand, we initiate our planned synthetic sequence. The unprecedented crucial biomimetic cyclization reaction of dienyne **1** to get the decaline derivative **3** required some optimization in terms of finding the best protic acid, temperature, and concentration. Finally, we found that reaction of a 0.1 M solution of dienyne **1** in dibromomethane (as solvent and source of bromide) with 1 equiv of tetrafluoroboric acid (HBF_4) at room temperature for 1 h resulted in the formation of the desired alkenyl bromide **3**. In order to demonstrate the scalability of this biomimetic cyclization, we performed the reaction with 5.6 g of the starting dienyne **1**. In addition, we found that the crude of this reaction could be used in the next step without purification.

Crude alkenyl bromide **3** was treated with *tert*-butyllithium (2.5 equiv) in diethyl ether at −78 °C to obtain the anticipated organolithium compound **8**. Although the simple addition of paraformaldehyde led to the formation of the desired allylic alcohol **12**, better results in terms of reliability were obtained when this transformation was performed through a two-step sequence involving the initial treatment of organolithium compound **8** with *N*,*N*-dimethylformamide followed by reduction of the so-formed aldehyde with sodium borohydride. Without purification, the crude alcohol **12** was treated with butyl vinyl ether in the presence of 0.5 mol % of palladium(II) trifluoroacetate and 0.5 mol % of bathophenanthroline (BPhen) to obtain the desired enol ether **7**.[12] Again, this product could be used in the next step without purification. Although the planned Claisen rearrangement of enol ether **7** could be performed under conventional heating, a much more efficient protocol included the use of microwave irradiation conditions. Thus, when a 1 M solution of enol ether **7** was heated in 1,4-dioxane at 195 °C under microwave irradiation, we observed the clean formation of the desired rearranged aldehyde in just 2 h. This result further demonstrates the convenience of microwave irradiation to improve and speed up some chemical processes.[13] The direct treatment of the crude of this reaction with sodium borohydride led to alcohol **6**. Without purification, this alcohol **6** was subjected to reaction with tetrafluoroboric acid (15 mol %) to deliver the final product **5**. A simple final column chromatography over silica gel was enough to obtain 2.6 g of pure (±)-9-*epi*-Ambrox (**5**), which exhibited the expected strong, nice, and rich ambery odor. Importantly, the global yield of the process from enyne **1** was relatively high (35%; 86% average yield per step), and it should be noted that the complete synthetic sequence from enyne **1** to (±)-9-*epi*-Ambrox (**5**) was performed on a multigram scale and without purification of any intermediate.

This robust synthetic protocol can be easily adapted for the construction of analogues of 9-*epi*-Ambrox with potential utility in the fragrance industry. As an example, we have synthesized the 12-alkyl-substituted analogues **13** and **14** without problems and in high global yield (Scheme 4). These compounds were obtained submitting enol ether **7** to the microwave-promoted

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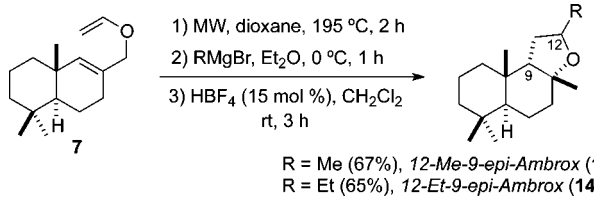
Scheme 4. Synthesis of the 9-*epi*-Ambrox Analogues 13 and 14



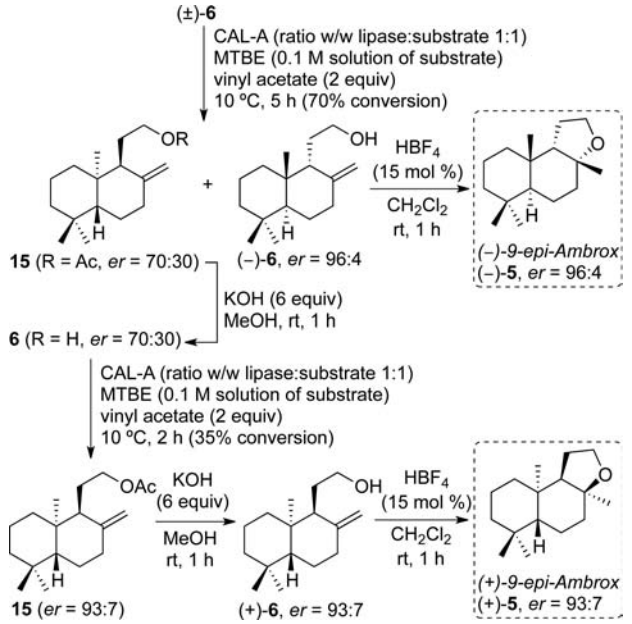
Claisen rearrangement followed by treatment of the so-formed aldehyde with methylmagnesium bromide or ethylmagnesium bromide, respectively. Finally, the corresponding secondary alcohol analogue to **6** was cyclized to get product **13** or **14** by the usual treatment with tetrafluoroboric acid (15 mol %).

At this point, it should be noted that studies of structure−odor relationships performed on Ambrox (**4**) demonstrated that the odor threshold of the enantiomer (+)-**4** is about 10 times weaker than that of (−)-**4**.[7] In addition, the racemate (±)-**4** is only slightly weaker than (−)-**4**. As far as we know, this kind of study has not been performed on 9-*epi*-Ambrox (**5**). In fact, the synthesis of the enantiomer (+)-**5** has not been described.[14] Having all this in mind, we considered the possibility of adapting our synthetic route to 9-*epi*-Ambrox (**5**) to obtain both enantiomers of the molecule. Under our circumstances, having developed a procedure to obtain high quantities of (±)-9-*epi*-Ambrox (**5**), we thought that the best and shortest option to obtain both enantiomers of this molecule would be the resolution of the racemic mixture of an advanced intermediate of our synthetic sequence. In particular, resolution of alcohol **6**, the direct precursor of 9-*epi*-Ambrox, seemed ideal. Although attractive, the resolution of such a molecule where the stereogenic centers are far away from the reactive site (alcohol) seemed challenging. In fact, we were aware of the usually low enantioselectivities described in the literature for lipase-catalyzed asymmetric acylations of primary alcohols,[15] particularly of those compounds such as **6** with remote stereogenic centers.[16] Despite these negative forewarnings, we decided to attempt the enzymatic resolution of the racemate (±)-**6** because it would provide the easiest and shortest option to get both enantiomers of 9-*epi*-Ambrox.

Our initial attempts to perform the asymmetric acylation using typical enzymes such as lipase AK (from *Pseudomonas fluorescens*), lipase PS (from *Burkholderia cepacia*, formerly called *Pseudomonas cepacia lipase*), or CAL-B (*Candida antarctica lipase B*) were unsuccessful. However, to our delight, appreciable enantioselectivities were observed with CAL-A (*Candida antarctica lipase A*). Thus, after some optimization, we found that the reaction of racemate (±)-**6** with 2 equiv of vinyl acetate in the presence of CAL-A (covalently attached to dry acrylic polymer beads) in methyl *tert*-butyl ether (MTBE) at 10 °C delivered, after 5 h (70% conversion), the acetate **15** (er = 70:30) along with unreacted alcohol (−)-**6** with high enantioselectivity (er = 96:4) (Scheme 5). The simple acid-promoted cyclization of this alcohol (−)-**6** led to (−)-9-*epi*-Ambrox [(−)-**5**].

To obtain the other enantiomer of the molecule, the acetate derivative **15** (er = 70:30) was hydrolyzed and the so-formed alcohol **6** was submitted to a second round of acetylation under conditions identical to those discussed above (Scheme 5). Thus, at 35% conversion, acetate **15** could be isolated with high enantioselectivity (er = 93:7). Hydrolysis of this acetate

Scheme 5. Synthesis of Both Enantiomers of 9-*epi*-Ambrox from Racemic Alcohol 6



derivative led to the alcohol (+)-**6** (er = 93:7), and finally, the acid-promoted cyclization of this alcohol led to (+)-9-*epi*-Ambrox [(+)-**5**]. As far as we know, this is the first synthesis of the (+)-enantiomer of 9-*epi*-Ambrox. Although a more detailed study is necessary, it seems that the odor characteristics and threshold of each enantiomer and the racemic mixture of 9-*epi*-Ambrox are slightly different. This could be an interesting way to create diverse perfume compositions by simply changing the enantiomeric purity of the molecule.

In conclusion, a new and straightforward synthesis of the powerful amber odorant 9-*epi*-Ambrox is described. The key step of the process is a new cationic cyclization/nucleophilic bromination reaction. This process, inspired by a reaction reported more than 40 years ago, is expected to find further application in the synthesis of other terpenes because the alkenyl bromides available by this reaction are very versatile reagents (they can be used as nucleophilic or electrophilic partners). By means of this new brominative biomimetic cyclization reaction, 9-*epi*-Ambrox could be obtained on a gram scale. A dienyne derivative, easily available from geraniol, was used as the starting material, and 9-*epi*-Ambrox was obtained following a sequence of seven steps (35% global yield) with just one purification process. We also describe access to both enantiomers of 9-*epi*-Ambrox by an enzymatic resolution of an advanced intermediate of the synthetic route. This resolution is not only a striking case of remote stereocenter discrimination but also an unusual example of enantioselective acylation of a primary alcohol. The application of the strategy here described in the context of "perfume discovery" by the synthesis of analogues of 9-*epi*-Ambrox and the possibility of performing the synthetic sequence in-flow are interesting issues to consider in the near future.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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