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Asymmetric synthesis of enantiomerically pure zingerols by lipase-catalyzed transesterification and efficient synthesis of their analogues

Takashi Kitayama [a,*], Sachiko Isomori [a], Kaoru Nakamura [b]

[a] *Department of Advanced Bioscience, Graduate School of Agriculture, Kinki University, Nara 631-8505, Japan*
[b] *Graduate School of Human Development and Environment, Faculty of Human Development, Kobe University, Kobe 657-8501, Japan*

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ABSTRACT

The achiral zingerone **1**, readily available from ginger, can be easily transformed into chiral derivatives. Zingerol **2**, a reduced product of zingerone **1** is expected to be an important new medicinal lead compound. We have achieved a concise synthesis of optically active zingerol (*R*)-**2** and (*S*)-**2** by the lipase-catalyzed stereoselective transesterification of racemic **2**. Under the optimized conditions, a lipase from *Alcaligenes* sp. (Meito QLM) and vinyl acetate in *i*-Pr_2O or hexane at 35 °C within 1 h gave the alcohol (*S*)-**2** and the acetate (*R*)-**9** with high enantioselectivity without producing acetylated by-products. Since optically active (*S*)-**2** and (*R*)-**9** were obtained through lipase-catalyzed transesterification, other enantiomerically pure novel compounds could all be synthesized.

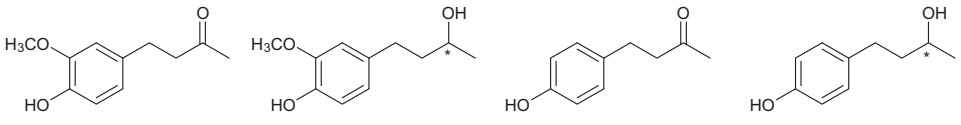
1. Introduction

The stereochemical aspects of optically active compounds often control biological function. The use of small chiral building blocks in the search for new biologically active molecules has great potential, since the range of derivatization would increase when the lead compound has a small compact frame. Since numerous natural products have reactive groups suitable for organic synthesis,[1,2] we have focused on comparatively small molecules that are readily available or easily obtained by derivatization of small natural products. Therefore, the synthesis of derivatives from biologically active natural products with a small compact frame as potential lead compounds is an important challenge.

Herein we focused on achiral 4-(4-hydroxy-3-methoxyphenyl)butan-2-one **1** (zingerone) from *Zingiber officinale*, an essential aromatic compound with a phenylbutane frame, showing various biological functions,[3,4] such as an activity that attracts a wide range of fruit fly species,[3] as shown in Scheme 1.

Zingerol **2**, a reduced product of **1**, inhibits colonic motility in rats[5] and shows the same biological activity as zingerone.[3] This is expected to play an important role as a novel medicinal lead compound. Moreover, the stereochemistry of **2** might affect the specific affinity for a target receptor or enzyme. For example, 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMPs) with a stereogenic secondary alcohol binding to a phenyl group, showed different biological activities for each different stereochemistry.[6,7]

Establishing an efficient method for synthesizing optically active zingerol **2** as a chiral building block is important in order to synthesize various derivatives and exploit them as tools of medicinal chemistry. Despite its very simple structure, synthetic methods for optically active zingerol **2** are not well known. (*R*)-Zingerol (*R*)-**2**, isolated from *Taxus baccata* by Das et al.,[8] has not yet been synthesized. Hamada et al. obtained (*S*)-zingerol (*S*)-**2** as



Scheme 1.

* Corresponding author. Fax: +81 742 43 8976.
E-mail address: kitayama@nara.kindai.ac.jp (T. Kitayama).

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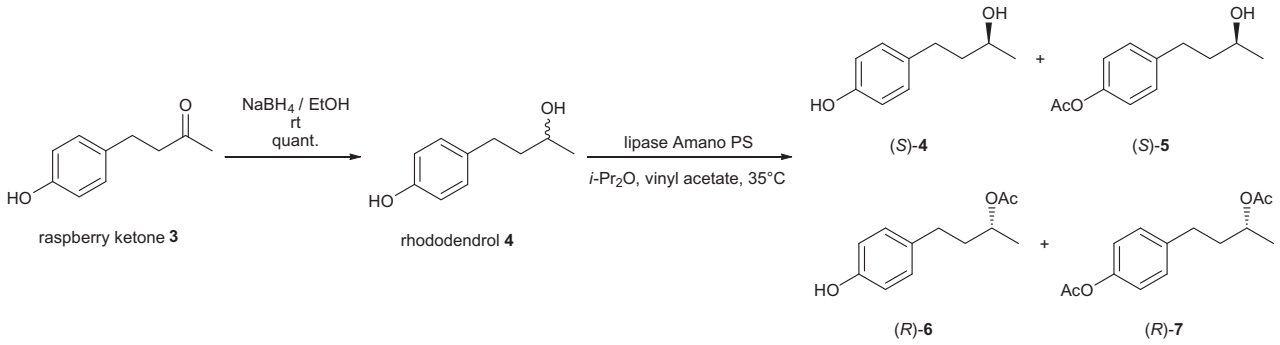
an intermediate in low yield via the asymmetric reduction of **1** using cultured cells of *Phytolacca americana*.[9] The precise determination of the specific rotation of these compounds has not yet been achieved.

Our previous studies[10,11] presented a guide for the selection of the solvent to be used in lipase-catalyzed high-enantioselective transesterifications. In the case of zerumbone derivatives with a medium cyclic compound, a hydrophobic solvent such as hexane, was recommended and exhaustive drying of the lipase of an *Alcaligenes* sp. (Meito QLM), acyl donor, and substrate gave rapid reactivity against lipase-catalyzed transesterification.[11] Therefore, we believe that the lipase-catalyzed transesterification of racemic **2** using our method is one of the best ways to obtain both enantiomers. Optically active rhododendrol **4**, a zingerol analogue, obtained by the reduction of 4-(4-hydroxyphenyl)butan-2-one **3** (raspberry ketone) which was isolated from *Rubus idaeus* and has the same framework as **1**, was obtained by lipase-catalyzed transesterification using *Pseudomonas fluorescens* (Amano PS) as the lipase.[12] The results showed that the reaction was very slow but that the stereoselectivity was reasonable. After this problem was resolved, the synthesis of (*R*)-zingerol and then the efficient production of (*S*)-zingerol using lipase-catalyzed transesterification were achieved and moreover, several novel optically active analogues were obtained. All of these structures are shown in Scheme 1.

2. Results and discussion

2.1. Optically active rhododendrol

Raspberry ketone **3** was reduced with sodium borohydride to afford racemic **4** in quantitative yield.[12] The lipase-catalyzed enantioselective transesterification of **4** was then investigated (Scheme 2).



Scheme 2.

Table 1 shows the results from the transesterification of racemic **4** with vinyl acetate in *i*-Pr_2O in the presence of Amano PS (runs 1, 2). The transesterification of **4** was monitored by gas chromatography (GC) using a capillary column (InertCap5) and the enantiomeric excess (ee) was also checked by GC using a capillary column (DEX-CB). Since the separation of the enantiomers of the alcohols was difficult, the alcohols were isolated and the ee of these products was determined after acetylation.

Yuasa et al.[12] showed that 96 h was required for the transesterification to achieve 50% conversion and to obtain the corresponding optically active compounds with high ee in run 1. In the case of zerumbone derivatives with a medium cyclic structure, exhaustive drying together with a hydrophobic solvent such as hexane, a substrate, vinyl acetate, and lipase Meito QLM gave rapid reactivity and excellent enantioselectivity for the lipase-catalyzed transesterification.[11] Of those tested in run 2, an exhaustive drying system was applied for the transesterification. The reaction rate and stereoselectivity increased markedly and the reaction time was shortened by approximately 8-fold compared to that in run 1. Our method for the medium cyclic compounds was also applicable to phenyl alkanol. A low water content in the reaction system might give advantageous reactivity and stereoselectivity for the transesterification. However, when hexane was used as a hydrophobic solvent, the reactivity and stereoselectivity did not change greatly compared with using *i*-Pr_2O as the solvent.

As shown in Table 2, the transesterification of **4** with two lipases, Meito QLM and lipase B from *Candida antarctica* (CAL-B), was studied in *i*-Pr_2O. The reaction rate was markedly increased using both lipases compared with Amano PS. Notably, the reaction finished in 10 min using CAL-B without generating any by-products, (*S*)-**5** and (*R*)-**7**; moreover the stereoselectivity was excellent. Lipase CAL-B gave the fastest reaction time, 10 min, and a high *E* value[13] of over 1000. The reaction was approximately 600-fold shorter than that in run 1 (Table 1) using Amano PS as the lipase.

When hexane was employed as a hydrophobic solvent, the reactivity and stereoselectivity using Meito QLM as a lipase did not show any major changes compared with using *i*-Pr_2O as the solvent, although the reactivity was markedly reduced using CAL-B as a lipase. This suggested that the steric structure at the active site of CAL-B was affected extensively by the solvent polarity. More-

Table 1
Kinetic resolution of racemic 4 by lipase-catalyzed transesterification using Amano PS

Run	Solvent	Time (h)	Conversion (%)[a]			
			(*S*)-**4** (% ee)	(*S*)-**5** (% ee)	(*R*)-**6** (% ee)	(*R*)-**7** (% ee)
1[b]	*i*-Pr_2O	96	42 (78)	7 (78)	42 (98)	9 (98)
2	*i*-Pr_2O	12	31 (99)	19 (99)	37 (98)	13 (98)
3	Hexane	12	55 (78)	1 (77)	32 (99)	12 (99)

[a] Determination of the quantity by GC.
[B] Ref. 12

Table 2
Kinetic resolution of racemic **4** by lipase-catalyzed transesterification using various lipases

Run	Lipase	Solvent	Time (h)	Conversion[a] (%)				*E* Value
				(*S*)-4 (% ee)	(*S*)-5 (% ee)	(*R*)-6 (% ee)	(*R*)-7 (% ee)	
1	Meito QLM	*i*-Pr_2O	1	43 (63)	19 (59)	28 (99)	10 (99)	—
2	Meito QLM	*i*-Pr_2O	2	34 (91)	19 (84)	32 (99)	15 (99)	—
3	Meito QLM	*i*-Pr_2O	5	36 (95)	15 (95)	28 (98)	21 (99)	—
4	Meito QLM	Hexane	5	27 (97)	23 (99)	22 (99)	28 (99)	—
5	CAL-B	*i*-Pr_2O	10 min	50 (>99)	0	50 (>99)	0	>1000
6	CAL-B	*i*-Pr_2O	1	40 (99)	4(99)	52 (79)	4 (72)	—
7	CAL-B	Hexane	10 min	92 (8)	0	8 (99)	0	—

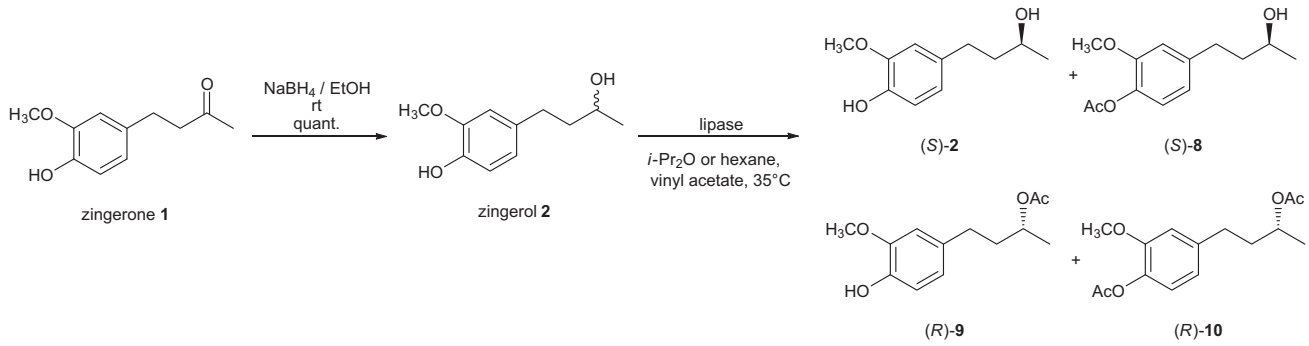
[a] Determination of the quantity by GC.

over, the acetylation seemed to proceed on the hydroxyl group at the stereogenic carbon stereoselectively and then on the phenolic hydroxyl group.

From the results of the screening experiments shown in Tables 1 and 2, we found that run 5 in Table 2 represented the optimum reaction conditions. A large-scale experiment using this system showed the same results as on a screening scale.

2.2. Optically active zingerol 2

Compound **1** was reduced with sodium borohydride to afford racemic **2** in quantitative yield.[14] The lipase-catalyzed kinetic transesterification of **2** was then investigated using Amano PS, Meito QLM, and CAL-B as lipases based on the above results, as shown in Scheme 3.



Scheme 3.

The transesterification of **2** was monitored by GC using a capillary column (InertCap5) and the conversion was assessed by GC. The ee of (*R*)-**9** and (*R*)-**10** were determined directly and those of (*S*)-**2** and (*S*)-**8** were determined after synthesizing the corresponding acetates by GC using a capillary column (CP-CD; CP-cyclodextrin-B-236-M-19). Surprisingly, compounds **8** and **9** with, simple structures, were novel compounds.

Of those tested in *i*-Pr_2O under an exhaustive drying system, the stereoselectivity of the lipase-catalyzed transesterification was higher using Meito QLM and CAL-B as was the transesterification of rhododendrol **4**, as shown in Table 3. The reactivity and stereoselectivity of the transesterification of **4** using Amano PS under the optimized conditions were almost the same as those for **2** without generating acetylated by-products **8** and **10**. CAL-B and Meito QLM gave a short reaction time and Meito QLM gave a good *E* value although CAL-B reduced the stereoselectivity. Under the optimized conditions, Meito QLM and vinyl acetate in *i*-Pr_2O or hexane at 35 °C within 1 h gave the alcohol (*S*)-**2** and the acetate (*R*)-**9**, with an *E* value of 300 without producing the acetylated by-products. When hexane was employed as the hydrophobic solvent, the reactivity and stereoselectivity were not improved using Amano PS and CAL-B compared with using *i*-Pr_2O as a solvent; however, Meito QLM showed a similar result when using hexane as the solvent. From these results, exhaustive drying in combination with a hydrophobic solvent such as *i*-Pr_2O and any lipases

Table 3
Kinetic resolution of racemic **2** by lipase-catalyzed transesterification using various lipases

Run	Lipase	Solvent	Time (h)	Conversion[a] (%)				*E* Value
				(*S*)-**2**(% ee)	(*S*)-**8** (% ee)	(*R*)-**9** (% ee)	(***R***)-**10** (% ee)	
1	AmanoPS	*i*-Pr_2O	4	53 (88)	0	47 (99)	0	600
2	AmanoPS	Hexane	4	66(51)	0	34 (99)	0	—
3	Meito QLM	*i*-Pr_2O	30 min	68 (46)	0	32 (99)	0	300
4	Meito QLM	*i*-Pr_2O	1	46 (91)	6 (91)	45 (99)	3 (99)	—
5	Meito QLM	Hexane	1	58 (59)	5 (59)	37 (99)	0	—
6	CAL-B	*i*-Pr_2O	10 min	52 (86)	0	48 (92)	0	70
7	CAL-B	*i*-Pr_2O	20 min	46 (95)	0	54 (80)	0	—
8	CAL-B	*i*-Pr_2O	1	41 (99)	0	59 (70)	0	—
9	CAL-B	Hexane	10 min	93 (7)	0	7 (99)	0	

[a] Determination of the quantity by GC.

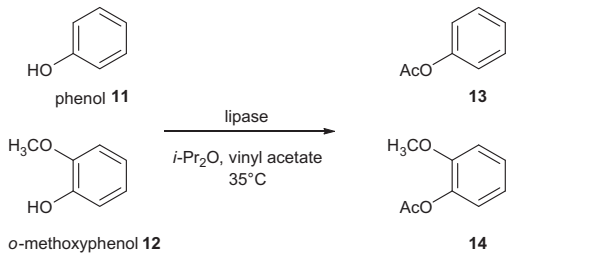
gave good results for stereoselectivity and reactivity of the lipase-catalyzed transesterification.

It should be noted that when Meito QLM was employed as the catalyst, the stereoselectivity and reactivity increased for zingerol. It is worth noting that the combination of Meito QLM and hexane with exhaustive drying gave the desired effect on the stereoselectivity and reactivity of the phenylbutane derivative with a chain structure during lipase-catalyzed transesterification as well as zerumbone with a medium cyclic structure; it was confirmed that our method[11] can be applied to various structures.

From the results of the screening experiment shown in Table 3, we found that run 3 represented the optimum conditions. A large-scale experiment using this system showed the same results as on the screening scale.

The transesterification of **2** produced a less acetylated by-product than that of **4**, perhaps due to the steric hindrance or electronic efficiency of the 3′-methoxy group. Lipase-catalyzed transesterification of phenol **11** and *o*-methoxyphenol **12**, to give acetates **13** and **14**, using three lipases was studied in an effort to elucidate the reactivity of the acetylation in the presence of the 3′-methoxy group on the phenolic frame, as shown in Table 4.

Table 4
Transesterification of phenol and *o*-methoxyphenol using various lipases



Run	Substrate	Lipase	Time (h)	Conversion[a] (%)	
				13	**14**
1	**11**	AmanoPS	2	5	—
2	**12**	Amano PS	4	—	5
3	**11**	Meito QLM	2	20	—
4	**12**	Meito QLM	2	—	11
5	**11**	CAL-B	4	5	
6	**12**	CAL-B	24	—	0

[a] Determination of the quantity by GC.

The transesterification of the secondary alcohol was faster than that of the phenolic alcohol while the esterification of *o*-methoxyphenol was slower than that of phenol. The *o*-methoxy group reduced the rate of acetylation. The relative reactivity for the lipase-catalyzed transesterification of **11** and **12** was almost the same as that for **4** and **2**, respectively. This result suggested that the butyl group in **2** or **4** did not affect the esterification of the phenolic alcohol and that the acetylation proceeded independently regardless of the type of lipase.

Since enantiomerically pure (*S*)-**2** and (*R*)-**9** were obtained through lipase-catalyzed transesterification using adequate conditions, as shown in Table 3, we attempted to synthesize their derivatives (*R*)-**2**, (*R*)- and (*S*)-**8**, (*S*)-**9**, and (*R*)- and (*S*)-**10**. As shown in Scheme 4, a mixture of (*S*)-**2**, 1 or 5 equiv of acetic anhydride, and several drops of pyridine was stirred at room temperature for 20 min or 1 h to afford (*S*)-**8** and (*S*)-**10** in 83% and 80% yield, respectively. A powdered form of K_2CO_3 was added to (*S*)-**10** in MeOH and the mixture was stirred at room temperature for 4 h to afford (*S*)-**9** quantitatively. Acetylation of the phenolic hydroxide was faster than that of the normal hydroxide and hydrolysis proceeded at the phenolic position. Since enantiomerically pure (*S*)-**2** and (*R*)-**9** were obtained through lipase-catalyzed transesterification, all enantiomerically pure compounds, (*R*)-**2**, (*R*)- and (*S*)-**8**, (*S*)-**9**, (*R*)- and (*S*)-**10**, could be synthesized using this method.

2.3. Absolute configuration

The absolute configuration of (*R*)-[8] and (*S*)-[9]zingerol **2** and their specific optical rotation have been reported . The synthesis and determination of the absolute configuration of (*S*)- and (*R*)-**8**, (*S*)- and (*R*)-**9**, and (*S*)- and (*R*)-**10** were achieved by a combination of reactions using (*S*)-**2** and (*R*)-**9** as the starting materials as shown in Scheme 4.

3. Conclusion

The enantiomerically pure zingerols (*R*)-**2** and (*S*)-**2** were synthesized by the lipase-catalyzed stereoselective transesterification of racemic **2**. Under the optimized conditions, Meito QLM and vinyl acetate in *i*-Pr_2O at 35 °C for 30 min gave (*S*)-**2** and (*R*)-**9** with *E* values of over 1000 without producing acetylated by-products. It is worth noting that the combination of Meito QLM and hexane with exhaustive drying had the desired effect on the stereoselectivity and reactivity of phenylbutane derivatives with a chain structure during lipase-catalyzed transesterifications. Since enantiomerically pure (*S*)-**2** and (*R*)-**9** were obtained through lipase-catalyzed transesterification, the enantiomerically pure derivatives (*R*)-**2**, (*R*)- and (*S*)-**8**, (*S*)-**9**, (*R*)- and (*S*)-**10** could be synthesized and could be employed as chiral building blocks with a small molecular framework. An efficient route to optically active zingerol **2** and its derivatives was achieved enantioselectively by lipase-catalyzed transesterification using Meito QLM and vinyl acetate in an *i*-Pr_2O system under exhaustive drying. This opens up a route to using this readily available small molecule as a starting material for conversion to useful chiral products.

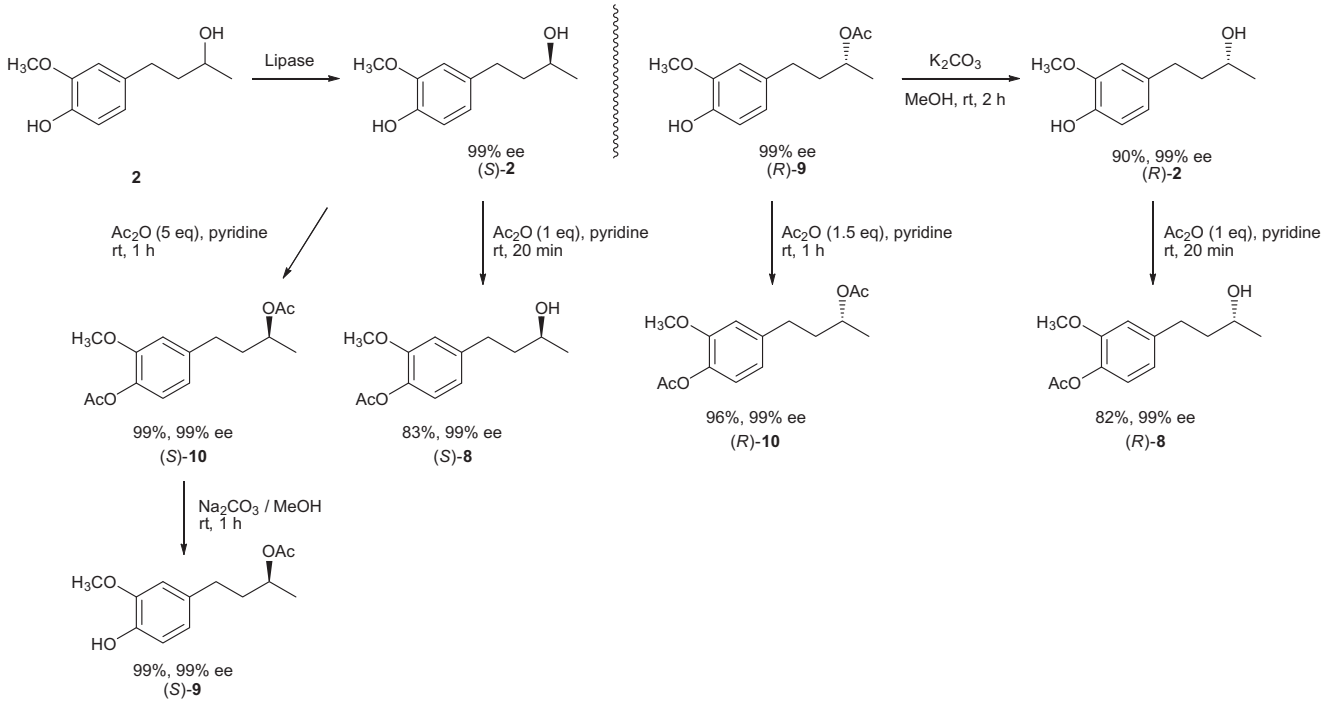
4. Experimental

4.1. General

Column chromatography was performed on silica gel (70–230 mesh). TLC was performed on Merck 60 F254 silica gel plates. GC data were recorded on a Shimadzu GC-2010. The enantiomeric excess (ee) values were determined by chiral GC (CHROMPACK, CP-CD; CP-cyclodextrin-B-236-M-19 and DEX-CB). NMR spectra were recorded on a Bruker instrument at 400 MHz for ^1H, and 100 MHz for ^{13}C in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) are reported in ppm from TMS. Infrared spectra were recorded on a Shimadzu FRIR-8200D spectrophotometer. Mass spectra were recorded at 70 eV, and high-resolution mass spectra (HRMS) were obtained by direct injection. Optical rotations were measured on a JASCO DIP-140 polarimeter. Chemicals were of commercially available reagent grade, and used without further purification.

4.2. Preparation of substrates, racemic zingerol 2

Zingerone **1** (1.0 g, 5.3 mmol) in MeOH (2 mL) was added to the suspension of $NaBH_4$ (150 mg, 3.9 mmol) in MeOH (1 mL) and stirred at room temperature for 2.5 h. After consumption of the substrate, H_2O (10 mL) was added to the reaction mixture. The aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated on a rotary evap-



Scheme 4.

orator to obtain a white solid. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded racemic **2** quantitatively as a white solid. Structural data were confirmed when compared with known data.[14]

4.3. Preparation of substrate, racemic rhododendrol 4

Raspberry ketone **3** (1.0 g, 6.2 mmol) in MeOH (2 mL) was added to a suspension of $NaBH_4$ (180 mg, 4.6 mmol) in MeOH (1 mL) and stirred at room temperature for 2 h. After consumption of the substrate, H_2O (10 mL) was added to the reaction mixture. The aqueous solution was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to obtain a white solid. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded racemic **4** quantitatively as a white solid. Structural data were confirmed when compared with known data.[12]

4.4. General procedure for the lipase-catalyzed transesterification of rhododendrol 4

After exhaustive drying of THF, substrate, and lipase under 0.1 mmHg conditions, substrate **4** (50 mg, 0.30 mmol), vinyl acetate (38.7 mg, 0.45 mmol), and the lipase (dry CAL-B, 25 mg) in *i*-Pr_2O (0.75 mL) with molecular sieves 4 Å were stirred for approximately 10 min at 35 °C until the conversion was approximately 50%. The reaction mixture was filtered and the filtrate was concentrated. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*S*)-rhododendrol (*S*)-**4**, and (*R*)-4-(4′-hydroxyphenyl)-2-butyl acetate (*R*)-**6** in 50 and 50% yield, respectively. (*S*)-4-(4′-Acetyloxyphenyl)-2-butanol (*S*)-**5**, and (*R*)-4-(4′-acetyloxyphenyl)-2-butyl acetate (*R*)-**7** were obtained under other conditions of lipase-catalyzed transesterification, as shown in Table 2, and purified by silica gel column chromatography using a 4:1 mixture of hexane and ethyl acetate as the eluent.

The reaction was followed by GC using a column of InertCap5 (detector and injection temperature, 200 °C; column temperature, 170 °C; carrier gas, He; linear velocity: 30 cm/s, FID detector). Under these conditions, the retention times of **4**, **5**, **6,** and **7** were 7.6, 10.9, 11.8, and 17.2 min, respectively. The enantiomeric excess of **6** and **7** were determined directly and those of **4** and **5** were determined after synthesizing the corresponding acetates by GC using a column of DEX-CB (detector and injection temperature, 200 °C; column temperature, 160 °C; carrier gas He; linear velocity: 30 cm/s, FID detector). Under these conditions, the retention times of (*R*)- and (*S*)-**4**, (*R*)- and (*S*)-**5**, (*R*)-**6**, (*S*)-**6**, (*R*)-**7**, and (*S*)-**7** were 11.0, 8.1, 13.6, 13.1, 8.8, and 8.3 min, respectively. Structural data were confirmed by being compared with known data.[12]

4.5. General procedure for the lipase-catalyzed transesterification of rhododendrol 4 on a gram scale

After exhaustive drying of THF, substrate, and lipase under 0.1 mmHg conditions, substrate **4** (5.00 g, 30.0 mmol), vinyl acetate (3.87 g, 45.0 mmol), and the lipase (dry CAL-B, 2.50 g) in *i*-Pr_2O (75.0 mL) with molecular sieves 4 Å were stirred for approximately 10 min at 35 °C until the conversion was approximately 50%. The reaction was followed by GC using a column of InertCap5 and ee was determined by GC using a column of DEX-CB. The reaction mixture was filtered and the filtrate was concentrated. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*S*)-rhododendrol (*S*)-**4** and (*R*)-4-(4′-hydroxyphenyl)-2-butyl acetate (*R*)-**6** in 50% and 50% yield, and 97% and 98% ee, respectively.

4.5.1. (*S*)-Rhododendrol (*S*)-4

$[\alpha]_D^{24} = +16.9$ (*c* 0.896, EtOH) 99% ee, $[\alpha]_D^{24} = +12.7$ (*c* 1.10, EtOH) 79% ee.[12] ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, $J = 6.2$ Hz, CH_3 at C1), 1.64 (s, 1H, OH at C2), 1.71–1.78 (m, 2H, CH_2 at C3), 2.57–2.71 (m, 2H, CH_2 at C4), 3.83 (m, 1H, CH at C2), 4.99 (s, 1H, OH at Ar), 6.75 (ddd, 2H, $J = 8.5$, 4.4, and 0.1 Hz, H at C3′ and C5′), 7.00 (ddd, 2H, $J = 8.5$, 4.4, and 0.1 Hz, H at C2′ and C6′).

4.5.2. (*S*)-4-(4′-Aacetyloxyphenyl)-2-butanol (*S*)-5

$[\alpha]_D^{24} = +15.8$ (*c* 0.632, EtOH) 99% ee, $[\alpha]_D^{24} = +14.4$ (*c* 1.32, EtOH) 79% ee.[12] ^{1}H NMR ($CDCl_3$): δ 1.23 (d, 3H, *J* = 6.2 Hz, CH_3 at C1), 1.73–1.79 (m, 2H, CH_2 at C3), 2.29 (s, 3H, CH_3 at $COCH_3$), 2.63–2.79 (m, 2H, CH_2 at C4), 3.84 (m, 1H, CH at C2), 6.99 (ddd, 2H, *J* = 8.5, 4.4, and 0.1 Hz, H at C3′ and C5′), 7.20 (ddd, 2H, *J* = 8.5, 4.4, and 0.1 Hz, H at C2′ and C6′).

4.5.3. (*R*)-4-(4′-Hydroxyphenyl)-2-butyl acetate (*R*)-6

$[\alpha]_D^{24} = +2.3$ (*c* 0.963, EtOH) 98% ee, $[\alpha]_D^{24} = +2.1$ (*c* 1.42, EtOH) 98% ee.[12] ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H, *J* = 6.3 Hz, CH_3 at C1), 1.71–1.94 (m, 2H, CH_2 at C3), 2.03 (s, 3H, $OCOCH_3$ at C2), 2.50–2.64 (m, 2H, CH_2 at C4), 4.91 (m, 1H, CH at C2), 6.75 (ddd, 2H, *J* = 8.5, 4.6, and 0.2 Hz, H at C3′ and C5′), 7.03 (ddd, *J* = 8.5, 4.6, and 0.2 Hz, 2H, H at C2′ and C6′).

4.5.4. (*R*)-4-(4′-Acetyloxyphenyl)-2-butyl acetate (*R*)-7

$[\alpha]_D^{24} = +8.6$ (*c* 0.244, EtOH) 99% ee), $[\alpha]_D^{24} = +6.1$ (*c* 1.64, EtOH) 98% ee.[12] ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H, *J* = 6.3 Hz, CH_3 at C1), 1.74–1.96 (m, 2H, CH_2 at C3), 2.02 (s, 3H, $OCOCH_3$ at C2), 2.28 (s, 3H, $OCOCH_3$ at Ar), 2.56–2.70 (m, 2H, CH_2 at C4), 4.93 (m, 1H, CH at C2), 6.99 (ddd, 2H, *J* = 8.5, 4.5, and 0.1 Hz, H at C3′ and C5′), 7.17 (ddd, 2H, *J* = 8.5, 4.5, and 0.1 Hz, H at C2′ and C6′).

4.6. General procedure of lipase-catalyzed transesterification of zingerol 2

After exhaustive drying of THF, substrate, and lipase under 0.1 mmHg conditions, substrate **2** (50 mg, 0.26 mmol), vinyl acetate (33.5 mg, 0.39 mmol), and the lipase (dry MeitoQLM, 25 mg) in *i*-Pr_2O (0.75 mL) with molecular sieves 4 Å were stirred for approximately 30 min at 35 °C. The reaction mixture was filtered and the filtrate was concentrated. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*S*)-zingerol ((*S*)-**2**) and (*R*)-4-(4′-hydroxy-3′-methoxyphenyl)-2-butyl acetate (*R*)-**9** in 68 and 32% yield, respectively. (*S*)-4-(4′-Acetyloxy-3′-methoxyphenyl)-2-butanol (*S*)-**8** and (*R*)-4-(4′-acetyloxy-3′-methoxyphenyl)-2-butyl acetate (*R*)-**10** were obtained under other conditions of lipase-catalyzed transesterification, as shown in Table 3, and purified by silica gel column chromatography using a 4:1 mixture of hexane and ethyl acetate as an eluent.

The reaction was followed by GC using a column of InertCap5 (detector and injection temperature, 220 °C; column temperature, 170 °C; carrier gas, He; linear velocity: 30 cm/s, FID detector). Under these conditions, the retention times of **2**, **8**, **9** and **10** were 8.8, 15.4, 12.9, and 22.9 min, respectively. The enantiomeric excess of **9** and **10** were determined directly and those of **2** and **8** were determined after synthesizing the corresponding acetates by GC using a column of CP-CD (detector and injection temperature, 200 °C; column temperature, 160 °C; carrier gas He; linear velocity: 30 cm/s, FID detector). Under these conditions, the retention times of (*R* and *S*)-**2**, (*R* and *S*)-**8**, (*R*)-**9**, (*S*)-**9**, (*R*)-**10**, and (*S*)-**10** were 33, 68, 40, 39, 80, and 78 min, respectively.

4.7. General procedure for the lipase-catalyzed transesterification of zingerol 2 on a gram scale

After exhaustive drying of THF, substrate, and lipase under 0.1 mmHg conditions, substrate **2** (5.00 g, 26.0 mmol), vinyl acetate (3.35 g, 39.0 mmol), and the lipase (dry MeitoQLM, 2.50 g) in *i*-Pr_2O (75.0 mL) with molecular sieves 4 Å were stirred for approximately 30 min at 35 °C. The reaction was followed by GC using a column of InertCap5 and the ee was determined by GC using a column of CP-CD. The reaction mixture was filtered and the filtrate was concentrated. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*S*)-**2** and (*R*)-**9** in 67 and 33% yield, and 46% and 99% ee, respectively. Enantiomerically pure (*S*)-**2** was obtained after same treatment with the above method under other conditions of lipase-catalyzed transesterification using Meito QLM or CAL-B as shown in Table 3.

4.8. Hydrolysis of (*R*)-9

Compound (*R*)-**9** in MeOH (1 mL) was added to K_2CO_3 (188 mg, 1.36 mmol) and stirred at room temperature for 2 h. Next, H_2O (10 mL) was added to the reaction mixture. The aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to obtain a colorless oil. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*R*)-**2** in 90% yield.

4.9. Acetylation of (*S*)-2

A mixture of (*S*)-**2** (71 mg, 0.36 mmol), 1 and 5 equiv of acetic anhydride, and several drops of pyridine was stirred at room temperature for 20 min and 60 min. The progress of the acetylation was monitored by TLC. After consumption of the substrate, H_2O (10 mL) was added to the reaction mixture. The aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution (3 × 30 mL) and brine (3 × 30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to obtain a colorless oil. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*S*)-**8** and (*S*)-**10** in 83% and 99% yield, respectively.

4.10. Acetylation of (*R*)-2

A mixture of (*R*)-**2** (71 mg, 0.36 mmol), 1 equiv of acetic anhydride, and several drops of pyridine was stirred at room temperature for 20 min. The progress of the acetylation was monitored by TLC. After consumption of the substrate, H_2O (10 mL) was added to the reaction mixture. The aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3 × 30 mL) and brine (3 × 30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to obtain a colorless oil. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*R*)-**8** in 82% yield.

4.11. Acetylation of (*R*)-9

A mixture of (*R*)-**9** (107 mg, 0.45 mmol), 1.5 equiv. of acetic anhydride, and several drops of pyridine was stirred at room temperature for 1 h. The progress of the acetylation was monitored by TLC. After consumption of the substrate, H_2O (10 mL) was added to the reaction mixture. The aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3 × 30 mL) and brine (3 × 30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to obtain a colorless oil. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*R*)-**10** in 96% yield.

4.12. Hydrolysis of (*S*)-10

A powder of Na_2CO_3 (97.9 mg, 0.90 mmol) was added to (*S*)-**10** (87.1 mg, 0.30 mmol) in MeOH and the mixture was stirred at room temperature for 4 h. After consumption of the substrate, H_2O (10 mL) was added to the reaction mixture. The aqueous solution was extracted with ethyl acetate (3 × 10 mL). The

combined organic extracts were washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to obtain a colorless oil. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and ethyl acetate, afforded (*S*)-**9** quantitatively.

4.13. Zingerol (*S*)- and (*R*)-2

(*S*)-**2**: $[\alpha]_D^{24} = +14.1$ (*c* 0.91, EtOH) 99% ee, $[\alpha]_D^{24} = +10.4$ (*c* 0.29, EtOH) ee: unknown.[8] (*R*)-**2**: $[\alpha]_D^{24} = -15.1$ (*c* 1.10, EtOH,) 99% ee, $[\alpha]_D^{25} = -16.3$ (*c* 0.26, EtOH) ee: unknown.[8] IR: 3502, 2964, 1764 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22 (d, 3H, *J* = 6.2 Hz, H at C1), 1.71–1.77 (m, 2H, H at C3), 2.60–2.69 (m, 2H, H at C4), 3.81–3.86 (m, 1H, H at C2), 3.86 (s, 3H,OCH_3 at Ar), 5.62 (br s, 1H, OH), 6.68 (dd, 1H, *J* = 2.0 and 7.9 Hz, H at C6′), 6.70 (d, 1H, *J* = 2.1, H at C2′), 6.82 (d, 1H, *J* = 7.9 Hz, H at C5′). ^{13}C NMR ($CDCl_3$): δ 23.6 (C1), 31.8 (C4), 41.1 (C3), 55.8 (OCH_3), 67.5 (C2), 110.0 (C2′), 114.3 (C5′), 120.8 (C6′), 133.9 (C1′), 143.7 (C4′), 146.4 (C3′). HRMS (M+Na^+) *m*/*z* calcd mass for $C_{11}H_{16}O_3Na$ 219.0997, found: 219.1023.

4.13.1. (*S*)-4-(4′-Acetyloxy-3′-methoxyphenyl)-2-butanol, (*S*)- and (*R*)-8

IR: 3502, 2964, 1764 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (d, 3H, *J* = 6.2 Hz, H at C1), 1.74–1.80 (m, 2H, H at C3), 2.31 (s, 3H, $OCOCH_3$ at Ar), 2.62–2.79 (m, 2H, H at C4), 3.82 (s, 3H,OCH_3 at Ar), 3.86 (m, 1H, H at C2), 6.77 (dd, 1H, *J* = 1.8 and 8.0 Hz, H at C6′), 6.80 (d, 1H, *J* = 1.8, H at C2′), 6.92 (d, 1H, *J* = 8.0 Hz, H at C5′).

^{13}C NMR ($CDCl_3$): δ 20.6 ($OCOCH_3$), 23.6 (C1), 32.0 (C4), 40.7 (C3), 55.7 (OCH_3), 67.3 (C2), 112.5 (C2′), 120.4 (C6′), 122.4 (C5′), 137.6 (C4′), 141.1 (C1′), 150.7 (C3′), 169.2 ($OCOCH_3$). HRMS (M + Na^+) *m*/*z* calcd mass for $C_{13}H_{18}O_4Na$ 261.1103, found: 261.1098. (*S*)-**8**: $[\alpha]_D^{24} = +12.9$ (*c* 0.97, EtOH) 99% ee, (*R*)-**8**: $[\alpha]_D^{24} = -13.9$ (*c* 0.84, EtOH) 99% ee.

4.13.2. 4-(4′-Hydroxy-3′-methoxyphenyl)-2-butyl acetate, (*S*)- and (*R*)-9

IR: 3431, 2937, 1730 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (d, 3H, *J* = 6.3 Hz, CH_3 at C1), 1.71–1.95 (m, 2H, CH_2 at C3), 2.04 (s, 3H, $OCOCH_3$ at C2), 2.50–2.64 (m, 2H, CH_2 at C4), 3.88 (s, 3H, OCH_3 at Ar), 4.94 (m, 1H, CH at C2), 6.65 (dd, 1H, *J* = 2.0 and 8.2 Hz, H at C6′), 6.67 (br, 1H, H at C2′), 6.83 (d, 1H, *J* = 8.3 Hz, H at C5′).

^{13}C NMR ($CDCl_3$): δ 20.0 (C1), 21.3 ($OCOCH_3$), 31.5 (C4), 37.9 (C3), 55.8 (OCH_3), 70.5 (C2), 110.9 (C2′), 114.3 (C5′), 120.8 (C6′), 133.4 (C1′), 143.7 (C4′), 146.4 (C3′), 170.8 ($OCOCH_3$). HRMS (M+Na^+) *m*/*z* calcd mass for $C_{13}H_{18}O_4Na$ 261.1103, found: 261.1101. (*S*)-**9**: $[\alpha]_D^{24} = -1.3$ (*c* 1.14, EtOH) 99% ee; (*R*)-**9**: $[\alpha]_D^{24} = +1.7$ (*c* 1.00, EtOH) 99% ee.

4.13.3. 4-(4′-Acetyloxy-3′-methoxyphenyl)-2-butyl acetate, (*S*)- and (*R*)-10

IR: 2977, 2937, 1764, 1733 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (d, 3H, *J* = 6.2 Hz, H at C1), 1.75–1.98 (m, 2H, H at C3), 2.04 (s, 3H, $OCOCH_3$ at C2), 2.30 (s, 3H, $OCOCH_3$ at Ar), 2.55–2.70 (m, 2H, H at C4), 3.82 (s, 3H, OCH_3 at Ar), 4.96 (m, 1H, H at C2), 6.74 (dd, 1H, *J* = 1.5 and 8.0 Hz, H at C6′), 6.77 (d, 1H, *J* = 1.6, H at C2′), 6.93 (d, 1H, *J* = 8.0 Hz, H at C5′). ^{13}C NMR ($CDCl_3$): δ 20.1 (C1), 20.7 (Ar-$OCOCH_3$), 21.4 ($CHOCOCH_3$), 31.8 (C4), 37.5 (C3), 55.8 (OCH3), 70.1 (C2), 112.5 (C2′), 120.3 (C6′), 122.5 (C5′), 137.8 (C4′), 140.5 (C1′), 150.8 (C3′), 169.3 (Ar-$OCOCH_3$), 170.8 ($CHOCOCH_3$). HRMS (M+Na^+) *m*/*z* calcd mass for $C_{15}H_{20}ONa$ 303.1208, found 303.1201. (*S*)-**10**: $[\alpha]_D^{24} = -3.9$ (*c* 0.96, EtOH) 99% ee, (*R*)-**10**: $[\alpha]_D^{24} = +4.8$ (*c* 1.00, EtOH) 99% ee.

4.14. General procedure for the lipase-catalyzed transesterification of phenol 11 or *o*-methoxyphenol 12

After exhaustive drying of THF, substrate, and lipase under 0.1 mmHg conditions, substrate **11** (50 mg, 0.53 mmol) or **12** (50 mg, 0.40 mmol), vinyl acetate (33.5 mg, 0.39 mmol), and the lipase (dry MeitoQLM, 25 mg) in *i*-Pr_2O (0.75 mL) with molecular sieves 4 Å were stirred for approximately 30 min at 35 °C. The reaction was followed by GC using a column of DB5 (detector and injection temperature, 280 °C; column temperature, 100 °C; carrier gas, He; linear velocity: 30 cm/s, FID detector). Under these conditions the retention times of **11**, **12**, **13,** and **14** were 3.6, 5.8, 5.1, and 14.0 min, respectively. Conversion was assessed by GC.

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