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Synthesis of (−)-elemoxide, a commercially important fragrance compound

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ABSTRACT

(−)-Elemoxide, a fragrant compound was synthesised using commercially available elemol in four steps with overall yield of 32%. The cyclic ether skeleton was constructed via intramolecular hydroalkoxylation using I_2 and $PhSiH_3$ catalytic system. Also, intramolecular oxymercuration-demercuration was employed as an alternate approach for cyclization. The various regioselective strategies involving epoxidation of alkene, reduction of epoxide and intramolecular cyclization were the highlights of the work. The key intermediate diol serves as a versatile intermediate for the synthesis of elemoxide and elemene.

Introduction

Fragrance or aroma compounds, traditionally used as perfumery, are volatile organic compounds of low molecular weight containing either aliphatic or aromatic structure found in flowers, plants, trees. Presently 90% of commercial fragrance compounds are synthetic chemicals [1]. In 2000, Karft *et al.* have published a review article on the chemistry, properties and SARs of many classes of perfumery agents [2]. These odorant molecules are having direct application as flavouring and perfumery agents in food and cosmetic industries such as spray perfumes, body care, home care, soaps & detergents and incense [3]. As a consequence, there is huge demand to explore fragrance chemistry through design and synthesis of new odorants. Sesquiterpenes are volatile compounds found in many natural sources, which are widely used as sources of many aroma industries [4]. Elemoxide is a multiordorant sesquiterpene oxide being combination of rhubarb, laurel, thyme and florex and is known to be a good flavoring agent. In 2004, the U.S. patent describes an article on elemoxide as a minor product of dehydration of naturally occurring elemol. The patent claims that this compound is a stronger and a better odorant in the class of sesquiterpenes [5]. Later, in 2006 Wahidulla *et al.* reported the study on dehydration and rearrangement of elemol under acidic condition and characterized few pharmacologically important products [6]. However, they succeeded in isolating trace amount (8%) of sesquiterpene oxide i.e. elemoxide during their column chromatographic purification step. Although, elemoxide is having commercial importance, but due to its scarcity from natural source and lack of synthetic methods, has hampered the research to explore the potentials of this compound for further study. Realising the importance of this compound for food and fragrance industry, we report here the facile synthetic approach for the building of elemoxide using 4 steps from (−)-elemol.

Results and discussion

Scheme 1 illustrates the retrosynthetic analysis of (−)-elemoxide (**5**) from (−)-elemol (**1**). It was envisaged that elemoxide could be synthesised from alcohol **4** via dehydration-isomerization reaction. Alcohol **4** in turn could be derived from regioselective cyclization of diol **3**. The ring opening of epoxide **2** via regioselective manner could lead to diol **3**. Epoxide **2** could be synthesised from commercially available elemol (**1**) via regioselective oxidation of double bond.

First, the common intermediate diol **3**, which was identified as advance intermediate **3** was synthesised for further conversion to elemoxide. Our synthetic approach for the synthesis of diol **3** is depicted in Scheme 2. One strategy to access this class of intermediates involves direct monoepoxidation of the corresponding diene. It has been well precedent in the literature that the regioselectivity of diene epoxidation is controlled by electronic factors, as with peracid oxidants [7], or by a directing group, as with Sharpless

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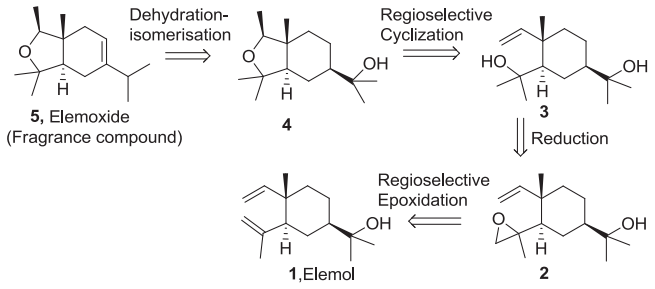
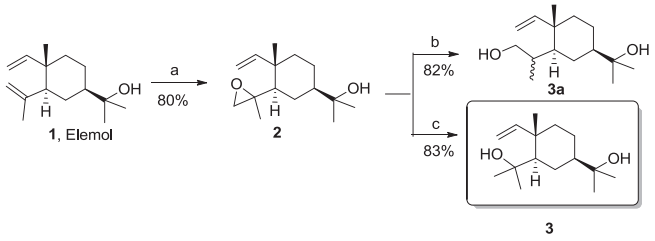


Scheme 1. Retrosynthesis of (−)-elemoxide a fragrant compound.

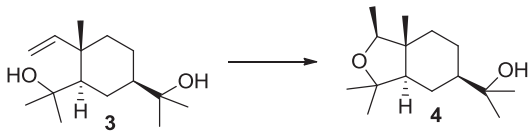


Scheme 2. Synthesis of Diol **3** via regioselective epoxidation Reagents and conditions: (a) *m*-CPBA (1.2 equiv), CH_2Cl_2, 0 °C (2 h) then rt (1 h); 80% (b) compd **2** (0.84 mmol), $LiAlH_4$ (1.5 equiv), anhyd THF (20 mL), 0 °C-rt, 82%; (c) compd **2** (4.20 mmol), $LiAlH_4$ (1.5 equiv), anhyd THF (7 mL), 0 °C-rt; 83%

epoxidation [8]. In the synthesis of liphagal, A. Manzaneda *et al.* clearly demonstrated the chemoselectivity of *m*-CPBA to oxidize the more hindered but also the more electron-rich alkene, regardless of the steric hindrance [9]. Pleasingly, oxidation of elemol (**1**) with *m*-CPBA at 0 °C in CH_2Cl_2 was found to be chemoselective producing requisite epoxide. The stereochemistry of epoxy ring of **2** was not of consequence in the further manipulation and was assumed to be *trans* (with respect to angular methyl group) based on ^{1}H NMR shift.

The reductive ring opening of epoxides, especially in enantiopure form, to the corresponding alcohols is a powerful tool in synthetic organic chemistry [10]. Reductive cleavage of oxiranes can be performed in the presence of various dissolving metals, metal hydrides [11]. $LiAlH_4$ is commonly used in epoxide reductive ring opening [12]. The reaction and regioselectivity of the product depends highly on the substitution of the epoxide ring carbons. Generally the opening of the epoxy ring occurs at the less substituted carbon; however when the reaction of epoxide was carried out using $LiAlH_4$ and THF (20 mL) under diluted condition, gave reverse selectivity i.e. primary alcohol **3a** as major product. Repetition of the reaction by changing temperature of reaction gave similar results. Interestingly, we found that the solvent volume used for the reaction could lead to expected regioselectivity. Subsequently, the expected alcohol **3** was obtained as the major product under $LiAlH_4$ reductive condition employing less amount of THF (7 mL) as solvent.

After synthesis of alcohol containing an olefinic moiety, our efforts were focused on the construction of a bicyclic skeleton of elemoxide through intramolecular cyclization methods (Scheme 3). After a brief survey of reaction conditions, we found that the intramolecular oxymercuration followed by demercuration on olefin shall provide us the required product. Hence, olefin was subjected to oxymercuration reaction under anhydrous condition wherein mercurial intermediate was generated *insitu*, which on reduction using standard conditions [13]. ($NaBH_4$ in the presence of aq. sodium hydroxide in THF) afforded the desired cyclized product **4** along with unreacted starting material. Low conversion



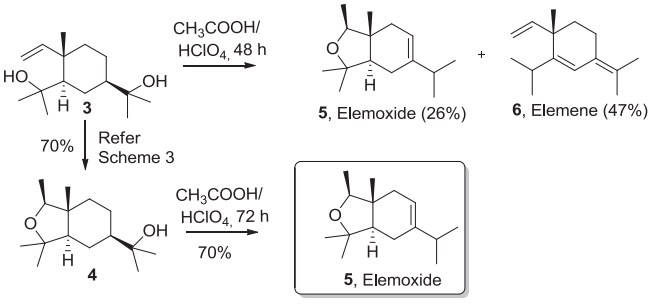
Sr No.	Reaction conditions	% Yield
1.	Hg $(OAc)_2$, anhyd THF, 24 h, reflux $NaBH_4$, NaOH	31
2.	Hg $(OAc)_2$, anhyd THF, Cs_2CO_3, 24 h, reflux $NaBH_4$, NaOH	55
3.	I_2 (10 mol%), CH_2Cl_2, $PhSiH_3$ (20 mol%), rt, 1 h	70

Scheme 3. Regioselective intramolecular cyclization.

yields were obtained using standard mercuration condition. The reason attributed to this low conversion could be the less nucleophilicity of hydroxyl group of alcohol. In next attempt, the yield of intramolecular cyclization was improved by employing modified condition using stoichiometric amount of Cs_2CO_3 during oxymercuration step.

Furthermore, to increase the efficiency for constructing the cyclic ether skeleton of elemoxide, various reagents such as $PdCl_2(PPh_3)_2$/CuCl, [14,15] $RuCl_2$(p-cymene)$_2$/CuOAc [16,17] and KO^{t}Bu/*n*-BuLi [18,19] were attempted without any success. In 2015, M. Shibuya and co-workers demonstrated the applicability of Silane–Iodine catalytic system for the intramolecular hydroalkoxylation of unactivated alkenes [20]. Using the same strategy, we treated olefin **3** with I_2 and $PhSiH_3$ to deliver expected cyclic ether in 70% yield. With the sufficient amount of cyclic ether **4** in hand, we subjected it to dehydration and isomerization using acetic acid/perchloric acid condition to give (−)-elemoxide (**5**) in 70% yield (Scheme 4). This completed the efficient synthesis of (−)-elemoxide a fragrant compound in 4 steps.

In 2006, Wahidulla, S. *et al.* had carried out dehydration of (−)-elemol (**1**) with glacial acetic acid and perchloric acid to give complex mixture of compounds wherein elemoxide was found in 8% yield [6]. We thought to overcome these drawbacks of complex mixture by making the particular intermediate which gets exclusively converted into elemoxide rather than other related products. The previously proposed mechanism claims that, the diol is one of the intermediate product in the formation of elemoxide. Hence our second synthetic attempt was the reaction of diol with glacial acetic acid and perchloric acid using Wahidulla's procedure. Herein, we obtained elemoxide in 26% yield along with other natural product α-elemene (**6**)[6] (47%). Hence, our experiment gives the experimental proof for the previously proposed mechanism for the formation of elemoxide.



Scheme 4. Synthesis of (−)-Elemoxide.

Conclusion

In conclusion, we have accomplished a new concise synthesis of (−)-elemoxide a fragrant compound in four steps involving 32% overall yield via regioselective epoxidation, regioselective ring opening and regioselective intramolecular cyclization as key steps. Out of 4 steps, 3 steps involves regioselectivity in formation of products, which is the highlight of this synthetic endeavour. α-Elemene was also synthesized in good yield starting from elemol. We believe that all chemistry employed in this study can be applied to the synthesis of elemoxide in gram scale with the potential of commercialization for perfumery or food industry.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.08.003.

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