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Syntheses and odor properties of optically active dimethyl octenone and its analogs

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ABSTRACT

The optically active isomers of dimethyl octenone, which is used in citrus accords, and its analogs, were synthesized from a common chiral intermediate prepared by the lipase-catalyzed desymmetrization of prochiral diol. The results of an olfactory evaluation of the prepared isomers are also reported.

1. Introduction

Essential oils obtained from citrus fruits, called citrus oils, such as bergamot, grapefruit, lemon, lime, mandarin, orange, and tangerine are important raw materials for citrus flavors.[1] Citrus flavors are popular in beverages as well as in sweet products, such as confectionery, cookies and desserts.[2] Moreover, they have become popular in sauces and dressings. As a result, the citrus oil industry produces the oils in large quantities. In 2007, for example, the amount of the oils that were produced from oranges, lemons, limes, and mandarin oranges were assumed to reach 51,000 t, 9,200 t, 1,800 t, and 460 t, respectively.[1]

Citrus oils are also used in perfumes, eau de toilettes, cosmetic products, toiletry and household products to give freshness and lightness.[1] A certain women's perfume, which is maybe the world's most famous, utilizes lemon and bergamot oils.[3] Synthetic ingredients as well as citrus oils are also used in fragrances. 2,6-Dimethyl-7-octen-2-ol (dihydromyrcenol) is a synthetic ingredient used in the fragrances for a citrus note (Fig. 1).[3] Some acetals and nitriles also possess a citrus character, for example, citronellal dimethyl acetal and citronellyl nitrile.[4] The racemic 4,7-dimethyl-6-octen-3-one (dimethyl octenone) **1b** has a citrus odor and is used in fragrance material to give a fresh top note.[5–8]

The enantiomers of many chemical compounds are perceived differently as odorants by the human nose; in plain terms, they smell differently.[9] Many natural aroma chemicals occur in Nature as specific enantiomers, and the aroma of such specific enantiomers can be distinctive and characteristic.[10] For example, (*R*)-(+)-limonene, present in citrus peel oils, has an orange odor, while (*S*)-(-)-limonene, found in oils from *Mentha* species, has a harsh odor.[10,11] The syntheses of both enantiomers of fragrance ingredients in highly enantiomerically pure form and the evaluation of the odor properties of both enantiomers are accordingly of great interest.[12–36]

We recently reported the syntheses of both enantiomers of Rosaphen® (2-methyl-5-phenyl-1-pentanol), valuable for adding floral notes in soaps and domestic fragrances,[37,38] and showed that the odors of the enantiomers are distinctive.[39] Moreover, we reported

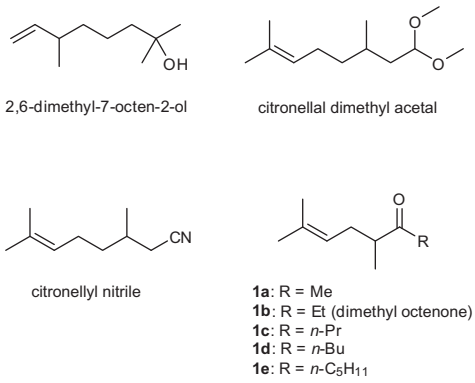

Figure 1. Synthetic ingredients with citrus odor.

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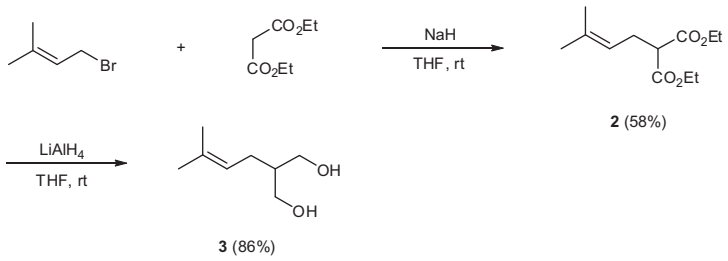
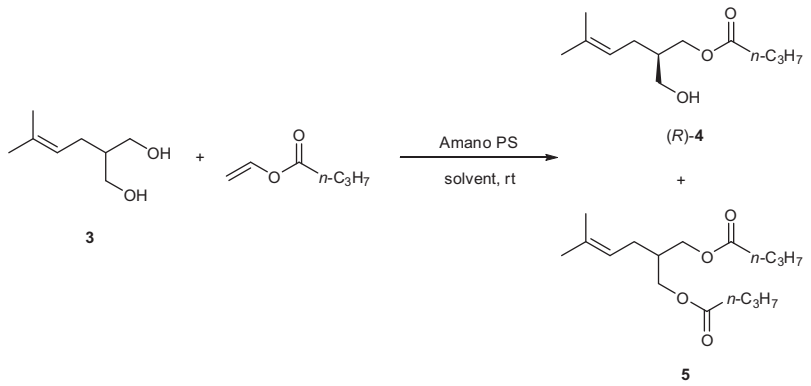


Scheme 1. Synthesis of prochiral diol **3**.



Scheme 2. Enantioselective transesterification of prochiral diol **3**.

the syntheses of both enantiomers of cyclamen aldehyde {2-methyl-3-(4-(1-methylethyl)phenyl)propanal}, an important component for obtaining special blossom notes in perfume composition,[40] and the differences in the odors between the enantiomers.[41]

Recently, Clarke et al. reported the asymmetric synthesis of (*S*)-**1b**.[42] However, this method required stoichiometric enantiomerically pure compounds to synthesize (*S*)-**1b**, and the absolute configuration was not determined. In addition, the enantiomeric excess was moderate (89%), and no evaluation of the odor profile of the synthesized (*S*)-**1b** was reported. We therefore became interested in developing a catalytic route to both enantiomers of **1b** and their odor profiles.

Herein we report the flexible syntheses of both enantiomers of **1b** and its analogs **1a**, **1c**–**e** and the evaluation of their odor profiles.

2. Results and discussion

2.1. Syntheses of the (*S*)-enantiomers of dimethyl octenone and its analogs

Prochiral diol **3** was easily prepared by the alkylation of diethyl malonate with 1-bromo-3-methyl-2-butene followed by $LiAlH_4$ reduction (Scheme 1).

In a previous study, we succeeded in the desymmetrization of two prochiral 2-substituted 1,3-propanediols by the lipase (Amano PS)-catalyzed transesterification with vinyl esters in a highly enantioselective manner.[39,41] We found vinyl butyrate to be the best acylation reagent for the enantioselective transesterification of 2-hydroxymethyl-5-phenyl-1-pentanol.[39] We therefore chose vinyl butyrate as an acylation reagent (Scheme 2). The prochiral selectivity of lipases has been found to depend on the nature of the solvent.[43] We therefore performed reaction solvent screening experiments (Table 1) and the highest prochiral selectivity (95% ee) was achieved with diisopropyl ether (entry 7). The absolute configuration of (*R*)-**4** was thought to be (*R*) on the basis of the empirical rule for the enantiopreference of the lipase.[44] Although we tried to use other esterification reagents such as vinyl acetate or propionate, we could not achieve an ee of more than 95%. On the basis of these results, we conducted a large scale desymmetrization of **3** in diisopropyl ether and obtained (*R*)-**4** with 95% ee {$[\alpha]_D^{22}$ = +14.2 (*c* 0.9, $CHCl_3$)} in 93% yield.

Table 1
Effect of organic solvents on the enantioselective transesterification of **3**

Entry	Solvent	Time (h)	**3**[c] (%)	(*R*)-**4**[c] (%)	ee (%)	**5**[c] (%)
1	1,4-Dioxane	4.5	3	95	94	2
2[a]	Acetonitrile	2.0	4	94	94	2
3	Acetone	7.0	6	93	92	1
4	THF	4.5	8	91	92	1
5[a]	Et_2O	1.8	2	96	92	2
6	CH_2Cl_2	1.8	15	85	94	0
7[a]	*i*-Pr_2O	1.0	0	94	95	6
8[b]	Toluene	1.8	9	89	92	2

Conditions: PS 20 mg/mL, diol **3** 100 mM, vinyl butyrate 500 mM, rt.
[a] PS 50 mg/mL.
[b] PS 5 mg/mL, vinyl butyrate 200 mM.
[c] The molar ratio was determined on the basis of the ratio of the peak areas of **3**, (*R*)-**4** and **5**.

The optically active monoester (*R*)-**4** obtained above was converted into the corresponding methanesulfonate (*S*)-**6** with methanesulfonyl chloride (MsCl) (Scheme 3). The methanesulfonate (*S*)-**6** was then treated with $LiAlH_4$ to give a mixture of the desired primary alcohol (*S*)-**7** and 1-butanol generated by the reduction of the butyrate moiety. Since no separation of the two alcohols occurred with thin layer chromatography, we abandoned the separation of the two alcohols with silica-gel chromatography. Evaporation for a long time did remove the 1-butanol from the mixture to afford (*S*)-**7** with 95% ee {$[\alpha]_D^{19}$ = −4.3 (*c* 1.0, CH_2Cl_2), lit.[45] $[\alpha]_D$ = −4.4 (*c* 3.8, CH_2Cl_2), (*S*), 95% ee}. However, this resulted