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## Graphical Abstract

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**Synthesis and olfactory evaluation of optically active ß-alkyl substituted γ-lactones and whiskey lactone analogues**

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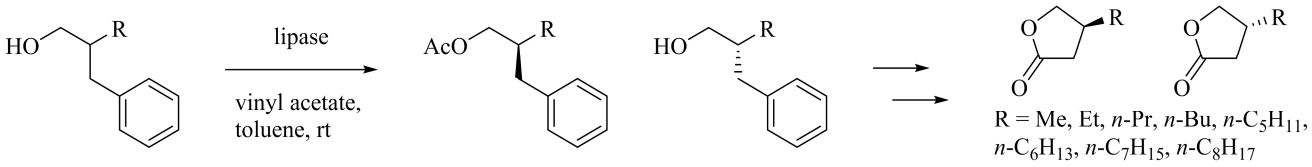


R = Me, Et, *n*-Pr, *n*-Bu, *n*-$C_5H_{11}$, *n*-$C_6H_{13}$, *n*-$C_7H_{15}$, *n*-$C_8H_{17}$

# Synthesis and olfactory evaluation of optically active *β*-alkyl substituted *γ*-lactones and whiskey lactone analogues

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## Abstract

Optically active *β*-alkyl substituted *γ*-lactones and whiskey lactone analogues were synthesized, and the odor properties were evaluated. During the preparation of the chiral intermediates, we found good reaction conditions for the highly enantioselective esterification of 3-arylmethyl-2-methyl-1-propanols to kinetically resolve them. The results of the olfactory evaluations of the synthesized lactones revealed that the alkyl groups on the *γ*-lactone rings played an important role for the odor profiles.

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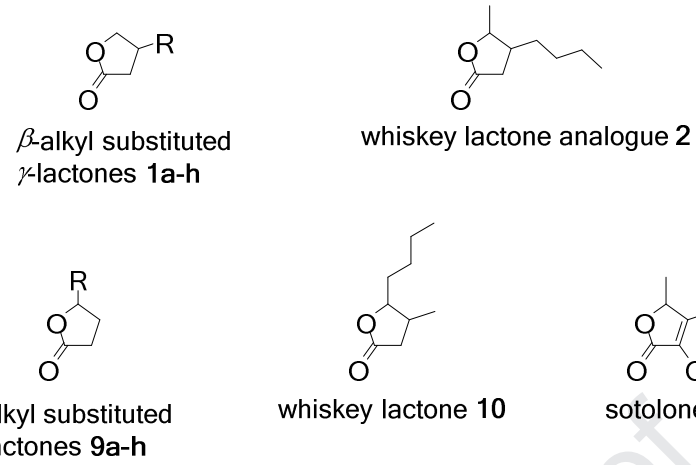
*Keywords:* Asymmetric synthesis; Lactone; Lipase; Odor; Whiskey lactone

## 1. Introduction

*γ*-Lactones are compounds containing a five-membered ring [1] and constitute the structural cores of numerous natural products [2]. They also occur in foods such as dairy products [3,4], fruit [5-7], and nuts [8,9] and are widely used as flavor and fragrance chemicals [10]. Representative of *γ*-lactones are shown in Fig. 1 [1,11]. For example, *γ*-decalactone **9f**, present in a wide variety of foods, has an odor reminiscent of peaches and is used in perfumery for flower odors. Whiskey lactone **10**, found as a mixture of *cis* (4*S*, 5*S*)- and *trans* (4*S*, 5*R*)-isomers in aged spirits such as whiskey and oakwood volatiles [12], has an intense, warm, sweet, and coumarin-like odor and is used in aroma compositions, for example, for beverages. Sotolone **11**, found in coffee and sake, is used in food flavoring, and its odor changes from a caramel-like one at low concentrations to a curry-like one at high concentrations.




| | a | b | c | d | e | f | g | h |
|---|---|---|---|---|---|---|---|---|
| R | Me | Et | *n*-Pr | *n*-Bu | *n*-$C_5H_{11}$ | *n*-$C_6H_{13}$ | *n*-$C_7H_{15}$ | *n*-$C_8H_{17}$ |

Fig. 1. γ-Lactones.

γ-Alkyl substituted γ-lactones **9a-h** are especially well-known γ-lactones [13]. They occur in various kinds of foods and are used for flavor ingredients in (non)alcoholic beverages, baked goods, gelatins, puddings, and soft candies. Mosandl *et al*. reported interesting findings on the odor properties of **9a-h** [14]. They synthesized all 16 enantiomers of **9a-h** and found that the (*R*)-enantiomers were responsible for pleasant, naturally fruity, and aroma notes. The enantiomers of many chemical compounds are perceived differently as odorants by the human nose [15].

Many flavors and fragrances occur in nature as specific enantiomers, and the aromas of such specific enantiomers can be distinctive and characteristic [10]. The synthesis of the enantiomers of fragrance ingredients and the evaluation of the odor properties of the enantiomers are accordingly of great interest and have been studied [16,17]. Besides Mosandl's report [14], there are reports on the evaluation of the odors of the enantiomers of γ-lactones [17a,k,m]. Shimotori *et al*. synthesized all four stereoisomers of whiskey lactone **10**. Although all the stereoisomers showed different odors, they had

a coconut-like odor commonly [17k]. Dai *et al*. synthesized all 12 enantiomers of *γ*-alkyl substituted *α*, *β*-unsaturated *γ*-lactone and reported that all the lactones more or less exhibited chiral discrimination in odor quality [17m]. We have been interested in the differences in the olfactory properties of the enantiomers of fragrance ingredients and have reported on the synthesis and the olfactory evaluations of the enantiomers of floral odorants, citrus odorants, and musky odorants [18-22], and are currently interested in researching differences in the olfactory properties of the enantiomers of *γ*-lactones with odors that have not been reported.

Compared with the *γ*-alkyl substituted *γ*-lactones **9a**-**h**, little is known about *β*-alkyl substituted *γ*-lactones **1a**-**h**. Lactone **1a** is a volatile component of a condensed fermented corn extractive [23] and contained in the smoke produced during the pyrolytic process of thyme [24]. To the best of our knowledge, the occurrence of **1b**-**h** in nature has not been reported. Although the use of racemic **1a** as a food flavoring has been mentioned in several patents [25-29], there have been no similar reports on the possibility of using **1b**-**h**. Furthermore, the relationship of the absolute stereochemistry and odor properties of **1a**-**h** have not been reported. We herein report the synthesis of all 16 enantiomers of *β*-alkyl substituted *γ*-lactones **1a**-**h** and the odor profiles.

We recently reported that the odors of Phantolide®, a representative synthetic musk odorant, analogues (±)-**12a**-**d** were stronger than those of Phantolide® analogues (±)-**13a**-**d** (Fig. 2) [22]. The positions of the acyl group and that of the methyl group contributed to the difference in the intensity of the odor. Whiskey lactone **10** has a methyl group and a *n*-butyl group on its five-membered ring. We therefore have been interested in the odor properties of whiskey lactone analogues **2**, which differs in the positions of the methyl group and the *n*-butyl group from **10**. We here also report on the

synthesis of all four stereoisomers of whiskey lactone analogue **2** and the evaluation of their odor profiles.

**12a-d** **13a-d**

**a**: R = Me; **b**: R = Et; **c**: R = *n*-Pr; **d**: R = *i*-Pr

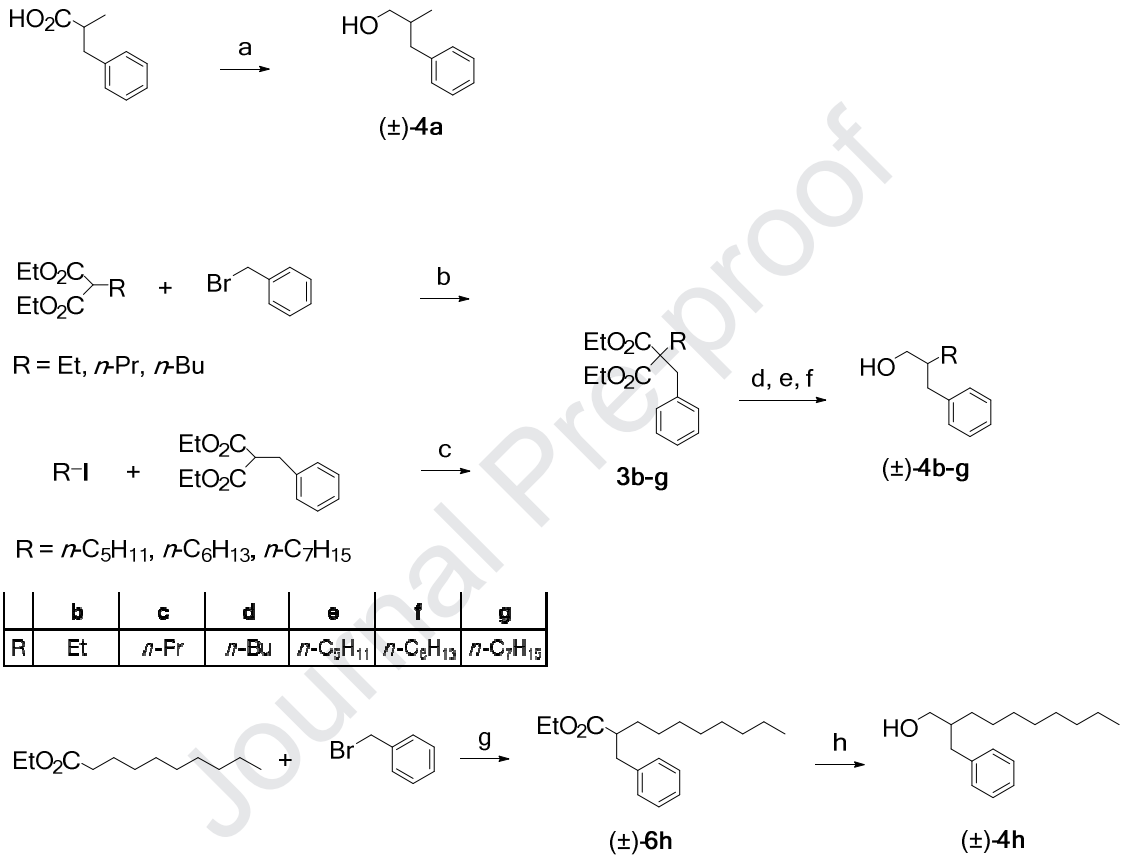
**Fig. 2.** Phantolide® analogues.

## 2. Results and discussion

### *2.1. Synthesis of optically active β-alkyl substituted γ-lactones (R)- and (S)-**1a-h***

Ciceri *et al*. recently reported the synthesis of optically active *β*-propyl-*γ*-lactone (*R*)-**1c** [30]. They resolved racemic alcohol (±)-**4c** shown in Scheme 1 into the enantiomers by lipase-catalyzed enantioselective transesterification with vinyl acetate and then transformed the resulting optically active alcohol (*R*)-**4c** into (*R*)-**1c**. We followed their method to synthesize all 16 enantiomers of **1a**-**h**. We began with the synthesis of racemic primary alcohols (±)-**4a**-**h** according to the route shown in Scheme 1. The primary alcohol (±)-**4a** was prepared from *α*-methylhydrocinnamic acid. Malonates **3b**-**d** were prepared from the corresponding diethyl alkylmalonates and benzyl bromide, and malonates **3e**-**g** were prepared from the corresponding alkyl iodides and diethyl benzylmalonate. Malonates **3b**-**g** were hydrolyzed to the corresponding dicarboxylic acids. The decarboxylation of the diacids gave the

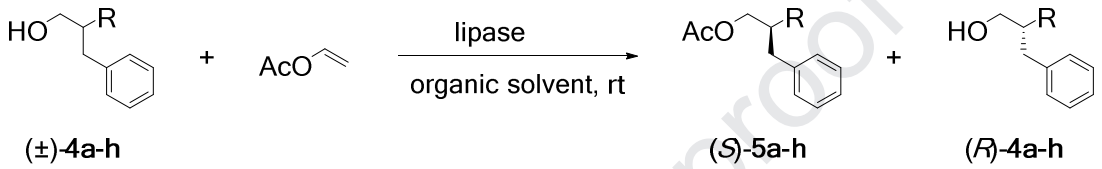
corresponding carboxylic acids, and the reduction of the acids gave the alcohols (±)-**4b-g**. Alcohol (±)-**4h** was prepared from ethyl 2-methylphenyldecanoate (±)-**6h** prepared from ethyl decanoate and benzyl bromide.




**Scheme 1.** Synthesis of racemic primary alcohols (±)-**4a-h.**
Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 94%; (b) NaH, THF, reflux, **3b**: 86%; **3c**: 83%; **3d**: 78%; (c) Na, EtOH, reflux, **3e**: 91%; **3f**: 93%; **3g**: 95%; (d) aq NaOH, EtOH, reflux; (e) Δ, xylene, reflux; (f) $LiAlH_4$, THF, 0 °C to rt, **4b**: 80% from **3b**; **4c**: 84% from **3c**; **4d**: 79% from **3d**; **4e**: 78% from **3e**; **4f**: 79% from **3f**; **4g**: 77% from **3g**; (g) LDA, HMPA, THF, -78 °C to 0 °C, 84%; (h) $LiAlH_4$, THF, 0 °C to rt, 80%.

The most important point of the present syntheses is to prepare all the primary alcohols **4a**-**h** in highly optically active forms. We achieved that by the optical resolution of (±)-**4a**-**h** *via* the lipase-catalyzed enantioselective transesterification of

(±)-**4a**-**h** with vinyl acetate (Scheme 2). Lipase, a kind of hydrolase, has been used as a catalyst for not only the enantioselective hydrolysis of esters in aqueous media but also the (trans)esterification of alcohols or carboxylic acids in organic solvents, and many esters, alcohols, and carboxylic acids have been kinetically resolved [31]. We have also been using lipase for the kinetic resolution of some alcohols [21,22].




(±)-**4a-h** (*S*)-**5a-h** (*R*)-**4a-h**

| | **a** | **b** | **c** | **d** | **e** | **f** | **g** | **h** |
|---|---|---|---|---|---|---|---|---|
| R | Me | Et | *n*-Pr | *n*-Bu | *n*-$C_5H_{11}$ | *n*-$C_6H_{13}$ | *n*-$C_7H_{15}$ | *n*-$C_8H_{17}$ |

**Scheme 2**. Lipase-catalyzed enantioselective transesterification of (±)-**4a-h** with vinyl acetate in organic solvent.

We initially describe the optical resolution of (±)-**4a**. Santaniello *et al*. showed that lipase from *Burkholderia cepacia* could catalyze the highly enantioselective (*E* value [32] >100) transesterification of (±)-**4a** with vinyl acetate in chloroform [33]. We, therefore, decided to use the lipase, called Amano PS, as a catalyst and then investigated the effects of reaction solvents on the enantioselectivity of the lipase to find better conditions for the enantioselective transesterification (Table 1). Because solvent hydrophobicity effects the enantioselectivity of enzymatic catalysis [34], we tried five organic solvents which varies in hydrophobicity. As a result of the screening of the five organic solvents, we found that toluene was the most suitable solvent (*E* = 207) for the transesterification. Next, we tried the small-scale transesterifications of (±)-**4b**-**h** with vinyl acetate in toluene (Table 2). All the transesterifications proceeded highly

enantioselectively, and all the (*S*)-enantiomers were selectively esterified. Neither the (trans)esterification of primary alcohols catalyzed by lipase from *Burkholderia cepacia* nor the hydrolysis of the esters of primary alcohols by the same one proceeds highly enantioselectively [35,36]. Our findings here are exceptions. Furthermore, Nordin *et al*. reported the transesterification of 3-arylmethyl-2-methyl-1-propanols catalyzed by the lipase proceeded highly enantioselectively [37]. Our and Nordin's findings suggest that a combination of Amano PS, vinyl acetate and toluene can be the first choice for the conditions for the resolution of 3-arylmethyl-2-alkyl-1-propanols.

**Table 1**
Amano PS-catalyzed transesterification of (±)-**4a** with vinyl acetate.

| solvent | time (h) | conversion[a] (%) | ee of (*S*)-**5a** (%) | ee of (*R*)-**4a** (%) | *E*[a] |
|---|---|---|---|---|---|
| 1,4-dioxane | 2.3 | 50 | 94 | 93 | 110 |
| dichloromethane | 5.0 | 49 | 95 | 90 | 121 |
| ethyl acetate | 2.3 | 50 | 95 | 94 | 139 |
| vinyl acetate | 2.0 | 51 | 94 | 98 | 149 |
| toluene | 2.5 | 50 | 96 | 97 | 207 |

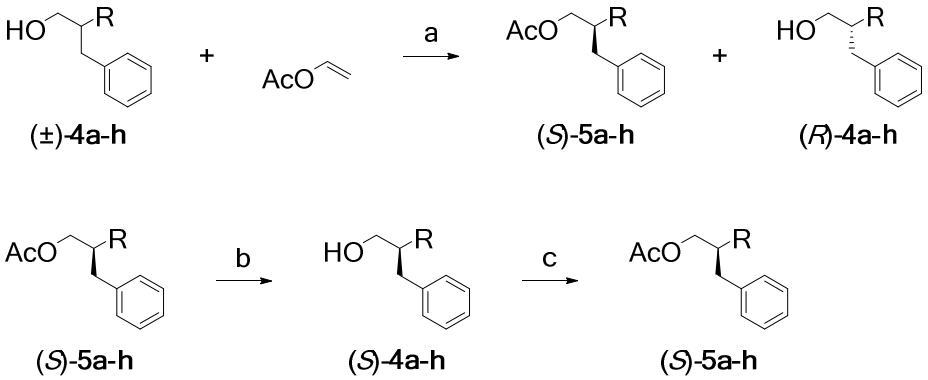
Conditions: Amano PS (20 mg $mL^{-1}$), (±)-**4a** (0.1 mol $L^{-1}$), vinyl acetate (1 mol $L^{-1}$), room temperature. Refer to Section 4.2.4 for details.
[a]Calculated from the ee of (*S*)-**5a** and that of (*R*)-**4a** [32].

**Table 2**
Amano PS-catalyzed transesterification of (±)-**4b-h** with vinyl acetate in toluene.

| alcohol | time (h) | conversion[a] (%) | ee of (*S*)-**5b-h** (%) | ee of (*R*)-**4b-h** (%) | *E*[a] |
|---|---|---|---|---|---|
| (±)-**4b** | 7.5 | 51 | 92 | 97 | 101 |
| (±)-**4c** | 4.6 | 54 | 82 | 96 | 39 |
| (±)-**4d** | 6.7 | 52 | 86 | 92 | 43 |
| (±)-**4e** | 1.8 | 51 | 93 | 96 | 108 |
| (±)-**4f** | 1.8 | 51 | 91 | 93 | 72 |
| (±)-**4g** | 2.0 | 51 | 92 | 94 | 85 |
| (±)-**4h** | 3.1 | 51 | 90 | 92 | 62 |

Conditions: Amano PS (10-100 mg $mL^{-1}$), (±)-**4b-h** (0.05-0.1 mol $L^{-1}$), vinyl acetate (0.5-1 mol $L^{-1}$), room temperature. Refer to Section 4.2.4 for details.
[a]Calculated from the ees of (*S*)-**5b-h** and those of (*R*)-**4b-h** [32].

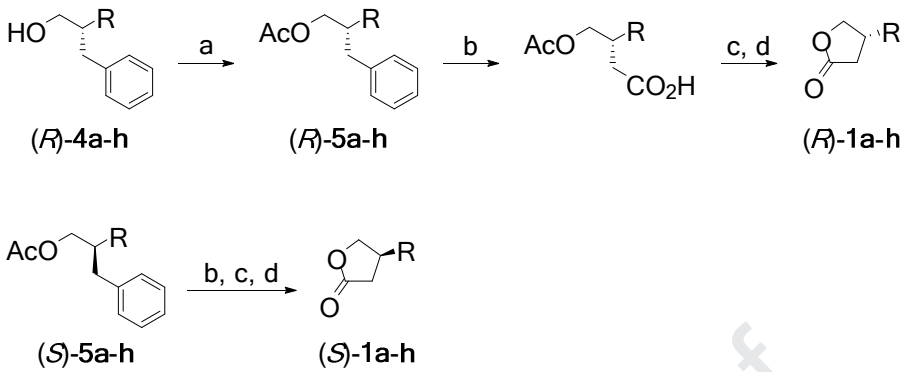
On the basis of the results shown in Table 1, we conducted the large-scale resolution of (±)-**4a** in toluene to obtain (*S*)-**5a** with 88% ee and (*R*)-**4a** with >99% ee, respectively (Scheme 3). The absolute configuration of (*R*)-**4a** was established by comparison of the value of optical rotation with that reported in the literature (See Section 4.2.5). We could also obtain (*R*)-**4b-h** with ≥99% ee and (*S*)-**5b-h** with 73-88% ee in the same manner. The absolute configurations of (*R*)-**4b-h** were established by comparison of the value of optical rotations with those reported in the literatures (See Supporting information).




**Scheme 3**. Preparation of (*R*)-**4a-h** and (*S*)-**5a-h**. (a) Amano PS, toluene, rt. (*S*)-**5a**: 53%, 88% ee; (*R*)-**4a**: 45%, >99% ee; (*S*)-**5b**: 53%, 85% ee; (*R*)-**4b**: 46%, >99% ee; (*S*)-**5c**: 57%, 73% ee; (*R*)-**4c**: 42%, >99% ee; (*S*)-**5d**: 58%, 74% ee; (*R*)-**4d**: 42%, 99% ee; (*S*)-**5e**: 53%, 88% ee; (*R*)-**4e**: 46%, >99% ee; (*S*)-**5f**: 55%, 81% ee; (*R*)-**4f**: 44%, 99% ee; (*S*)-**5g**: 54%, 87% ee; (*R*)-**4g**: 46%, >99% ee; (*S*)-**5h**: 52%, 83% ee; (*R*)-**4h**: 47%, >99% ee; (b) aq NaOH, EtOH, rt, (*S*)-**4a**: 94%, 88% ee; (*S*)-**4b**: 95%, 85% ee; (*S*)-**4c**: 93%, 73% ee; (*S*)-**4d**: 94%, 74% ee; (*S*)-**4e**: 92%, 88% ee; (*S*)-**4f**: 93%, 81% ee; (*S*)-**4g**: 92%, 87% ee; (*S*)-**4h**: 94%, 83% ee; (c) Amano PS, toluene, rt, (*S*)-**5a**: 86%, >99% ee; (*S*)-**5b**: 87%, >99% ee; (*S*)-**5c**: 60%, 99% ee; (*S*)-**5d**: 63%, 99% ee; (*S*)-**5e**: 89%, >99% ee; (*S*)-**5f**: 71%, >99% ee; (*S*)-**5g**: 84%, >99% ee; (*S*)-**5h**: 79%, >99% ee.

Ester (*S*)-**5a** obtained in the transesterification did not have a sufficiently high ee for use, and therefore we tried to prepare (*S*)-**5a** with a higher ee. Ester (*S*)-**5a** was hydrolyzed to the corresponding alcohol (*S*)-**4a** by the use of sodium hydroxide solution, and then it was subjected to Amano PS-catalyzed transesterification with vinyl acetate in toluene again to obtain (*S*)-**5a** with >99% ee (Scheme 3). We could also obtain (*S*)-**5b**-**h** with ≥99% ee in the same manner.

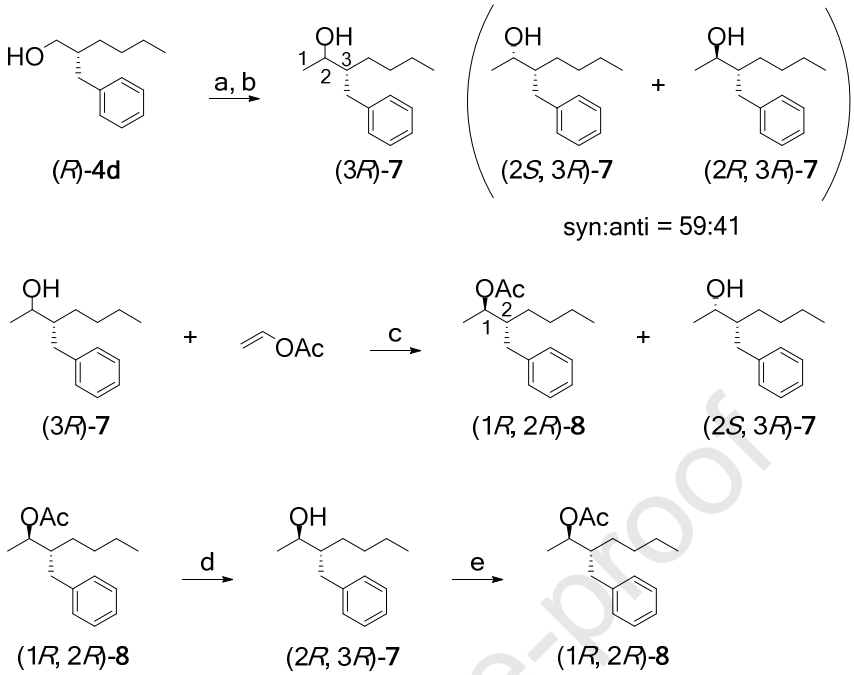
The treatment of (*R*)-**4a-h** with AcCl afforded the corresponding acetate (*R*)-**5a-h** (Scheme 4). The acetates (*R*)-**5a-h** were treated with $H_5IO_6$ and $RuCl_3$ to give the corresponding *γ*-acetoxycarboxylic acids. The synthesis of (*R*)-**1a-h** was accomplished by the hydrolysis of the ester moiety of the *γ*-acetoxycarboxylic acids and the subsequent lactonization of the resultant *γ*-hydroxycarboxylic acids. We could also synthesize lactones (*S*)-**1a-h** from (*S*)-**5a-h** in the same manner.




**Scheme 4**. Preparation of (*R*)- and (*S*)-**1a-h**. (a) AcCl, pyridine, $CH_2Cl_2$, 0 ºC to rt, (*R*)-**5a**: 95%; (*R*)-**5b**: 89%; (*R*)-**5c**: 94%; (*R*)-**5d**: 94%; (*R*)-**5e**: 92%; (*R*)-**5f**: 94%; (*R*)-**5g**: 90%; (*R*)-**5h**: 86%; (b) $RuCl_3$, $H_5IO_6$, $H_2O$, $CCl_4$, $CH_3CN$, 0 ºC to rt, (c) aq NaOH, rt, (d) aq HCl, rt, (*R*)-**1a**: 41% from (*R*)-**5a**; (*R*)-**1b**: 36% from (*R*)-**5b**; (*R*)-**1c**: 58% from (*R*)-**5c**; (*R*)-**1d**: 60% from (*R*)-**5d**; (*R*)-**1e**: 57% from (*R*)-**5e**; (*R*)-**1f**: 55% from (*R*)-**5f**; (*R*)-**1g**: 46% from (*R*)-**5g**; (*R*)-**1h**: 46% from (*R*)-**5h**; (*S*)-**1a**: 41% from (*S*)-**5a**; (*S*)-**1b**: 37% from (*S*)-**5b**; (*S*)-**1c**: 58% from (*S*)-**5c**; (*S*)-**1d**: 61% from (*S*)-**5d**; (*S*)-**1e**: 55% from (*S*)-**5e**; (*S*)-**1f**: 56% from (*S*)-**5f**; (*S*)-**1g**: 52% from (*S*)-**5g**; (*S*)-**1h**: 44% from (*S*)-**5h**.

### *2.2. Synthesis of all four stereoisomers of whiskey lactone analogues **2***

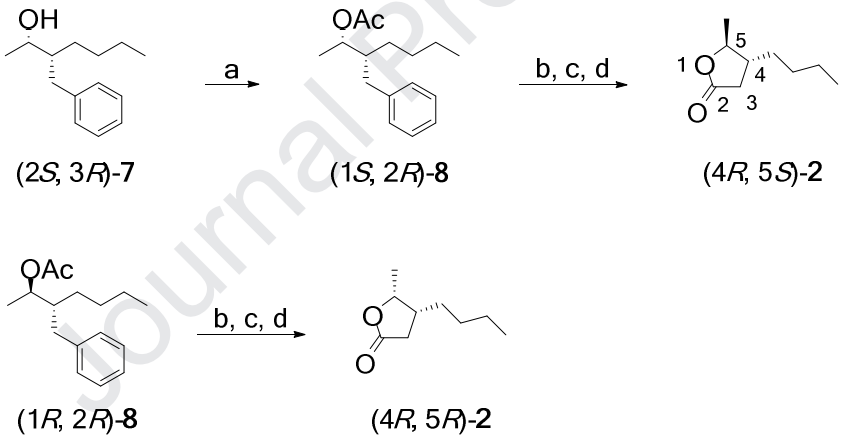
We began with the synthesis of secondary alcohol (3*R*)-**7** according to the route shown in Scheme 5. The primary alcohol (*R*)-**4d** prepared in Section 2.1 was oxidized with Dess-Martine periodinane to give the corresponding aldehyde, and the addition of methylmagnesium iodide to the aldehyde gave (3*R*)-**7**, which was composed of 59% of the syn-isomer (2*S*, 3*R*)-**7** and 41% of the anti-isomer (2*R*, 3*R*)-**7**.




**Scheme 5.** Preparation of highly diastereomerically pure (2*S*, 3*R*)-**7** and (1*R*, 2*R*)-**8.** (a) DMP, $CH_2Cl_2$, rt; (b) MeMgI, $Et_2O$, rt, then $H^+$, 63% from (*R*)-**4d**, syn:anti = 59:41; (c) Novozym 435, rt, (1*R*, 2*R*)-**8**: 38%; (2*S*, 3*R*)-**7**: 58%, syn:anti = >99:<1, >99% ee; (d) aq NaOH, EtOH, rt, 84%, syn:anti = 3:97, >99% ee; (e) Novozym 435, rt, 92%; syn:anti = <1:>99, >99% ee.

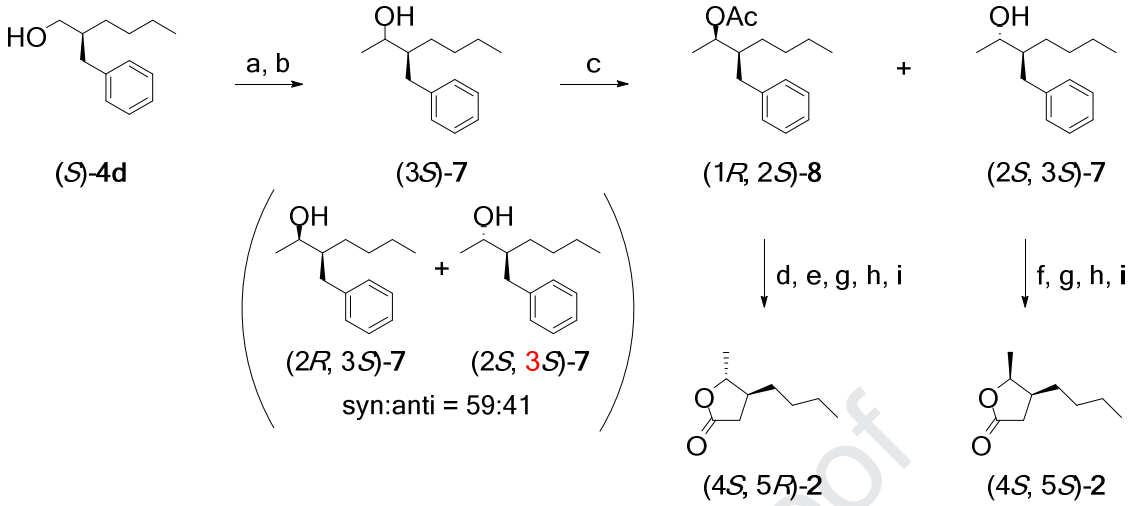
Unfortunately, the diastereomers could not be separated with silica gel column chromatography. However, we could achieve separation *via* the lipase (Novozym 435)-catalyzed diastereoselective transesterification of (3*R*)-**7** with vinyl acetate, working as an acyl donor and solvent. We first obtained (1*R*, 2*R*)-**8** and highly diastereomerically pure (2*S*, 3*R*)-**7** with >99% ee (Scheme 5). The ester (1*R*, 2*R*)-**8** was not highly diastereomerically pure (syn:anti = 3:97), and therefore we tried to prepare highly diastereomerically pure (1*R*, 2*R*)-**8**. The ester (1*R*, 2*R*)-**8** was hydrolyzed to the corresponding alcohol (2*R*, 3*R*)-**7** by the use of aqueous NaOH, and then it was subjected to Novozym 435-catalyzed transesterification with vinyl acetate again to obtain highly diastereomerically pure (1*R*, 2*R*)-**8** with >99% ee.

The diastereomerically and enantiomerically pure alcohol (2*S*, 3*R*)-**7** was treated with AcCl to afford the corresponding acetate (1*S*, 2*R*)-**8** (Scheme 6). The acetate (1*S*, 2*R*)-**8** was treated with $H_5IO_6$ and $RuCl_3$ to give the corresponding $\gamma$-acetoxycarboxylic acid. The synthesis of (4*R*, 5*S*)-**2** was accomplished by the hydrolysis of the ester moiety of the $\gamma$-acetoxycarboxylic acid and the subsequent lactonization of the resultant $\gamma$-hydroxycarboxylic acid. The $^1$H NMR data of the *trans* isomer of lactone **2**, though racemic, have been reported [38], and the data were identical to those of (4*R*, 5*R*)-**2**. Therefore, the absolute configuration of C5 of the lactone ring of (4*R*, 5*R*)-**2** is *R*. We could also synthesize (4*R*, 5*R*)-**2** from (1*R*, 2*R*)-**8** in the same manner.




**Scheme 6.** Synthesis of (4*R*, 5*S*)- and (4*R*, 5*R*)-**2**. (a) AcCl, pyridine, $CH_2Cl_2$, rt, 94%; (b) $RuCl_3$, $H_5IO_6$, $H_2O$, $CCl_4$, $CH_3CN$, 0 ºC to rt, (c) aq NaOH, rt, (d) aq HCl, rt, (4*R*, 5*S*)-**2**: 47% from (1*S*, 2*R*)-**8**, cis:trans = <1:>99, ee: >99%; (4*R*, 5*R*)-**2**: 60% from (1*R*, 2*R*)-**8**, cis:trans = >99:<1, ee: >99%.

We could also synthesize (4*S*, 5*R*)-**2** and (4*S*, 5*S*)-**2** from (*S*)-**4d** in the same manner as (4*R*, 5*S*)-**2** and (4*R*, 5*R*)-**2** (Scheme 7).




**Scheme 7**. Synthesis of (4*S*, 5*R*)- and (4*S*, 5*S*)-**2**. (a) DMP, $CH_2Cl_2$, rt; (b) MeMgI, $Et_2O$, rt, then $H^+$, 74% from (*S*)-**4d**, syn:anti = 59:41; (c) vinyl acetate, Novozym 435, rt, (1*R*, 2*S*)-**8**: 55%; (2*S*, 3*S*)-**7**: 57%, syn:anti = <1:>99, >99% ee; (d) aq NaOH, EtOH, rt, 92%, syn:anti = 98:2, >99% ee; (e) vinyl acetate, Novozym 435, rt, 86%; syn:anti = >99:<1, >99% ee. (f) AcCl, pyridine, $CH_2Cl_2$, rt, 53%; (g) $RuCl_3$, $H_5IO_6$, $H_2O$, $CCl_4$, $CH_3CN$, 0 ºC to rt, (h) aq NaOH, rt, (i) aq HCl, rt, (4*S*, 5*R*)-**2**: 57% in three steps, cis:trans = <1:>99, ee: >99%; (4*S*, 5*S*)-**2**: 46% in three steps, cis:trans = >99:<1, ee: >99%.

### *2.3. Olfactory evaluation of lactones **1a-h**, **2***

The odor profiles of the chiral lactones and racemic *β*-alkyl substituted *γ*-lactones (±)-**1a-h** (See the experimental section and supporting information for the preparation) were evaluated by seven skilled perfumers.

The results of the olfactory evaluation of all optically active *β*-alkyl substituted *γ*-lactones (*R*)- and (*S*)-**1a-h** are shown in Table 3. Mosandl *et al*. used 17 keywords to express the odor profiles of optically active *γ*-alkyl substituted *γ*-lactones (*R*)- and (*S*)-**9a-h** [14]. We also evaluated the odor properties of (*R*)- and (*S*)-**1a-h** by the use of the keywords here and showed the five keywords that showed the interesting results of evaluations. The numerical values in Table 3 express how many among the seven perfumers perceived the odor properties described with the keywords. All the results of

the olfactory evaluation of (*R*)- and (*S*)-**1a-h** are shown in Supporting information.

**Table 3**
Olfactory evaluation of (*R*)- and (*S*)-**1a-h**.

| | (*R*)-**1a** | (*R*)-**1b** | (*R*)-**1c** | (*R*)-**1d** | (*R*)-**1e** | (*R*)-**1f** | (*R*)-**1g** | (*R*)-**1h** |
|---|---|---|---|---|---|---|---|---|
| fatty | 2 | 4 | 4 | 3 | 6 | 3 | 4 | 4 |
| aldehydic | 2 | 3 | 4 | 6 | 6 | 5 | 5 | 5 |
| green | 1 | 2 | 6 | 6 | 4 | 4 | 4 | 4 |
| sweet | 4 | 3 | 3 | 1 | 1 | 1 | 1 | 1 |
| coconut | 5 | 3 | 4 | 1 | 3 | 1 | 0 | 0 |
| | (*S*)-**1a** | (*S*)-**1b** | (*S*)-**1c** | (*S*)-**1d** | (*S*)-**1e** | (*S*)-**1f** | (*S*)-**1g** | (*S*)-**1h** |
| fatty | 0 | 1 | 3 | 5 | 4 | 7 | 6 | 7 |
| aldehydic | 1 | 1 | 6 | 6 | 4 | 5 | 7 | 6 |
| green | 2 | 2 | 5 | 4 | 3 | 4 | 4 | 2 |
| sweet | 4 | 3 | 2 | 4 | 1 | 2 | 1 | 1 |
| coconut | 6 | 4 | 2 | 1 | 0 | 0 | 1 | 2 |

More than half of the perfumers perceived fatty odors in (*R*)-**1b**, **c**, **e**, **g**, **h**, and (*S*)-**1d-h**, and interestingly, the number of perfumers who perceived fatty odors in (*S*)-**1a-h** roughly increased with the length of the alkyl groups of (*S*)-**1a-h**. Mosandl *et al*. reported that fatty odors were perceived in (*R*)-**9b**, **e-g** and (*S*)-**9c-h** [14]. Fatty odors were roughly found to be ones common to the *β*- and *γ*-alkyl substituted *γ*-lactones.

More than half of the perfumers perceived aldehydic odors in (*R*)- and (*S*)-**1c-h** and green odors in (*R*)-**1c-h** and (*S*)-**1c**, **d**, **f**, **g**. Mosandl *et al*. reported that aldehydic odors were perceived in (*R*)-**9h** and (*S*)-**9g** and a green odor was perceived in (*R*)-**9d** [14]. These results led to the conclusion that the aldehydic odors and the green odors could be attributed to the existence of the alkyl groups in the *β*-positions of *γ*-lactone rings.

The number of perfumers who perceived sweet odors in (*R*)- and (*S*)-**1a-h** roughly decreased with the length of the alkyl groups of (*R*)- and (*S*)-**1a-h**, and only three

lactones (*R*)-**1a**, (*S*)-**1a**, and (*S*)-**1d** had sweet odors which more than half of the perfumers perceived. On the other hand, 11 chiral lactones among the 18 chiral *γ*-alkyl substituted *γ*-lactones (*R*)- and (*S*)-**9a-h** had sweet odors [14]. The number of perfumers who perceived coconut odors in (*R*)- and (*S*)-**1a-h** also roughly decreased with the length of the alkyl groups of (*R*)- and (*S*)-**1a-h**, and only four lactones (*R*)-**1a**, (*R*)-**1c**, (*S*)-**1a**, and (*S*)-**1b** had coconut odors which more than half of the perfumers perceived. On the other hand, eight chiral lactones among the 18 chiral *γ*-alkyl substituted *γ*-lactones (*R*)- and (*S*)-**9a-h** had coconut odors [14]. These results led to the conclusion that the coconut and the sweet odors could be attributed to the existence of the alkyl groups in the *γ*-positions of *γ*-lactone rings.

We have reported interesting interactions, such as masking, mutual negation and combination effects, between the odors of the enantiomers of the Phantolide® analogues [22] and therefore evaluated not only the odor profiles of the optically active *β*-alkyl substituted *γ*-lactones (*R*)- and (*S*)-**1a-h** but also those of the corresponding racemates (±)-**1a-h**. The results of the olfactory evaluation of (±)-**1a-h** were shown in Table 4. Although more than half of the perfumers perceived that both (*R*)- and (*S*)-**1a** had coconut odors, only one perfumer perceived that (±)-**1a** had a coconut odor. The odors of (*R*)- and (*S*)-**1a** negated each other's coconut odors, and therefore (±)-**1a** did not show a clearly perceptible coconut odor. The mutual negation effect was also observed in the green odor. Only a small number of perfumers perceived green odors in (±)-**1a-g** compared to in (*R*)- and (*S*)-**1a-g**.

**Table 4**
Olfactory evaluation of (±)-**1a-h**.

| | (±)-**1a** | (±)-**1b** | (±)-**1c** | (±)-**1d** | (±)-**1e** | (±)-**1f** | (±)-**1g** | (±)-**1h** |
|---|---|---|---|---|---|---|---|---|
| fatty | 2 | 2 | 2 | 3 | 2 | 4 | 6 | 6 |
| aldehydic | 2 | 0 | 4 | 4 | 2 | 3 | 4 | 6 |
| green | 0 | 1 | 4 | 1 | 2 | 3 | 3 | 3 |
| sweet | 6 | 5 | 3 | 2 | 1 | 1 | 1 | 2 |
| coconut | 1 | 4 | 3 | 4 | 3 | 0 | 1 | 0 |

More than half of the perfumers perceived that lactone (±)-**1d** had a coconut odor, but only one perfumer perceived that both (*R*)- and (*S*)-**1d** had a coconut odor. The combination of the odors of (*R*)- and (*S*)-**1d** produced a clearly perceptible coconut odor.

The results of the olfactory evaluation of whiskey lactone analogue **2** are shown in Table 5. A difference in the odor profiles was found between the enantiomers. (4*R*, 5*S*)- and (4*R*, 5*R*)-**2** had coconut odors although weak. However, neither (4*S*, 5*R*)- nor (4*S*, 5*S*)-**2** had coconut odors.

**Table 5**
Olfactory evaluation of **2**.

| Compound | Odor properties |
|---|---|
| (4*R*, 5*S*)-**2** | slightly coconut-like, slightly γ-nonalactone (**9e**)-like, green, herbaceous, iris-like, powdery lactone-like, slightly ionone-like, slightly oily, spicy, strong, sweet, thick |
| (4*S*, 5*R*)-**2** | 2-acetylpyridine-like, citrous, powdery, dusty, oily, slightly iris-like |
| (4*R*, 5*R*)-**2** | citrous, slightly coconut-like, dry, fruity, green, slightly γ-decalactone (**9f**)-like, heavy, powdery, weak |
| (4*S*, 5*S*)-**2** | citrous, elegant, green, heavy, herbaceous, light, powdery, weak |

Shimotori *et al*. reported that all four stereoisomers of whiskey lactone **10** had

coconut odors [17k]. However, (4*R*, 5*S*)- and (4*R*, 5*R*)-**2** had slightly coconut-like odors. Furthermore, no perfumers perceived coconut odors in (4*S*, 5*R*)- or (4*S*, 5*S*)-**2**. These results led to the conclusion that the positions of the methyl groups and the *n*-butyl groups contributed to the presence and the intensity of the coconut odors. Interestingly, (4*S*, 5*R*)-**2** did not even have a lactone-like odor.

## 3. Conclusions

We synthesized optically active *β*-alkyl substituted *γ*-lactones **1a**-**h**. During the preparations of the intermediates of the chiral lactones, we found good reaction conditions for the lipase-catalyzed enantioselective transesterification of 3-arylmethyl-2-alkyl-1-propanols to kinetically resolve: Amano PS as lipase, vinyl acetate as an acyl donor, and toluene as solvent. We believe that our findings will reduce the time taken to screen for the optimal conditions for the resolutions of 3-arylmethyl-2-alkyl-1-propanols.

We compared the odor profiles of **1a**-**h** with the odor profiles of *γ*-alkyl substituted *γ*-lactones **9a**-**h**, which Mosandl *et al.* originally reported [14]. The existence of the alkyl groups in the *β*-positions of *γ*-lactone rings were attributed to aldehydic odors and green odors and the existence of the alkyl groups in the *γ*-positions of *γ*-lactone rings were attributed to coconut odors and sweet odors.

We also found the mutual negation effect of the enantiomers of some *β*-alkyl substituted *γ*-lactones by evaluating not only the odors of the optically active isomers but also those of the racemates. This finding shows the importance of the olfactory evaluation of the enantiomers of odorous compounds, and even racemic compounds

establishing a firm position as odorous compounds.

We could synthesize all four stereoisomers of whiskey lactone analogues **2** by the use of the chiral intermediates of (*R*)- and (*S*)-**1d**. Although all the stereoisomers of whiskey lactones **10** showed coconut odors [17k], all the isomers of **2** showed weak or no coconut odor.

## 4. Experimental

### *4.1. General*

All commercially available reagent chemicals were obtained from Aldrich, Kanto Kagaku, Nacalai Tesque, Tokyo Kasei, and Wako Chemicals and used without further purification. Ruthenium chloride hydrate ($RuCl_3 \cdot nH_2O$) was used as an anhydrous salt (n = 0). Lipase Amano PS was purchased from Amano Enzyme and dried over $P_2O_5$ for three days at room temperature. Lipase Novozym 435 was donated by Novozymes Japan. HMPA was distillated (70.1-72.1 ºC/0.5 mmHg) from $CaH_2$. Dry $Et_2O$ for the Grignard reaction was distilled from Na/benzophenone under an argon atmosphere. Water refers to deionized water. NMR spectra were recorded on a Bruker Advance II 400 spectrometer ($^1$H 400 MHz and $^{13}$C 100 MHz). Chemical shifts ($\delta$) are reported in parts per million (ppm) and referenced to TMS ($\delta$ = 0.00 ppm). IR spectra were recorded on a Jasco FT/IR-410 spectrometer. MS was performed on a Jeol MStation JMS-700 instrument. Optical rotations were recorded on a Jasco P-1300 polarimeter. Gas chromatography (GC) analyses were performed on a Shimadzu GC-2014 gas chromatograph equipped with InertCap 1 capillary column (GL Sciences, 0.25 mm $\phi$ ×

30 m), GAMMA DEX$^{TM}$ 120 capillary column (SUPELCO, 0.25 mm $\phi$ × 30 m) and CP-Cyclodextrin-$\beta$-2,3,6-M-19 capillary column (Agilent, 0.25 mm $\phi$ × 25 m). High performance liquid chromatography (HPLC) analyses were performed on a Shimadzu LC-20AD intelligent pump with a Shimadzu SPD-20A UV detector using a CHIRALCEL OD-H column, CHIRALCEL OZ-H column, CHIRALPAK AS-H column (Daicel, 4.6 mm $\phi$ × 250 mm).

### *4.2. Synthesis of racemic and optically active dihydro-4-methyl-2(3H)-furanone **1a***

#### *4.2.1. (±)-2-Methyl-3-phenyl-1-propanol (±)- **4a***

$\alpha$-Methylhydrocinnamic acid (5.100 g, 31.06 mmol) in dry THF (19 mL) was added dropwise to a suspension of $LiAlH_4$ (1.532 g, 40.37 mmol) in dry THF (20 mL) at 0 ºC under an argon atmosphere. The reaction mixture was stirred for 26 h at room temperature. The reaction was quenched with water (30 mL) and aqueous HCl (6 mol $L^{-1}$, 30 mL) at 0 ºC. The mixture was extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with water (30 mL), aqueous NaOH (6 mol $L^{-1}$, 30 mL), and brine (30 mL). The organic layers were dried over anhydrous $Na_2SO_4$ and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/acetone = 3/2) to afford (±)-**4a** (4.387 g, 94%) as a colorless oil. $^1$H NMR data were identical to those reported in the literature [39].

#### *4.2.2. (±)-2-Methyl-3-phenylpropyl acetate (±)- **5a***

Acetyl chloride (1.816 g, 23.14 mmol) was added slowly to a solution of (±)-**4a** (1.728 g, 11.50 mmol) and dry pyridine (2.757 g, 34.85 mmol) in dry $CH_2Cl_2$ (30 ml) at

0 ºC. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (30 mL) at 0 ºC. The mixture was extracted with $Et_2O$ (50 mL). The organic layer was washed with brine (30 mL), dried over anhydrous $Na_2SO_4$ and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to afford (±)-**5a** (2.079 g, 94%) as a colorless oil. $^1$H NMR data were identical to those reported in the literature [40].

*4.2.3. (±)-Dihydro-4-methyl-2(3H)-furanone (±)-* ***1a***

A solution of $H_5IO_6$ (48.570 g, 21.308 mmol) in water (60 mL) was added to a solution of (±)-**5a** (2.079 g, 10.81 mmol) in $CCl_4$ (40 mL) and $CH_3CN$ (40 mL) at 0 ºC. $RuCl_3 \cdot nH_2O$ (0.465 g, 2.24 mmol) was added slowly to the mixture at 0 ºC, and the resultant mixture was vigorously stirred for 20 h at room temperature. The reaction was quenched with $Et_2O$ (50 mL) at 0 ºC, and the mixture was stirred for 30 min. The mixture was extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$ and filtered. After removal of the solvent, a deep yellow oil (2.125 g) was obtained. The oil was dissolved in aqueous NaOH (3 mol $L^{-1}$, 40 mL), and the resulting solution was stirred overnight at room temperature. The solution was washed with $Et_2O$ (30 mL) and acidified with aqueous HCl (6 mol $L^{-1}$, 40 mL) at 0 ºC. The mixture was stirred overnight at room temperature. The aqueous layer was saturated with NaCl; however, the saturation process was not applied to the synthesis of lactones **1b-h**, **2**. The mixture was extracted with $Et_2O$ (5 × 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried over anhydrous $Na_2SO_4$ and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel

(hexane/acetone = 2/1) and subsequent distillation (119-138 ºC/13.5 mmHg) to afford (±)-**1a** (0.380 g, 35%) as a colorless oil. $^1$H NMR data were identical to those reported in the literature [41].

*4.2.4. Amano PS-catalyzed transesterification of (±)-2-methyl-3-phenyl-1-propanol (±)-**4a** with vinyl acetate (screening experiments)*

In a typical experiment, 1 mL of solution of (±)-**4a** (15.0 mg, 0.0999 mmol) and vinyl acetate (86.1 mg, 1.00 mmol) in an organic solvent was added to a vial in which Amano PS (20.0 mg) was placed. The suspension was stirred at room temperature. The reaction was monitored by GC (InertCap 1 capillary column, 170 °C) and terminated at approximately 50% conversion by the filtration of the lipase. The extent of the conversion was calculated from the ratio of the peak area of the produced ester **5a** to the total of the peak areas of **5a** and the unreacted alcohol **4a**. The peak area of **5a** was corrected on the basis of the number of the carbon atoms in the molecules of **4a** and **5a** [42]. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 10/1 to 1/1) packed in a short column (9 mm $\phi$ × 60 mm) to afford **5a** and **4a**. The enantiomeric excess (ee) of **4a** was determined by HPLC using a CHIRALCEL OD-H column (hexane/2-propanol = 91/9).

The ee of **5a** was determined by measuring the ee of the corresponding alcohol **4a** prepared by hydrolysis. The ester **5a** obtained above was dissolved in EtOH (0.5 mL), and ten drops of aqueous NaOH (6 mol $L^{-1}$) were added to the solution. The mixture was stirred overnight at room temperature. The ethanol was removed under reduced pressure, and water was added to the residue. The mixture was extracted with $Et_2O$ (15 mL). The organic layer was washed with brine (10 mL), dried over anhydrous $Na_2SO_4$

and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/EtOAc = 10/1 to 1/1) packed in a short column (9 mm $\phi$ × 60 mm) to afford **4a**. The ee of **4a** was determined by HPLC using a CHIRALCEL OD-H column (hexane/2-propanol = 91/9).

*4.2.5. Preparative resolution of (±)-2-methyl-3-phenyl-1-propanol (±)-**4a***

Amano PS (1.450 g) was added to a solution of (±)-**4a** (4.377 g, 29.14 mmol) and vinyl acetate (25.089 g, 29.143 mmol) in dry toluene (260 mL), and the resulting suspension was stirred at room temperature. The reaction was monitored by GC (InertCap 1 capillary column, 185 °C) and terminated at approximately 52% conversion (approximately 4.2 h, see the first paragraph of Section 4.2.4 for determining the extent of the conversions) by the suction filtration of the lipase with Celite®. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/EtOAc = 5/1 to 1/1) to afford (*S*)-**5a** (2.971 g, 53%) as a colorless oil and (*R*)-**4a** (1.985 g, 45%) as a colorless oil.

(*R*)-**4a**: $^1$H NMR data were identical to those of (±)-**4a**. ee: >99% (HPLC, CHIRALCEL OD-H column, hexane/2-propanol = 91/9); $[\alpha]_D^{22}$ = +12 (*c* 0.96, $CHCl_3$), {Lit [39]. $[\alpha]_D^{25}$ = +11.62 (*c* 1.0, $CHCl_3$, *R*)}.

Aqueous NaOH (6 mol $L^{-1}$, 5 mL) was added to a solution of (*S*)-**5a** (2.971 g, 15.45 mmol) obtained above in EtOH (25 mL), and the mixture was stirred overnight at room temperature. The ethanol was removed under reduced pressure, and water was added to the residue. The mixture was extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$ and filtered. After removal of the solvent, the residue was purified by chromatography on silica gel (hexane/EtOAc

= 1/1) to afford (*S*)-**4a** (2.192 g, 94%) as a colorless oil.

(*S*)-**4a**: $^1$H NMR data were identical to those of (±)-**4a**. ee: 88% (HPLC, CHIRALCEL OD-H column, hexane/2-propanol = 91/9).

*4.2.6. (R)-2-Methyl-3-phenylpropyl acetate (R)-**5a***

This was prepared from (*R*)-**4a** (1.984 g, 13.21 mmol, >99% ee), AcCl (2.083 g, 26.54 mmol), and dry pyridine (3.181 g, 40.21 mmol) in dry $CH_2Cl_2$ (30 mL) in 95% yield (2.418 g, colorless oil) according to the procedure shown in Section 4.2.2. $^1$H NMR data were identical to those of (±)-**5a**. $[\alpha]_D^{22}$ = -14 (*c* 0.87, benzene), {Lit [43]. $[\alpha]_D$ = +14 (*c* 1.15, benzene, *S*, 98% ee)}.

*4.2.7. (R)-Dihydro-4-methyl-2(3H)-furanone (R)-**1a***

This was prepared from (*R*)-**5a** (2.418 g, 12.58 mmol) as the starting material in 41% yield (0.522 g, colorless oil) according to the procedure shown in Section 4.2.3. The reagents and reaction solvents for the preparation are as below: $CCl_4$ (50 mL), $CH_3CN$ (50 mL), $H_5IO_6$ (57.231 g, 251.08 mmol), water (75 mL), $RuCl_3 \cdot nH_2O$ (0.522 g, 2.52 mmol), aqueous NaOH (3 mol $L^{-1}$, 40 mL), aqueous HCl (6 mol $L^{-1}$, 30 mL). Ethyl acetate was used for the extraction of (*R*)-**1a**. $^1$H NMR data were identical to those of (±)-**1a**. Bp: 129-165 ºC/16.5 mmHg; $[\alpha]_D^{21}$ = +26 (*c* 0.73, MeOH), {Lit [44]. $[\alpha]_D$ = +21.6 (*c* 0.5, MeOH, *R*, 98% ee)}.

*4.2.8. (S)-2-Methyl-3-phenylpropyl acetate (S)-**5a***

Amano PS (0.363 g) was added to the solution of (*S*)-**4a** (2.191 g, 14.59 mmol, 88% ee) and vinyl acetate (12.613 g, 14.651 mmol) in dry toluene 130 mL, and the resulting

suspension was stirred at room temperature. The reaction was monitored by GC (InertCap 1 capillary column, 185 °C) and terminated at approximately 86% conversion (approximately 4.3 h, see the first paragraph of Section 4.2.4 for determining the extent of the conversions) by the suction filtration of the lipase with Celite®. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to afford (*S*)-**5a** (2.410 g, 86%) as colorless oil. $^1$H NMR data were identical to those of (±)-**5a**. The ee of (*S*)-**5a** was determined by measuring the ee of the corresponding alcohol (*S*)-**4a** prepared by hydrolysis; a drop of (*S*)-**5a** was hydrolyzed to (*S*)-**4a** according to the procedure shown in the second paragraph of Section 4.2.4, and the ee of (*S*)-**4a** was determined by HPLC (CHIRALCEL OD-H column, hexane/2-propanol = 91/9) to be >99%. $[\alpha]_D^{21}$ = +15 (*c* 0.79, benzene), {Lit [43]. $[\alpha]_D$ = +14 (*c* 1.15, benzene, *S*, 98% ee)}.

*4.2.9. (S)-Dihydro-4-methyl-2(3H)-furanone (S)-**1a***

This was prepared from (*S*)-**5a** (2.399 g, 12.48 mmol) as the starting material in 41% yield (0.517 g, colorless oil) according to the procedure shown in Section 4.2.3. The reagents and reaction solvents for the preparation are as below: $CCl_4$ (50 mL), $CH_3CN$ (50 mL), $H_5IO_6$ (56.072 g, 245.99 mmol), water (75 mL), $RuCl_3 \cdot nH_2O$ (0.516 g, 2.49 mmol), aqueous NaOH (4 mol $L^{-1}$, 30 mL), aqueous HCl (6 mol $L^{-1}$, 30 mL). Ethyl acetate was used for the extraction of (*S*)-**1a**. $^1$H NMR data were identical to (±)-**1a**. Bp: 126-146 ºC/16 mmHg; $[\alpha]_D^{22}$ = - 26 (*c* 0.69, MeOH), {Lit [44]. $[\alpha]_D$ = +21.6 (*c* 0.5, MeOH, *R*, 98% ee)}.

*4.3. Synthesis of two stereoisomers of whiskey lactone analogue {(4R, 5S)- and (4R,*

*5R)-4-butyldihydro-5-methyl-2(3H)-furanone} (4R, 5S)- and (4R, 5R)-**2***

*4.3.1. (3R)-3-Benzyl-2-heptanol (3R)-**7***

A solution of (*R*)-**4d** (0.905 g, 4.71 mmol, >99% ee) prepared according to the procedure for the preparative resolution of (±)-**4d** shown in Supporting information in dry $CH_2Cl_2$ (3 mL) was added dropwise to a suspension of 95% Dess-Martin periodinane (2.395 g, 5.4 mmol) in dry $CH_2Cl_2$ (9 mL) at room temperature under an argon atmosphere, and the reaction mixture was stirred for 30 min. $Et_2O$ (30 mL), saturated aqueous $Na_2S_2O_3$ (10 mL), and saturated aqueous $NaHCO_3$ (10 mL) were successively added to the mixture. The resulting mixture was extracted with $Et_2O$. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and filtered. After removal the solvent, the residue was purified by column chromatography on silica gel (hexane/acetone = 10/1) to afford the corresponding aldehyde (0.735 g, 82%) as a colorless oil. The product was immediately used without characterization.

Mg shavings (0.378 g, 15.5 mmol) were placed in a three-necked flask. The shavings were covered with about 1 mL of a solution of distilled (44.5 °C) iodomethane (2.051 g, 14.45 mmol) in dry $Et_2O$ (12 mL) under an argon atmosphere. When the reaction started, the remainder of the solution was slowly added. The mixture was gently refluxed with a mantle heater for 30 min to give methylmagnesium iodide. After cooling to room temperature, a solution of the aldehyde obtained above (0.735 g, 3.86 mmol) in dry $Et_2O$ (10 mL) was slowly added to the solution of the methylmagnesium iodide at room temperature. The reaction mixture was stirred overnight under an argon atmosphere. After cooling the mixture to 0 ºC, saturated aqueous $NH_4Cl$ and water were successively added. Unreacted Mg shavings were removed by suction filtration with

Celite®. The filtrate was extracted three times with $Et_2O$. The combined organic layers were washed with water, aqueous NaOH (1 mol $L^{-1}$), and brine. The organic layers were dried over anhydrous $Na_2SO_4$ and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) to afford (3*R*)-**7** {0.612 g, 63% from (*R*)-**4d**} as a diastereomeric mixture {syn:anti = 59:41 (GC, GAMMA DEX™ 120 capillary column, 160 °C)} and a colorless oil. Refer to the $^1$H NMR data of (2*S*, 3*R*)-**7** shown in Section 4.3.2 and those of (2*S*, 3*S*)-**7** shown in Supporting information.

*4.3.2. Separation of diastereomers of (3R)-3-benzyl-2-heptanol (3R)-7*

Novozym 435 (2.672 g) was added to a solution of (3*R*)-**7** (0.544 g, 2.64 mmol, syn:anti = 59:41) in vinyl acetate (53 mL), and the resulting suspension was stirred at room temperature. The reaction was monitored by GC (GAMMA DEX™ 120 capillary column, 160 °C) and terminated at approximately 42% conversion (approximately 22 h, see the first paragraph of Section 4.2.4 for determining the conversion) by the suction filtration of the lipase with Celite®. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/acetone = 10/1 to 1/1) to afford (1*R*, 2*R*)-**8** (0.248 g, 38%) as a colorless oil and (2*S*, 3*R*)-**7** as a yellow oil. Alcohol (2*S*, 3*R*)-**7** was purified again by column chromatography on silica gel (hexane/acetone = 3/1) to become a colorless oil (0.315 g, 58%).

(2*S*, 3*R*)-**7**: IR (neat): 3358 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.86 (3H, t, $J$ = 7.2 Hz), 1.20 (3H, d, $J$ = 6.4), 1.17-1.37 (5H, m), 1.39-1.48 (1H, m), 1.65-1.73 (1H, m), 2.59 (1H, dd, $J$ = 7.6, $J$ = 14), 2.67 (1H, dd, $J$ = 6.8, $J$ = 14), 3.82-3.87 (1H, m), 7.17-7.34 (5H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.04, 19.78, 23.02, 28.84, 29.49, 36.13,

46.91, 68.96, 125.75, 128.27, 129.09, 141.35; MS (EI): m/z 206 ($M^+$); HRMS: Calcd for $C_{14}H_{22}O$ 206.1671, Found 206.1672; syn:anti = >99:<1 (GC, CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 120 °C); ee: >99% (GC, CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 120 °C); $[\alpha]_D^{22}$ = +8.3 (*c* 0.73, $CHCl_3$).

Ester (1*R*, 2*R*)-**8** (0.248 g, 0.999 mmol) obtained above was hydrolyzed to the corresponding alcohol (2*R*, 3*R*)-**7** with aqueous NaOH (6 mol $L^{-1}$, 0.5 mL) in EtOH (5 mL) according to the procedure shown in the second paragraph of Section 4.2.5. The crude product was purified by chromatography on silica gel (hexane/EtOAc = 3/1) to afford (2*R*, 3*R*)-**7** (0.173 g, 84%) as a colorless oil.

(2*R*, 3*R*)-**7**: $^1$H NMR data were almost identical to those of (2*S*, 3*S*)-**7** shown in Supporting information. syn:anti = 3:97 (GC, CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 120 °C); ee: >99% (GC, CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 120 °C).

*4.3.3. (1S, 2R)-2-Benzyl-1-methylhexyl acetate (1S, 2R)-**8***

This was prepared from (2*S*, 3*R*)-**7** (0.306 g, 1.48 mmol) and AcCl (0.214 g, 2.73 mmol) with dry pyridine (0.503 g, 6.36 mmol) in dry $CH_2Cl_2$ (5 mL) according to the procedure Section 4.2.2. The crude product was purified by chromatography on silica gel (hexane/acetone = 10/1) to afford (1*S*, 2*R*)-**8** (0.347 g, 94%) as a colorless oil. IR (neat): 1245, 1737 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.84 (3H, t, *J* = 7.0), 1.22 (3H, d, *J* = 6.4), 1.25-1.39 (6H, m), 1.82-1.90 (1H, m), 2.00 (3H, s), 2.54 (1H, dd, *J* = 8.4, *J* = 14), 2.69 (1H, dd, *J* = 6.4, *J* = 14), 4.94 (1H, qd, *J* = 4.8, *J* = 6.4), 7.15-7.30 (5H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.95, 16.67, 21.34, 22.87, 28.96, 28.99, 36.48, 44.11,

72.26, 125.86, 128.30, 128.96, 140.88, 170.71; MS (EI): m/z 248 ($M^+$); HRMS: Calcd for $C_{16}H_{24}O_2$ 248.1776, Found 248.1785; $[\alpha]_D^{22}$ = +4.2 (*c* 0.73, $CHCl_3$).

*4.3.4. (4R, 5S)-4-Butyldihydro-5-methyl-2(3H)-furanone (4R, 5S)-**2***

This was prepared from (1*S*, 2*R*)-**8** (0.332 g, 1.34 mmol) according to the procedure shown in Section 4.2.3. The reagents and reaction solvents for the preparation are as below: $CCl_4$ (7 mL), $CH_3CN$ (7 mL), $H_5IO_6$ (6.076 g, 26.66 mmol), water (11 mL), $RuCl_3 \cdot nH_2O$ (0.057 g, 0.27 mmol), aqueous NaOH (1 mol $L^{-1}$, 10 mL), aqueous HCl (6 mol $L^{-1}$, 10 mL). The organic layer obtained by extraction with $Et_2O$ after oxidation was washed with water, saturated aqueous $Na_2S_2O_3$ and brine. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) and subsequent distillation (156-187 ºC/16.5 mmHg) to afford (4*R*, 5*S*)-**2** (0.098 g, 47%) as a colorless oil. $^1$H NMR data were identical to those reported in the literature [38]. cis:trans = <1:>99 (GC, CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 110 °C); ee: >99% (GC, CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 110 °C); $[\alpha]_D^{22}$ = -69 (*c* 0.76, $CHCl_3$).

*4.3.5. (1R, 2R)-2-Benzyl-1-methylhexyl acetate (1R, 2R)-**8***

Novozym 435 (1.707 g) was added to a solution of (2*R*, 3*R*)-**7** (0.173 g, 0.839 mmol, syn:anti = 3:97) obtained in Section 4.3.2 in vinyl acetate (17 mL), and the resulting suspension was stirred at room temperature. The reaction was monitored by GC (GAMMA DEX$^{TM}$ 120 capillary column, 160 °C) and terminated at approximately 92% conversion (approximately 7.5 h; see the first paragraph of Section 4.2.4 for determining the conversion) by the suction filtration of the lipase with Celite®. After removal of the solvent, the residue was purified by column chromatography on silica

gel (hexane/acetone = 10/1) to afford a yellow oil, and the oil was purified again by the chromatography to afford (1*R*, 2*R*)-**8** (0.191 g, 92%) as a colorless oil. IR (neat): 1034, 1245, 1736 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.85 (3H, t, *J* = 7.2), 1.19 (3H, d, *J* = 6.4), 1.23-1.35 (6H, m), 1.81-1.88 (1H, m), 1.99 (3H, s), 2.48 (1H, dd, *J* = 7.6, *J* = 14), 2.70 (1H, dd, *J* = 6.4, *J* = 14), 4.96 (1H, qd, *J* = 4.0, *J* = 6.4), 7.12-7.29 (5H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 13.97, 15.95, 21.31, 22.88, 29.26, 29.43, 36.18, 44.40, 71.93, 125.80, 128.26, 129.10, 141.11, 170.67; MS (EI): m/z 248 ($M^+$); HRMS: Calcd for $C_{16}H_{24}O_2$ 248.1776, Found 248.1765; $[\alpha]_D^{18}$ = +11 (*c* 0.77, $CHCl_3$).

A drop of (1*R*, 2*R*)-**8** was hydrolyzed to (2*R*, 3*R*)-**7** to determine the syn/anti ratio and the ee according to the procedure shown in the second paragraph of Section 4.2.4. The crude products were purified by column chromatography on silica gel (hexane/EtOAc = 3/1). syn:anti = <1:>99 (GC, CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 120 °C); ee: >99% (GC, CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 120 °C).

*4.3.6. (4R, 5R)-4-Butyldihydro-5-methyl-2(3H)-furanone (4R, 5R)-**2***

This was prepared from (1*R*, 2*R*)-**8** (0.128 g, 0.515 mmol) according to the procedure shown in Section 4.2.3. The reagents and reaction solvents for the preparation are as below: $CCl_4$ (3 mL), $CH_3CN$ (3 mL), $H_5IO_6$ (2.493 g, 10.94 mmol), water (4 mL), $RuCl_3 \cdot nH_2O$ (0.024 g, 0.12 mmol), aqueous NaOH (1 mol $L^{-1}$, 10 mL), aqueous HCl (6 mol $L^{-1}$, 2 mL). The organic layer obtained by extraction with $Et_2O$ after oxidation was washed with water, saturated aqueous $Na_2S_2O_3$ and brine. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) and subsequent distillation (160-190 ºC/18 mmHg) to afford (4*R*, 5*R*)-**2** (0.048 g, 60%) as a colorless oil.

IR (neat): 1044, 1174, 1778 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.91 (3H, t, $J$ = 7.0), 1.21-1.39 (5H, m), 1.27 (3H, d, $J$ = 6.8), 1.42-1.51 (1H, m), 2.27 (1H, dd, $J$ = 7.6, $J$ = 16), 2.46-2.54 (1H, m), 2.56 (1H, dd, $J$ = 8.0, $J$ = 16), 4.71 (1H, app quintet, $J$ = 6.8); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 13.94, 15.42, 22.70, 28.35, 29.90, 33.79, 38.92, 79.41, 176.79; MS (EI): m/z 156 ($M^+$); HRMS: Calcd for $C_9H_{16}O_2$ 156.1150, Found 156.1133; cis:trans = >99:<1 (GC, CP-Cyclodextrin-$\beta$-2,3,6-M-19 capillary column, 110 °C); ee: >99% (GC, CP-Cyclodextrin-$\beta$-2,3,6-M-19 capillary column, 110 °C); $[\alpha]_D^{22}$ = +2.0 (*c* 0.68, $CHCl_3$).

*4.4.Odor profiles evaluation*

An undiluted sample was attached to the tip of filter paper (5 mm × 10 cm) in small quantities and evaluated by seven trained panelists.



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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://

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**Legends**

**Fig. 1.** $\gamma$-Lactones.

**Fig. 2.** Phantolide® analogues.

**Scheme 1.** Synthesis of racemic primary alcohols (±)-**4a**-**h**.

Reagents and conditions: (a) $LiAlH_4$, THF, 0 ºC to rt, 94%; (b) NaH, THF, reflux, **3b**: 86%; **3c**: 83%; **3d**: 78%; (c) Na, EtOH, reflux, **3e**: 91%; **3f**: 93%; **3g**: 95%; (d) aq

NaOH, EtOH, reflux; (e) Δ, xylene, reflux; (f) $LiAlH_4$, THF, 0 ºC to rt, **4b**: 80% from **3b**; **4c**: 84% from **3c**; **4d**: 79% from **3d**; **4e**: 78% from **3e**; **4f**: 79% from **3f**; **4g**: 77% from **3g**; (g) LDA, HMPA, THF, -78 ºC to 0 ºC, 84%; (h) $LiAlH_4$, THF, 0 ºC to rt, 80%.

**Scheme 2.** Lipase-catalyzed enantioselective transesterification of (±)-**4a-h** with vinyl acetate in organic solvent.

**Scheme 3.** Preparation of (*R*)-**4a-h** and (*S*)-**5a-h**. (a) Amano PS, toluene, rt. (*S*)-**5a**: 53%, 88% ee; (*R*)-**4a**: 45%, >99% ee; (*S*)-**5b**: 53%, 85% ee; (*R*)-**4b**: 46%, >99% ee; (*S*)-**5c**: 57%, 73% ee; (*R*)-**4c**: 42%, >99% ee; (*S*)-**5d**: 58%, 74% ee; (*R*)-**4d**: 42%, 99% ee; (*S*)-**5e**: 53%, 88% ee; (*R*)-**4e**: 46%, >99% ee; (*S*)-**5f**: 55%, 81% ee; (*R*)-**4f**: 44%, 99% ee; (*S*)-**5g**: 54%, 87% ee; (*R*)-**4g**: 46%, >99% ee; (*S*)-**5h**: 52%, 83% ee; (*R*)-**4h**: 47%, >99% ee; (b) aq NaOH, EtOH, rt, (*S*)-**4a**: 94%, 88% ee; (*S*)-**4b**: 95%, 85% ee; (*S*)-**4c**: 93%, 73% ee; (*S*)-**4d**: 94%, 74% ee; (*S*)-**4e**: 92%, 88% ee; (*S*)-**4f**: 93%, 81% ee; (*S*)-**4g**: 92%, 87% ee; (*S*)-**4h**: 94%, 83% ee; (c) Amano PS, toluene, rt, (*S*)-**5a**: 86%, >99% ee; (*S*)-**5b**: 87%, >99% ee; (*S*)-**5c**: 60%, 99% ee; (*S*)-**5d**: 63%, 99% ee; (*S*)-**5e**: 89%, >99% ee; (*S*)-**5f**: 71%, >99% ee; (*S*)-**5g**: 84%, >99% ee; (*S*)-**5h**: 79%, >99% ee.

**Scheme 4.** Preparation of (*R*)- and (*S*)-**1a-h**. (a) AcCl, pyridine, $CH_2Cl_2$, 0 ºC to rt, (*R*)-**5a**: 95%; (*R*)-**5b**: 89%; (*R*)-**5c**: 94%; (*R*)-**5d**: 94%; (*R*)-**5e**: 92%; (*R*)-**5f**: 94%; (*R*)-**5g**: 90%; (*R*)-**5h**: 86%; (b) $RuCl_3$, $H_5IO_6$, $H_2O$, $CCl_4$, $CH_3CN$, 0 ºC to rt, (c) aq NaOH, rt, (d) aq HCl, rt, (*R*)-**1a**: 41% from (*R*)-**5a**; (*R*)-**1b**: 36% from (*R*)-**5b**; (*R*)-**1c**: 58% from (*R*)-**5c**; (*R*)-**1d**: 60% from (*R*)-**5d**; (*R*)-**1e**: 57% from (*R*)-**5e**; (*R*)-**1f**: 55% from (*R*)-**5f**; (*R*)-**1g**: 46% from (*R*)-**5g**; (*R*)-**1h**: 46% from (*R*)-**5h**; (*S*)-**1a**: 41% from (*S*)-**5a**; (*S*)-**1b**: 37% from (*S*)-**5b**; (*S*)-**1c**: 58% from (*S*)-**5c**; (*S*)-**1d**: 61% from (*S*)-**5d**; (*S*)-**1e**: 55% from (*S*)-**5e**; (*S*)-**1f**: 56% from (*S*)-**5f**; (*S*)-**1g**: 52% from (*S*)-**5g**; (*S*)-**1h**: 44% from (*S*)-**5h**.

**Scheme 5.** Preparation of highly diastereomerically pure (2*S*, 3*R*)-**7** and (1*R*, 2*R*)-**8**. (a) DMP, $CH_2Cl_2$, rt; (b) MeMgI, $Et_2O$, rt, then $H^+$, 63% from (*R*)-**4d**, syn:anti = 59:41; (c) Novozym 435, rt, (1*R*, 2*R*)-**8**: 38%; (2*S*, 3*R*)-**7**: 58%, syn:anti = >99:<1, >99% ee; (d) aq NaOH, EtOH, rt, 84%, syn:anti = 3:97, >99% ee; (e) Novozym 435, rt, 92%; syn:anti = <1:>99, >99% ee.

**Scheme 6.** Synthesis of (4*R*, 5*S*)- and (4*R*, 5*R*)-**2**. (a) AcCl, pyridine, $CH_2Cl_2$, rt, 94%; (b) $RuCl_3$, $H_5IO_6$, $H_2O$, $CCl_4$, $CH_3CN$, 0 ºC to rt, (c) aq NaOH, rt, (d) aq HCl, rt, (4*R*, 5*S*)-**2**: 47% from (1*S*, 2*R*)-**8**, cis:trans = <1:>99, ee: >99%; (4*R*, 5*R*)-**2**: 60% from (1*R*, 2*R*)-**8**, cis:trans = >99:<1, ee: >99%.

**Scheme 7.** Synthesis of (4*S*, 5*R*)- and (4*S*, 5*S*)-**2**. (a) DMP, $CH_2Cl_2$, rt; (b) MeMgI, $Et_2O$, rt, then $H^+$, 74% from (*S*)-**4d**, syn:anti = 59:41; (c) vinyl acetate, Novozym 435, rt, (1*R*, 2*S*)-**8**: 55%; (2*S*, 3*S*)-**7**: 57%, syn:anti = <1:>99, >99% ee; (d) aq NaOH, EtOH, rt, 92%, syn:anti = 98:2, >99% ee; (e) vinyl acetate, Novozym 435, rt, 86%; syn:anti = >99:<1, >99% ee. (f) AcCl, pyridine, $CH_2Cl_2$, rt, 53%; (g) $RuCl_3$, $H_5IO_6$, $H_2O$, $CCl_4$, $CH_3CN$, 0 ºC to rt, (h) aq NaOH, rt, (i) aq HCl, rt, (4*S*, 5*R*)-**2**: 57% in three steps, cis:trans = <1:>99, ee: >99%; (4*S*, 5*S*)-**2**: 46% in three steps, cis:trans = >99:<1, ee: >99%.

**Table 1**

Amano PS-catalyzed transesterification of (±)-**4a** with vinyl acetate.

**Table 2**

Amano PS-catalyzed transesterification of (±)-**4b**-**h** with vinyl acetate in toluene.

**Table 3**

Olfactory evaluation of (*R*)- and (*S*)-**1a**-**h**.

**Table 4**

Olfactory evaluation of (±)-**1a**-**h**.

**Table 5**

Olfactory evaluation of **2**.

Highlights

• Optically active $\beta$-alkyl substituted $\gamma$-lactones and whiskey lactone analogues were synthesized.

• Good reaction conditions for the highly enantioselective esterification of 3-arylmethyl-2-methyl-1-propanols to kinetically resolve them were found.

• Alkyl groups on the $\gamma$-lactone rings played an important role for the odor properties.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: