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Lipase-catalyzed preparation of optically active isomers of cyclamen aldehyde

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ABSTRACT

The optically active isomers of cyclamen aldehyde **1a** were synthesized from a chiral intermediate prepared by lipase-catalyzed enantioselective transesterification of a prochiral diol with vinyl acetate. The absolute configuration of the enantiomer of **1a** with dextrorotatory in chloroform was determined to be (*S*)-configuration. The results of an olfactory evaluation of the prepared isomers are also reported.

1. Introduction

The enantiomers of many organic compounds are perceived differently as odorants by the human nose, which means they smell differently [1]. Since the olfactory epithelium in the human nose, like all biological tissues, is composed of biomolecules consisting of L-amino acids and has a specific chiral environment, it should be able to distinguish one chiral molecule from its antipode [2]. For example, *l*-menthol, used in toothpaste and other oral care products, in confectionery, tobacco and some cosmetic products [3], smells differently from *d*-menthol [4]. Accordingly, the synthesis of fragrance ingredients in highly enantiomerically pure form and the evaluation of their odor properties are of great interest, and many reports on the synthesis and the odor properties of both enantiomers of fragrance ingredients have been published [5–24].

Among many fragrances, floral notes are very much appreciated and widely used [13], and there are several important materials **1** used especially for muguet notes. They have similar structures; a methylpropanal chain with an aromatic ring and an asymmetric carbon (Fig. 1) [25]. Cyclamen aldehyde **1a**, commercially available in racemic form, is an important component for obtaining special blossom notes in perfume compositions, particularly the cyclamen type and also used as the top note in many other blossom fragrances because of its fresh-flowery aspect [26]. Although the asymmetric syntheses of **1b** [27–32], **1c** [33], **1d** [31], and **1e** [28,29,34,35] have been reported, there is no report on the asymmetric synthesis of **1a**. There are three reports on the preparations of the optically active isomers of **1a** by optical resolution [36,37] and by deracemization [38]. However, these methods required stoichiometric optically pure compounds to prepare optically active **1a** and they did not determine the absolute configurations of the chiral **1a** that they prepared. Therefore, we became interested in developing an enantioselective catalytic route to (*R*)-**1a** and (*S*)-**1a**, and in the determination of the absolute configurations.

We recently reported the synthesis of both enantiomers of Rosaphen® **2** (2-methyl-5-phenyl-1-pentanol), which are valuable for adding floral notes in soaps and domestic fragrances [39,40], and showed that the odors of the enantiomers are distinctive (Scheme 1) [41]. We synthesized both enantiomers from a chiral primary alcohol prepared by lipase-catalyzed enantioselective transesterification of a prochiral diol with vinyl butanoate. Lipase-catalyzed reactions play an important role in the optical resolutions of the racemates and in desymmetrizations of prochiral substrates, and the obtained enantiopure substrates are used for the further synthesis [42,43]. Many enantiomerically enriched odorants have also been prepared *via* lipase-catalyzed reactions [22–24].

Herein we report the application of our methodology to the synthesis of both enantiomers of **1a**, the determination of the

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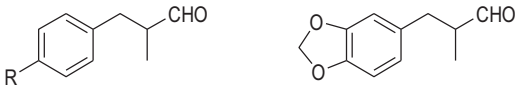


1a: R=$CH(CH_3)_2$ **1e**

1b: R=$C(CH_3)_3$

1c: R=$CH_2CH(CH_3)_2$

1d: R=OCH_3

Fig. 1. Cyclamen aldehyde and its analogs.

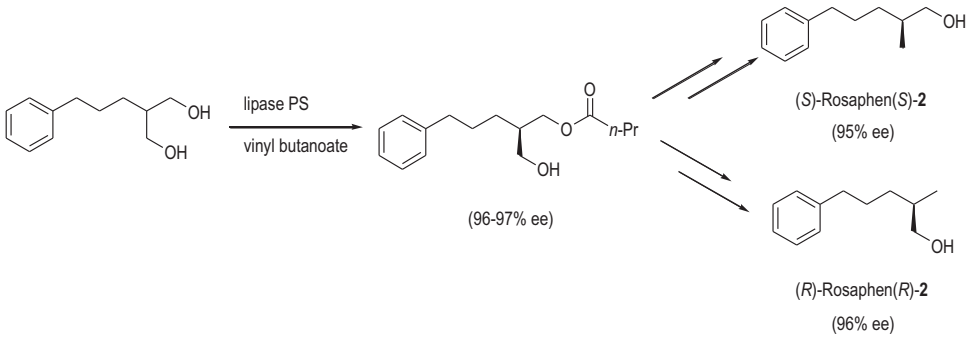
absolute configurations, and the evaluation of the odor profiles of the optically active isomers.

2. Results and discussion

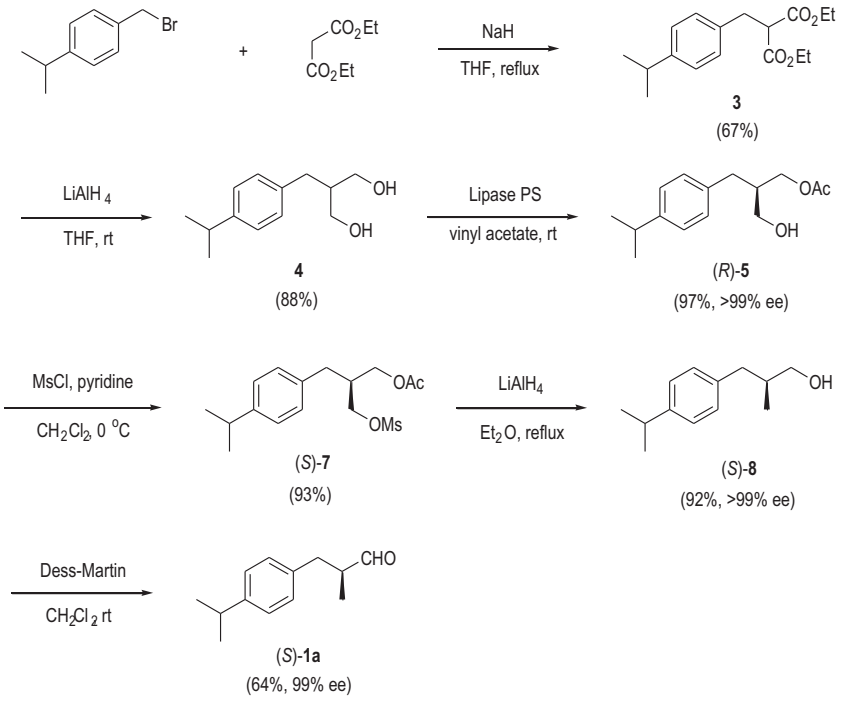
2.1. Asymmetric synthesis of (S)-*1a*

The prochiral diol, 2-hydroxymethyl-3-(4-isopropylphenyl)-1-propanol **4**, was prepared by the alkylation of diethyl malonate with 4-isopropylbenzyl bromide followed by $LiAlH_4$ reduction in the yields of 67% and 88%, respectively (Scheme 2).

The key step for the preparation of (*S*)-**1a** is the lipase-catalyzed enantioselective transesterification of **4** with vinyl acetate. We succeeded in the highly enantioselective lipase-catalyzed transesterification of two 2-substituted 1,3-propandiols, analogs of **4**, with vinyl esters [41,44]. Therefore, we tried the enantioselective transesterification of **4** with lipase PS (from *Burkholderia cepacia*, Amano) as a catalyst and vinyl acetate as an acyl donor. We used vinyl butanoate as an acyl donor in our previous study (Scheme 1), because lipase PS did not show high enantioselectivity for the transesterification of the diol with vinyl acetate [41]. We gave vinyl acetate the first choice for an acyl donor in the present study, because vinyl acetate is widely used for an acyl donor in lipase-catalyzed transesterification [42,43]. The reaction was followed by gas chromatography. When the ratio of the peak area of the monoester **5** to the total that of the diol **4** and the diacetate **6** reached about 99 to 1, the reaction was stopped. After the isolation of **5** in 97% yield, its ee was measured with HPLC and found to be >99% {$[\alpha]_D^{23}$ +22.5° (*c* 1.1, EtOH)}. Itoh *et al.* [45], Yokomatsu *et al.* [46], and our group [44] have reported that lipase PS-catalyzed transesterification of ten 2-arylmethyl-1,3-propandiols, analogs of **4**, with vinyl acetate proceeded enantioselectively. The



Scheme 1. Asymmetric synthesis of Rosaphen® **2**.



Scheme 2. Synthesis of (*S*)-cyclamen aldehyde (*S*)-**1a**.