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Facile preparation of methyl 5-aryl-4-hydroxyhex-2(*E*)-enoate, chiral synthon of bisabolane-type sesquiterpenes, based on lipase-catalyzed kinetic resolution and rearrangement of an aryl group

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ABSTRACT

The lipase-catalyzed enantioselective acetylation of racemic methyl (4*S**,5*S**)-4-aryl-5-hydroxyhex-2(*E*)-enoates **1a**–**h** was performed and efficient resolutions were achieved (*E* >400) by using CAL-B. After brosylation of the obtained optically active **1a**–**h**, solvolysis of brosylates **13a**–**h** afforded the corresponding methyl (4*S**,5*S**)-5-aryl-4-hydroxyhex-2(*E*)-enoates **3a**–**h** (26–94% yield). The yields of **3a** and **3c** on the solvolysis of the corresponding **13** were 92% and 40%, respectively, while solvolysis of the corresponding tosylate was reported at 70% and 17%, respectively. This procedure is a facile and practical route to the synthesis of bioactive and optically active bisabolane-type sesquiterpenes.

1. Introduction

Optically active methyl (4*S**,5*S**)-4-aryl-5-hydroxyhex-2(*E*)-enoates **1** are considered as important chiral building blocks for the synthesis of natural products, especially bisabolane-type sesquiterpene, since the stereoselective rearrangement of the aryl group of tosylate **2** to optically active methyl (4*S**,5*S**)-5-aryl-4-hydroxyhex-2(*E*)-enoates **3** via a phenonium ion has been developed (Scheme 1).[1–3] Due to the antifungal and antitumor activity of bisabolane-type sesquiterpenes, such as xanthorrizol **4**,[4,5] curcuquinone **5**, curcuphenol **6**, curcudiol **7**,[6] and curcumene **8**,[7] much attention has been paid to their synthesis (Fig. 1). For example, Fuganti and Serra reported the synthesis of (+)-xanthorrizol (+)-**4**, (+)-curcuquinone (+)-**5**, and (+)-curcuphenol (+)-**6** based on bakers' yeast reduction of α,β-unsaturated aldehyde.[8] Manatti and Döts demonstrated the asymmetric synthesis of (−)-curcuquinone (−)-**5** involving a regioselective [3+2+1]-benzannulation reaction and Sharpless epoxidation.[9] Kamal et al. reported the chemoenzymatic syntheses of curcuphenol and curcumene using lipase-catalyzed optical resolution of ethyl 3-arylbutanoate.[10]

Previously, we reported the lipase-catalyzed enantioselective hydrolysis of (4*S**,5*S**)-methyl 5-acetyl-4-arylhex-2(*E*)-enoate **9**, but failed to resolve the enantiomers effectively.[11] To obtain optically active **1**, synthetic methods by way of optically active (4*S**,5*S**)-methyl 4,5-epoxyhex-2(*E*)-enoate **10** as a chiral synthon from *rac*-**10** were developed (Scheme 2).[12,13] Acetate *rac*-**11** obtained from *rac*-**10** was subjected to lipase-catalyzed enantioselective hydrolysis by lipase P to give (4*S*,5*S*)-**11** and (4*R*,5*R*)-**12**. Then, recovered (4*S*,5*S*)-**11** was hydrolyzed to (4*S*,5*S*)-**12**. Both enantiomers of **12** were converted to corresponding optically active **10**, after which **10** was treated with aromatic compounds bearing an electron-donating group in the presence of boron trifluoride ether complex to afford optically active **1**. Furthermore, in the synthetic application of **1**, both enantiomers of bisabolane-type sesquiterpenes such as curcudiol **7** and curcumene **8** were synthesized from optically active **1**. However, direct resolution of *rac*-**1** is desired for the practical and efficient synthesis of the bisabolane-type sesquiterpenes.

Herein we report the direct resolution of *rac*-**1** by *Candida antarctica* lipase B (CAL-B) and improvements in the rearrangement of optically active **1** via phenonium ion to chiral synthon **3** for the synthesis of bisabolane-type sesquiterpenes.

2. Results and discussion

2.1. Preparation of 1

Substrates **1a**–**h** for the lipase-catalyzed kinetic resolution were prepared from *rac*-**10** and anisole derivatives in the presence of $BF_3{\cdot}Et_2O$ by following the reported procedure;[3] the yields of **1a**–**h** are shown in Scheme 3.

2.2. Kinetic resolution of 1

Initially several lipases were investigated for stereoselectivity in the transesterification against *rac*-**1a** since normally sterically hindered substrates around the active site of the lipase were not found to be suitable. As a result, CAL-B was found to convert (4*R*,5*R*)-**1a** to

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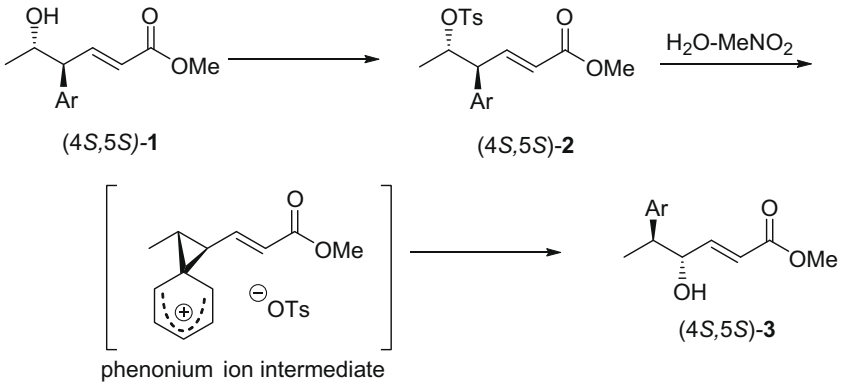


Scheme 1.

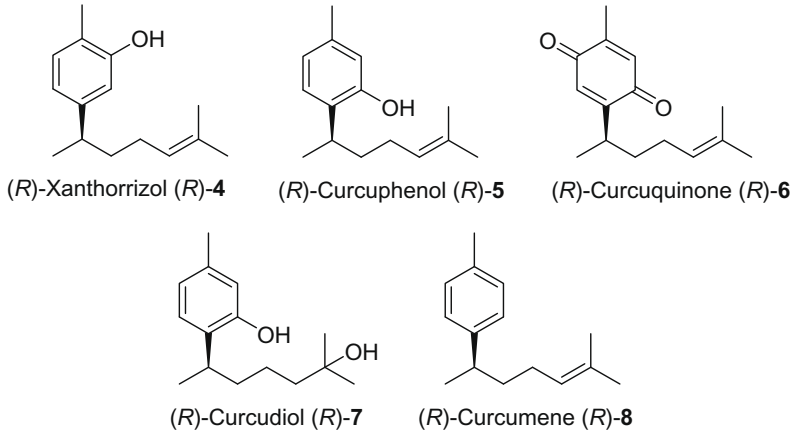
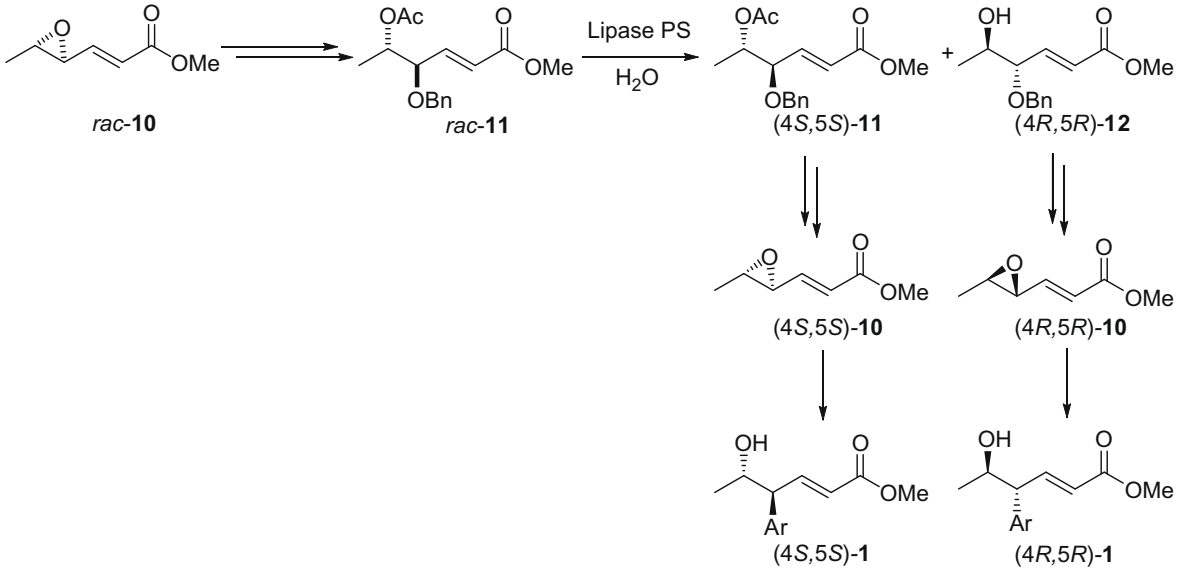
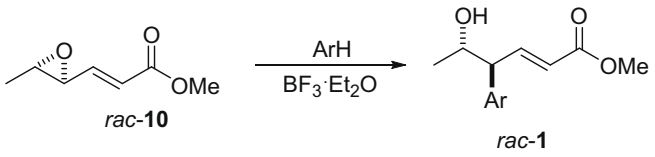


Figure 1. Structures of typical bisabolane-type sesquiterpenes.



Scheme 2.

the corresponding acetate (4*R*,5*R*)-**9a** stereoselectively. CAL-B (200 mg) and *rac*-**1a** (1.0 g) in vinyl acetate (10 mL) were stirred for 3 days at 25 °C, after which (4*R*,5*R*)-**9a** was obtained in 49% yield and 99.8% ee; recovered (4*S*,5*S*)-**1a** was obtained in 50% yield and >99.9% ee (Table 1, entry 1). While lipases Amano AK and Amano PS catalyzed the reaction, the conversions after 2 weeks were only 23% and 6.8%, respectively. The absolute configuration of (4*S*,5*S*)-**1a** from the CAL-B-catalyzed reaction was determined by



Ar = 4-MeOPh **1a**: 72%
Ar = 2-MeO-4-MePh **1b**: 34%,
2-Me-4-MeOPh **1c**: 45%
Ar = 3-Me-4-MeOPh **1d**: 64%
Ar = 2-MeO-5-MePh **1e**: 80%
Ar = 2,5-$(MeO)_2$Ph **1f**: 72%
Ar = 3,4-$(MeO)_2$Ph **1g**: 92%
Ar = 2,5-$(MeO)_2$-4-Me-Ph **1h**: 71%

Scheme 3.

comparison of the specific rotation ($[\alpha]_D$ = +21.2) with the reported value ($[\alpha]_D$ = +21.3);[2] the *E*-value of the reaction was over 1000. The recognition of the stereocenter at the 5′-position of the reaction against **1a** was similar to the empirical rule for the kinetic resolution of the secondary alcohols (Fig. 2).[14] The recovered lipase was reused for the next reaction and similar results were obtained as shown in Table 1 (entry 2).

The reaction was then demonstrated on a large scale. When 40.5 g of *rac*-**1a** was treated with 3.0 g of lipase CAL-B in 400 mL of vinyl acetate for 7 days, 20.1 g (49.6%) of (4*S*,5*S*)-**1a** was recovered in >99.9% ee and 22.5 g (48%) of (4*R*,5*R*)-**9a** was obtained in 99.9% ee. Methanolysis of (4*R*,5*R*)-**9a** by CAL-B in diisopropylether and methanol afforded (4*R*,5*R*)-**1a** in 93% yield and >99.9% ee (Scheme 4).

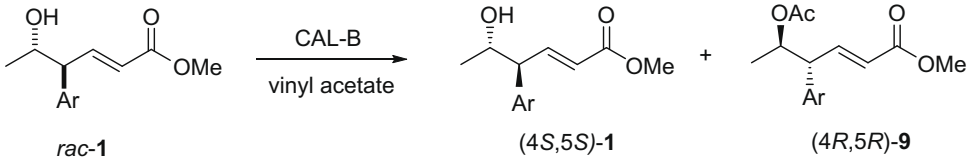
Next, several methyl 4-aryl-5-hydroxyhex-2(*E*)-enoates **1b**–**h** were subjected to enzymatic resolution, and the corresponding acetates **9b**–**h** and remaining alcohols **1a**–**h** were obtained in high yields with excellent ees as shown in Table 1. The *E*-values of the kinetic resolution in Table 1 were over 417 in every case.

The preparation of optically active **1** from *rac*-**10** had required seven steps for (4*R*,5*R*)-**1** and eight steps for (4*S*,5*S*)-**1** in the previous method, but the present method shortened the procedure to three and two steps, respectively.[15]

2.3. Rearrangement of 1 to 3

Previously, we reported the solvolysis of tosylate **2** to afford rearranged product **3** via phenonium ion.[3] However, the reaction took an extended period of time (3–12 days) and gave low yield (15–70%). In order to shorten the reaction time,

Table 1
Kinetic resolution of *rac*-**1** by *Candida antarctica* lipase B (CAL-B)



Substrate	(4*S*,5*S*)-**1**		(4*R*,5*R*)-**9**		*E*
	Yield (%)	Ee (%)	Yield (%)	Ee (%)	
1a (Ar = 4-MeOPh)	50	>99.9	49	99.8	>1000
1a[a]	50	99.9	49	99.9	>1000
1b (Ar = 2-MeO-4-MePh)	46	>99.9	50	98.5	>1000
1c (Ar = 4-MeO-2-MePh)	50	>99.9	50	99.8	>1000
1d (Ar = 4-MeO-3-MePh)	49	99.3	46	98.2	622
1e (Ar = 2-MeO-5-MePh)	50	98.2	48	99.8	>1000
1f (Ar = 2,5-$(MeO)_2$Ph)	52	95.2	46	98.2	417
1g (Ar = 3,4-$(MeO)_2$Ph)	48	98.6	50	98.0	492
1h (Ar = 2,5-$(MeO)_2$-4-MePh)	49	99.8	46	99.8	>1000

Conditions: *rac*-**1**; 1 g, lipase CAL-B; 200 mg, vinyl acetate 20 mL, at 25 °C for 3–4 days.
[a] CAL-B was reused for the reaction.

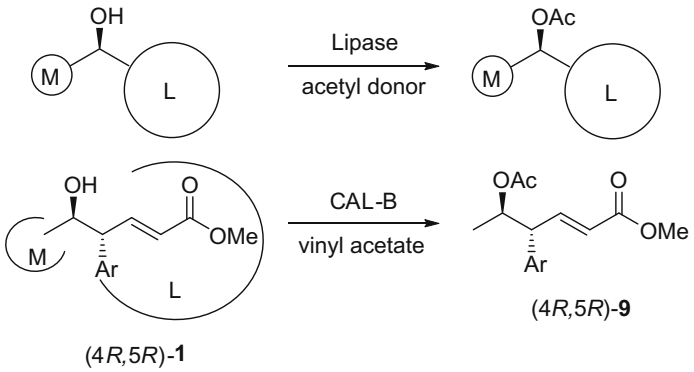
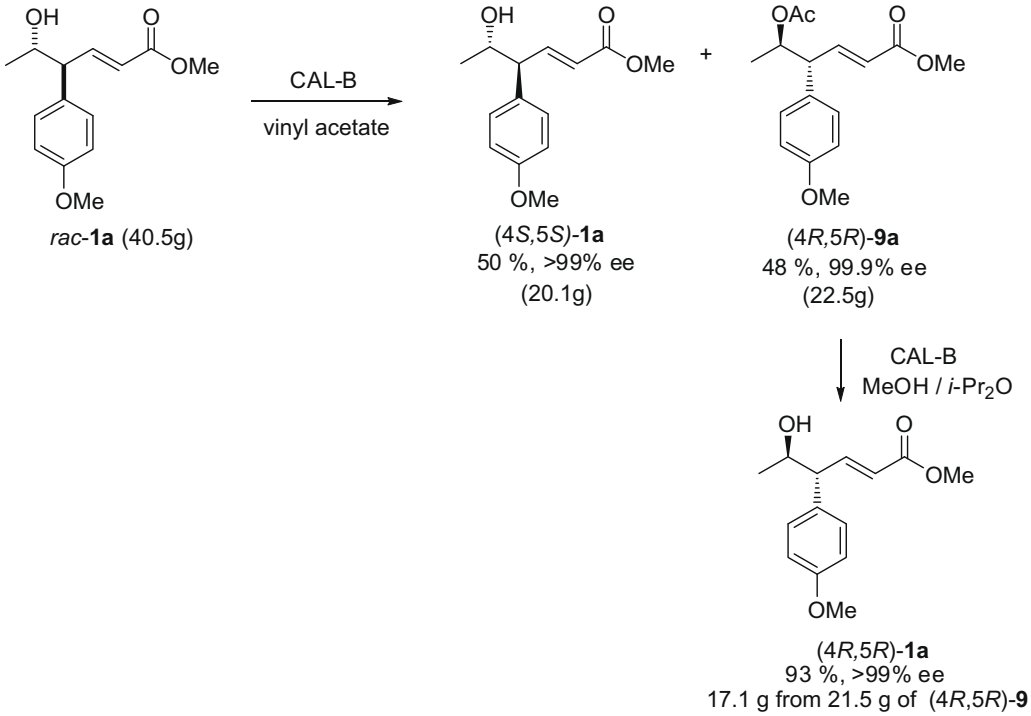


Figure 2. Empirical rule of enantiopreference for lipase-catalyzed reaction of secondary alcohol.



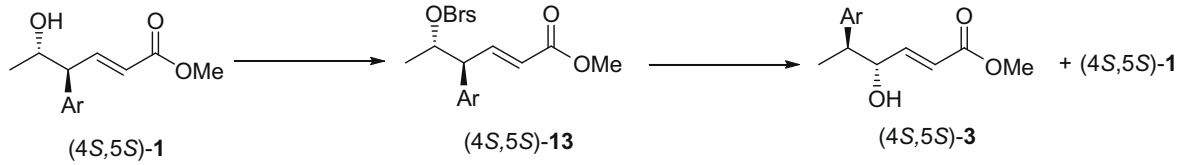
Scheme 4.

4-bromobenzenesulfonyl (brosyl) group was employed as a better leaving group. The obtained optically active (4*S*,5*S*)-**1a** (>99% ee) was converted to the corresponding brosylate (4*S*,5*S*)-**13a** in 89% yield. Rearrangement of (4*S*,5*S*)-**13a** in water saturated nitromethane gave a rearranged product (4*S*,5*S*)-**3a** in 92% yield and an unrearranged (4*S*,5*S*)-**1a** in 7.2% yield (Table 2, entry 1). Optical purity of the product (4*S*,5*S*)-**3a** was retained as that of starting material (4*S*,5*S*)-**1a** (>99% ee). The enantiomer (4*R*,5*R*)-**13a** from (4*R*,5*R*)-**1a** was converted to (4*R*,5*R*)-**3a** by the same procedure in 94% yield (Table 2, entry 2).

In contrast, the rearrangement of tosylate (4*S*,5*S*)-**2a** was reported to afford (4*S*,5*S*)-**3a** in 70% yield. Considering the mechanism by way of the phenonium ion shown in Scheme 1, the regioselectivity of the reaction seemed not to be affected by the type of leaving group. However, the ratio of products **3a**/**1a** of the reaction increased. To ensure this phenomenon, solvolysis of (4S^*,5S^*)-**2a** and (4S^*,5S^*)-**13a** was investigated several times. The ratio of the products (**3a** /**1a**) on the reaction of **2a** was 7.0 ± 0.8, while that of **13a** was 11.5 ± 0.7. The results showed that the regioselectivity of the reaction was clearly affected by the leaving group. Rearrangement of the aryl group via the phenonium ion was well studied by Cram et al. and Schreiber et al.[16] As the reaction involved an S_N2-type concerted mechanism, the regioselectivity was affected by the leaving group. The reason for the regioselectivity by the leaving group is still unclear, so further study on the mechanism is currently underway.

Optically active (4*S*,5*S*)-**1b**–**h** were converted to corresponding brosylates (4*S*,5*S*)-**13b**–**h**, which were then subjected to a rearrangement reaction to afford the corresponding compounds **3b**–**h**. The results are summarized in Table 2. The rearrangement of

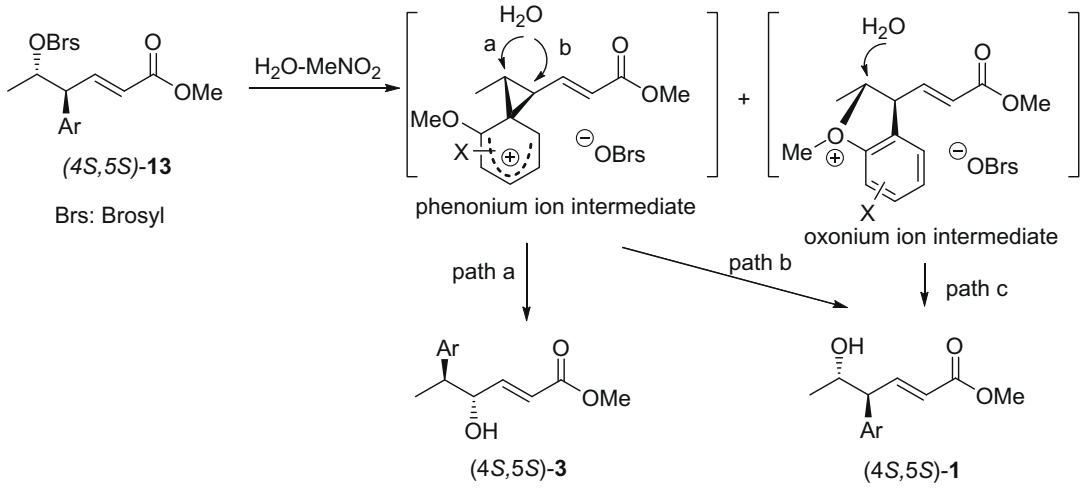
Table 2
The yield on the conversion from (4*S*,5*S*)-**1** to (4*S*,5*S*)-**3**



Substrate	Isolated yield (%)		
	(4*S*,5*S*)-**13**	(4*S*,5*S*)-**3**	(4*S*,5*S*)-**1**
(4*S*,5*S*)-**1a** (Ar = 4-MeOPh)	89	92 (70)[a]	7.2
(4*R*,5*R*)-**1a**	85	94	5.5
(4*S*,5*S*)-**1b** (Ar = 2-MeO-4-MePh)	69	26 (47)[a]	73
(4*S*,5*S*)-**1c** (Ar = 4-MeO-2-MePh)	94	40 (17)[a]	58
(4*S*,5*S*)-**1d** (Ar = 4-MeO-3-MePh)	89	94 (51)[a]	0.3
(4*S*,5*S*)-**1e** (Ar = 2-MeO-5-MePh)	92	61 (19)[a]	26
(4*S*,5*S*)-**1f** (Ar = 2,5-$(MeO)_2$Ph)	71	37	62
(4*S*,5*S*)-**1g** (Ar = 3,4-$(MeO)_2$Ph)	73	87	11
(4*S*,5*S*)-**1h** (Ar = 2,5-$(MeO)_2$-4-MePh)	84	45 (19) [a]	42

Conditions: see experimental.

[a] Reported yield (%) on reaction of the corresponding tosylate in parentheses.[3]



Scheme 5.

(4*S*,5*S*)-**13a**–**h** afforded the corresponding (4*S*,5*S*)-**3a**–**h** (26–94% yield). The yields of (4*S*,5*S*)-**3c**, (4*S*,5*S*)-**3d**, (4*S*,5*S*)-**3e,** and (4*S*,5*S*)-**3h** were higher than those of the reaction of the corresponding tosylate **2**. The reaction of (4*S*,5*S*)-**13b** exhibited a lower yield than that of (4*S*,5*S*)-**2b**. This might be dependent on the stability of (4*S*,5*S*)-**13b** (reaction time of (4*S*,5*S*)-**13b**: 6 h, **2b**: 3 days). In the case of the reactions of **13** possessing an *ortho*-substituent, the rearrangement afforded a considerable amount of corresponding **1**. The proposed reaction pathways are shown in Scheme 5.[3] The formation of **3a** and **1a** was explained by way of the phenonium ion (path a and path b, respectively). A substituent at the 2′-position on the aromatic ring prevented production of **3** by forming an oxonium intermediate (path c) and/or by preferable nucleophilic attack of water to the 5′-position of phenonium intermediate (path b) as described in a previous report.[3] As a result, solvolysis of **13b**, **13c**, **13e**, **13f,** and **13h** could afford the corresponding **3** in low yield.

3. Conclusion

The lipase-catalyzed enantioselective acetylation of racemic **1a**–**h** was performed and efficient optical resolutions were achieved (*E* >400). The procedure for the preparation of optically active **1** was shortened by direct enzymatic resolution of *rac*-**1** when compared to a previously reported procedure. After the brosylation of optically active **1a**–**h**, the rearrangement of **13a**–**h** afforded the corresponding **3a**–**h** (26–94% yield). Compounds **3a**, **3d,** and **3g** without a substituent at the 2'-position were obtained in over 87% yield, and the yield of the reaction was improved by the use of brosylate **13** in comparison with tosylate **2**. The obtained optically active (4*S*,5*S*)-**3a** can be expanded to optically active xanthorrizol **4** and curcumene **8**; (4*S*,5*S*)-**3e** also can be expanded to curcuphenol by our reported procedure.[1,2] This present procedure is useful for the synthesis of bisabolane-type sesquiterpenes from methyl sorbate. Moreover, **1** and **3** are well-functionalized compounds possessing a hydroxyl group and α,β-unsaturated ester moiety; these compounds could be important chiral building blocks for natural product synthesis.

4. Experimental

4.1. General

The NMR spectra were recorded in $CDCl_3$ on JEOL-AL-400 spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR). Mass spectra were measured by JEOL JMS-AM II 50. IR spectra were carried out on JASCO FT/IR 4100 using ATR method (neat). Specific rotation was measured on JASCO P-2200. HPLC analysis was performed on SSC-3210 pump equipped with chiral column, SSC-5200 UV detector, and SIR Chromatocordor 21.

Chemicals were purchased from Tokyo Kasei Industry Co., Ltd, Wako Chemicals or Aldrich Inc. otherwise indicated. *Candida antarctica* lipase B (CAL-B) supported on acrylic resin was purchased from Sigma–Aldrich Inc. and was used in this study. Racemic **1a**–**e** were synthesized by following the reported procedure from *rac*-methyl 4,5-epoxyhex-(2*E*)-enoate and the corresponding anisole derivatives. The absolute configurations of **1d**, **1e,** and **1h** were determined by comparison with the retention time of the corresponding authentic sample prepared from optically active epoxide **10** on HPLC analysis.

4.2. General procedure for CAL-B-catalyzed kinetic resolution of 1

To a solution of *rac*-**1** (1.0 g) in vinyl acetate (50 mL) was added lipase CAL-B (200 mg) and the resulting mixture was stirred at 25 °C. The ee of **1** and/or **9** was monitored by HPLC, and the reaction was stopped by filtration through a pad of Celite 545. The reaction time for **1a**, **1d**, **1e,** and **1g** was 3 days and that for **1b**, **1c,** and **1f** was 4 days. The residue was washed with ethyl acetate and then the filtrate was evaporated under reduced pressure and afforded the mixture of the substrate and the corresponding product. The residue was purified by silica gel column chromatography (silica gel 30 g, *n*-hexane/AcOEt = 6/1) to afford **1** and **9**. The ees of **1** and **9** were determined by HPLC analysis and the results are shown in Table 1.

4.2.1. Kinetic resolution of (4*S**,5*S**)-methyl 5-hydroxy-4-(4-methoxyphenyl)-hex-2(*E*)-enoate rac-1a

From *rac*-**1a** (1.00 g, 4.00 mmol) to (4*S*,5*S*)-**1a** (500 mg, 2.00 mmol, 50%) and (4*R*,5*R*)-methyl 5-acetoxy-4-(4-methoxyphenyl)hex-2(*E*)-enoate (4*R*,5*R*)-**9a** (575 mg, 1.97 mmol, 49%).

(4*S*,5*S*)-**1a**: $[\alpha]_D^{23} = +21.2$ (*c* 2.07, $CHCl_3$); Lit.[2] $[\alpha]_D^{25} = +21.3$ (*c* 2.12, $CHCl_3$); ^1H NMR: δ 1.10 (3H, d, *J* = 6.0 Hz), 2.04 (1H, brs) 3.32 (1H, dd, *J* = 8.8, 7.2 Hz), 3.71 (3H, s), 3.79 (3H, s), 4.05 (1H, qd, *J* = 6.0, 7.2 Hz), 5.89 (1H, dd, *J* = 1.2, 15.6 Hz), 6.78 (2H, d, *J* = 6.4 Hz), 7.11 (2H, d, *J* = 6.4 Hz), 7.26 (1H, dd, *J* = 8.8, 15.6 Hz); ^{13}C NMR: δ 21.2, 51.5, 55.2, 56.0, 70.5, 114.2 (2C), 122.8, 129.1 (2C), 131.9, 148.7, 158.6, 166.8; HR-EI-MS calcd for $C_{14}H_{18}O_4$: 250.1205; found: 250.1210; HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 20/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**1a**; t_R = 17.3 min, (4*S*,5*S*)-**1a**; t_R = 22.0 min.

(4*R*,5*R*)-**9a**: $[\alpha]_D^{21} = -5.5$ (*c* 2.44, $CHCl_3$); ^{1}H NMR: δ 1.11 (3H, d, *J* = 6.4 Hz), 2.03 (3H, s) 3.47 (1H, t, 8.4 Hz), 3.71 (3H, s), 3.79 (3H, s), 5.16–5.23 (1H, m), 5.82 (1H, dd, *J* = 1.2, 15.6 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 7.13 (2H, d, *J* = 8.4 Hz), 7.16 (1H, dd, *J* = 8.4, 15.6 Hz); ^{13}C NMR: δ 18.4, 21.1, 51.5, 53.2, 55.2, 72.4, 114.3 (2C), 122.5, 129.2 (2C), 130.8, 147.8, 158.8, 166.8, 170.4; IR: 1721, 1654, 1611, 1512, 1235 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 292.1311; found: 292.1313; HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 20/1, flow rate; 0.5 mL/min, detection; 254 nm, (4*R*,5*R*)-**9a**; t_R = 17.5 min, (4*S*,5*S*)-**9a**; t_R = 14.7 min.

4.2.2. Large-scale preparation of optically active 1

To a solution of *rac*-**1a** (40.5 g, 0.162 mol) in vinyl acetate (400 mL) was added lipase CAL-B (3.0 g) and the resulting mixture was stirred at 25 °C for 7 days. The reaction was stopped by filtration through a glass filter. The residue was washed with ethyl acetate and then the filtrate and ether solution were combined, and evaporated under reduced pressure to afford the mixture of the substrate and the corresponding product. The residue was purified by silica gel column chromatography (silica gel 500 g, *n*-hexane/AcOEt = 6/1) to afford (4*R*,5*R*)-**1a** (20.1 g, 80.4 mmol, 50%, >99.9% ee) and (4*R*,5*R*)-**9a** (22.5 g, 77.1 mmol, 48%, 99.8% ee).

(4*R*,5*R*)-**1a**: To the solution of (4*R*,5*R*)-**9a** (21.5 g, 73.7 mmol) in diisopropylether (400 mL) and methanol (100 mL) was added the CAL-B (3 g) that was recovered from the above-mentioned reaction. The mixture was stirred for 4 days at rt, after which it was filtered by glass filter and the residue was washed with ether. The filtrate and the ethereal solution were combined and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel 100 g, *n*-hexane/AcOEt = 7/1) to afford (4*R*,5*R*)-**1a** (17.1 g, 68.3 mmol 93%, >99.9% ee). $[\alpha]_D^{23} = -21.8$ (*c* 1.00, $CHCl_3$).

4.2.3. Kinetic resolution of (4*S**,5*S**)-methyl 5-hydroxy-4-(4-methoxy-2-methylphenyl)hex-2(*E*)-enoate *rac*-1b

From *rac*-**1b** (1.10 g, 4.17 mmol) to (4*S*,5S)-**1b** (546 mg, 2.07 mmol, 50%) and (4*R*,5*R*)-methyl 5-acetoxy-4-(4-methoxy-2-methylphenyl)hex-2(*E*)-enoate ((4*R*,5*R*)-**9b**) (590 mg, 1.97 mmol, 46%). (4*S*,5*S*)-**1b:** $[\alpha]_D^{23} = +2.0$ (*c* 1.10, $CHCl_3$). Lit.[1] $[\alpha]_D^{23} = +5.8$ (*c* 1.17, $CHCl_3$); ^{1}H NMR: δ 1.11 (3H, d, *J* = 6.2 Hz), 1.75 (1H, br) 2.30 (3H, s), 3.57 (1H, dd, *J* = 8.0, 8.4 Hz), 3.71 (3H, s), 3.78 (3H, s), 4.06–4.13 (1H, m), 5.85 (1H, d, *J* = 15.6 Hz), 6.70–6.78 (2H, m), 6.97 (1H, d, *J* = 8.4 Hz), 7.22 (1H, dd, *J* = 8.0, 15.6 Hz); ^{13}C NMR: δ 20.4, 21.7, 52.0, 52.1, 55.8, 71.1, 112.3, 116.9, 123.1, 128.9, 131.1, 138.0, 149.7, 158.7, 167.5; IR: 3445, 1714, 1651, 1608, 1577, 1504, 1272, 1048 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1365; HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 50/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**1b**; t_R = 29.8 min, (4*S*,5*S*)-**1b**; t_R = 40.0 min.

(4*R*,5*R*)-**9b:** $[\alpha]_D^{23} = +1.8$ (*c* 1.12, $CHCl_3$); ^{1}H NMR: δ 1.06 (3H, d, *J* = 6.4 Hz), 1.98 (3H, s), 2.25 (3H, s), 3.61 (3H, s), 3.63–3.72 (1H, m) 3.70 (3H, s), 5.20 (1H, dq, *J* = 8.4, 6.4 Hz), 5.71 (1H, dd, *J* = 0.8, 15.6 Hz), 6.65–6.70 (2H, m), 6.98–7.06 (2H, m); ^{13}C NMR: δ 18.2, 19.9, 21.0, 48.5, 51.2, 54.9, 72.3, 111.6, 116.2, 121.9, 128.4, 129.0, 137.2, 148.0, 156.1, 166.5, 170.2; IR: 1730, 1654, 1608, 1577, 1504, 1245, 1044 cm^{-1}; HR-EI-MS calcd for $C_{17}H_{22}O_5$: 306.1467; found: 306.1475; HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 50/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**9b**; t_R = 9.7 min, (4*S*,5*S*)-**9b**; t_R = 8.7 min.

4.2.4. Resolution of (4*S**,5*S**)-methyl 5-hydroxy-4-(2-methoxy-4-methylphenyl)hex-2(*E*)-enoate *rac*-1c

From *rac*-**1c** (1.10 g, 4.17 mmol) to (4*S*,5*S*)-**1c** (547 mg, 2.07 mmol, 50%) and (4*R*,5*R*)-methyl 5-acetoxy 4-(2-methoxy-4-methylphenyl)hex-2(*E*)-enoate (4*R*,5*R*)-**9c** (635 mg, 2.08 mmol, 50%). **1c**: $[\alpha]_D^{29} = -14.2$ (*c* 1.00, $CHCl_3$). Lit.[1] (4*S*,5*S*)-**1c** $[\alpha]_D^{23} = -12.9$ (*c* 2.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (3H, d, *J* = 6.4 Hz), 1.81 (1H, br s) 2.33 (3H, s), 3.71 (3H, s), 3.71–3.81 (1H, m), 3.81 (3H, s), 4.14–4.22 (1H, m), 5.90 (1H, d, *J* = 15.6 Hz), 6.70 (1H, s), 6.74 (1H, d, *J* = 7.9 Hz), 7.01 (1H, d, *J* = 7.9 Hz), 7.34 (1H, dd, *J* = 8.8, 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 21.4, 50.5, 51.4, 55.4, 69.6, 112.0, 121.5, 122.8, 125.3, 129.0, 138.2, 148.4, 156.6, 166.9. IR: 3445, 1722, 1650, 1611, 1579, 1506, 1267, 1039 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 264.1362, Found: 264.1352; The ee of **1c** was determined by HPLC analysis after acetylation of **1c**–**9c** by acetic anhydride and pyridine. HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 50/1, flow rate; 0.3 mL/min, detection; 254 nm, (4*R*,5*R*)-**9c**; t_R = 22.6 min, (4*S*,5*S*)-**9c**; t_R = 21.6 min. (4*R*,5*R*)-**9c**: $[\alpha]_D^{29} = +18.6$ (*c* 1.11, $CHCl_3$); ^{1}H NMR: δ 1.13 (3H, d, *J* = 6.4 Hz), 2.04 (3H, s), 2.35 (3H, s), 3.72 (3H, s), 3.83 (3H, s), 3.95 (1H, dd, *J* = 8.0, 8.4 Hz), 5.35 (1H, dq, *J* = 6.4, 8.0 Hz), 5.84 (1H, d, *J* = 15.8 Hz), 6.71 (1H, s), 6.75 (1H, d, *J* = 7.6 Hz), 7.03 (1H, d, *J* = 7.6 Hz), 7.20 (1H, dd, *J* = 8.0, 15.8 Hz); ^{13}C NMR: δ 18.5, 21.2, 21.4, 47.5, 51.4, 55.3, 71.9, 111.9, 121.3, 122.3, 129.0, 138.4, 148.0, 146.7, 156.7, 166.9, 170.5; IR: 1726, 1654, 1508, 1235 cm^{-1}; HR-EI-MS calcd for $C_{17}H_{22}O_5$: 306.1467; found: 306.1476.

4.2.5. Resolution of (4*S**,5*S**)-methyl 5-hydroxy-4-(4-methoxy-3-methylphenyl)hex-2(*E*)-enoate *rac*-1d

From *rac*-**1d** (1.11 g. 4.02 mmol) to (4*S*,5*S*)-**1d** (547 mg, 2.07 mmol, 49%) and (4*R*,5*R*)-methyl 5-acetoxy-4-(4-methoxy-3-methylphenyl)hex-2(*E*)-enoate (4*R*,5*R*)-**9d** (594 mg, 1.94 mmol, 46%).

$[\alpha]_D^{27} = +17.6$ (*c* 1.01, $CHCl_3$); ^{1}H NMR: δ 1.11 (3H, d, *J* = 6.6 Hz), 1.81 (1H, br) 2.20 (3H, s), 3.28 (1H, dd, *J* = 8.0, 8.4 Hz), 3.72 (3H, s), 3.81 (3H, s), 4.01–4.09 (1H, m), 5.90 (1H, d, *J* = 15.6 Hz), 6.77 (1H, d, *J* = 7.6 Hz), 6.96 (1H, s), 6.97 (1H, d, *J* = 7.6 Hz), 7.34 (1H, dd, *J* = 8.4, 15.6 Hz); ^{13}C NMR: δ 16.3, 21.2, 51.5, 55.3, 56.1, 70.6, 110.1, 122.7, 126.3, 127.1, 130.3, 131.3, 148.8, 156.8, 166.8; IR: 3443, 1714, 1650, 1504, 1258, 1038 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1363; HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 50/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**1d**; t_R = 40.0 min, (4*S*,5*S*)-**1d**; t_R = 29.8 min.

(4*R*,5*R*)-**9d**: $[\alpha]_D^{27} = -10.0$ (*c* 1.01, $CHCl_3$); ^{1}H NMR: δ 1.08 (3H, d, *J* = 6.4 Hz), 2.01 (3H, s), 2.17 (3H, s), 3.39 (1H, t, *J* = 8.4 Hz), 3.68 (3H, s), 3.78 (3H, s), 5.35 (1H, dq, *J* = 8.4, 6.4 Hz), 5.84 (1H, d, *J* = 15.6 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 6.93 (1H, d, *J* = 2.0 Hz), 6.94 (1H, dd, *J* = 2.0, 7.6 Hz), 7.09 (1H, dd, *J* = 8.4, 15.6 Hz); ^{13}C NMR: δ 16.2, 18.5, 21.2, 51.5, 53.5, 55.3, 72.5, 110.1, 122.3, 126.4, 127.1, 130.3 (2C), 148.8, 157.0, 166.7, 170.4; IR: 1726, 1655, 1508, 1235, 1051 cm^{-1}; HR-EI MS calcd for $C_{17}H_{22}O_5$: 306.1467; found: 306.1465. HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 50/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**9d**; t_R = 10.0 min, (4*S*,5*S*)-**9d**; t_R = 7.2 min.

4.2.6. Resolution of (4*S**,5*S**)-methyl 5-hydroxy-4-(2-methoxy-5-methylphenyl)hex-2(*E*)-enoate *rac*-1e

From *rac*-**1e** (1.01 g, 3.83 mmol) to (4*S*,5*S*)-**1e** (507 mg, 1.92 mmol, 50%) and (4*R*,5*R*)-methyl 5-acetoxy-4-(2-methoxy-5-methylphenyl)hex-2(*E*)-enoate (4*R*,5*R*)-**9e** (560 mg, 1.83 mmol, 48%). (4*S*,5*S*)-**1e**: $[\alpha]_D^{28} = -1.7$ (*c* 1.08, $CHCl_3$); ^{1}H NMR: δ 1.11 (3H, d, *J* = 6.4 Hz), 1.92 (1H, br s) 2.27 (3H, s), 3.72 (3H, s), 3.71–3.81 (1H, m), 3.80 (3H, s), 4.14–4.21 (1H, m), 5.92 (1H, d, *J* = 15.6 Hz), 6.78 (1H, d, *J* = 7.8 Hz), 6.94 (1H, s), 7.01 (1H, d, *J* = 7.8 Hz), 7.34 (1H, dd, *J* = 8.8, 15.6 Hz); ^{13}C NMR: δ 23.5, 24.2, 53.8, 54.5, 58.6, 72.6, 114.0, 126.0, 131.1, 131.4, 132.8, 133.1, 151.3, 157.6, 169.9; IR: 3444, 1714, 1650, 1504, 1241, 1034 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1358; HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 50/1, flow rate; 0.3 mL/min, detection; 254 nm; (4*R*,5*R*)-**1e**; t_R = 24.0 min, (4*S*,5*S*)-**1e**; t_R = 20.9 min. (4*R*,5*R*)-**9e**: $[\alpha]_D^{23} = +12.5$ (*c* 1.07, $CHCl_3$); ^{1}H NMR: δ 1.13 (3H, d,

J = 6.4 Hz), 2.05 (3H, s), 2.29 (3H, s), 3.73 (3H, s), 3.82 (3H, s), 3.97 (1H, t, J = 6.4 Hz), 5.36 (1H, dq, J = 8.4, 6.4 Hz), 5.84 (1H, d, J = 15.6 Hz), 6.78 (1H, d, J = 8.4 Hz), 6.96 (1H, d, J = 2.0 Hz), 7.04 (1H, dd, J = 2.0, 8.4 Hz), 6.94 (1H, dd, J = 8.4, 15.6 Hz); ^{13}C NMR: δ 18.5, 20.4, 21.2, 47.7, 51.4, 55.5, 71.9, 110.9, 122.4, 126.9, 128.6, 129.8, 129.9, 147.9, 154.8, 166.9, 170.5; IR: 1731, 1655, 1504, 1241 cm^{-1}; HR-EI-MS calcd for $C_{17}H_{22}O_5$: 306.1467; found: 306.1476. HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 50/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**9e**; t_R = 7.4 min, (4*S*,5*S*)-**9e**; t_R = 6.3 min.

4.2.7. Resolution of *rac*-methyl 5-hydroxy-4-(2′,5′-dimethoxyphenyl)hex-2(*E*)-enoate 1f

From *rac*-**1f** (1.01 g, 3.60 mmol) to (4*S*,5*S*)-**1f** (528 mg, 1.89 mmol, 52%) and (4*R*,5*R*)-methyl 5-acetoxy-4-(2-methoxy-5-methylphenyl)hex-2(*E*)-enoate (4*R*,5*R*)-**9f** (538 mg, 1.67 mmol, 46%). (4*S*,5*S*)-**1f**: $[\alpha]_D^{24}$ = +4.1 (*c* 1.10, $CHCl_3$); Lit.[11] $[\alpha]_D^{18}$ = −3.55 (*c* 1.52, $CHCl_3$, (4*R*,5*R*)-**1f**, 90%ee); ^{1}H NMR: δ 1.12 (3H, d, J = 6.0 Hz), 1.94 (1H, br s) 3.72 (3H, s), 3.74–3.80 (1H, m), 3.76 (3H, s), 3.78 (3H, s), 4.14–4.21 (1H, m), 5.92 (1H, dd, J = 1.2, 15.6 Hz), 6.70–6.77 (2H, m), 6.82 (1H, d, J = 8.0 Hz), 7.31 (1H, dd, J = 8.8, 15.6 Hz); ^{13}C NMR: δ 21.2, 50.8, 51.6, 55.7, 56.0, 69.6, 111.9, 112.0, 115.8, 123.1, 129.6, 148.0, 151.0, 153.7, 166.8; IR: 3471, 1717, 1650, 1497, 1225, 1043 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_5$: 280.1311; found: 280.1315. HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 30/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**1f**; t_R = 46.8 min, (4*S*,5*S*)-**1f**; t_R = 34.0 min. (4*R*,5*R*)-**9f**: $[\alpha]_D^{25}$ = +6.5 (*c* 1.03, $CHCl_3$). Lit.[11] $[\alpha]_D^{18}$ = −4.9 (*c* 3.28, $CHCl_3$, (4*S*,5*S*)-**9f**, 67%ee); ^{1}H NMR: δ 1.12 (3H, d, J = 6.4 Hz), 2.03 (3H, s), 3.71 (3H, s), 3.75 (3H, s), 3.78 (3H, s), 3.95 (1H, dd, J = 8.4, 8.8 Hz), 5.32 (1H, dq, J = 8.4, 6.4 Hz), 5.84 (1H, d, J = 15.6 Hz), 6.71 (1H, d, J = 2.8 Hz), 6.96 (1H, d, J = 2.8, 8.8 Hz), 6.80 (1H, dd, J = 8.8 Hz), 7.18 (1H, dd, J = 8.8, 15.6 Hz); ^{13}C NMR: δ 18.5, 21.2, 47.7, 51.5, 55.7, 56.0, 71.8, 110.9, 112.3, 115.7, 122.7, 128.3, 147.5, 151.1, 153.6, 166.8, 170.5; IR: 1729, 1653, 1594, 1497, 1231, 1042 cm^{-1}. HR-EI-MS calcd for $C_{17}H_{22}O_6$: 322.1416; found: 322.1411. Ee of **9f** was determined by HPLC analysis after **9f** was converted to **1f** by methanolysis using K_2CO_3.

4.2.8. Resolution of *rac*-methyl 5-hydroxy-4-(3′,4′-dimethoxyphenyl)hex-2(*E*)-enoate 1g

From *rac*-**1g** (920 mg) to (4*S*,5*S*)-**1g** (452 mg, 50%) and (4*R*,5*R*)-methyl 5-acetoxy-4-(2-methoxy-5-methylphenyl)hex-2(*E*)-enoate (4*R*,5*R*)-**9g** (501 mg, 48%). (4*S*,5*S*)-**1g**: $[\alpha]_D^{27}$ = +15.1 (*c* 1.26, $CHCl_3$); Lit.[11] $[\alpha]_D^{24}$ = −8.2 (*c* 2.10, $CHCl_3$, (4*R*,5*R*)-**1g**, 62%ee); ^{1}H NMR: δ 1.12 (3H, d, J = 6.4 Hz), 2.15 (1H, br s) 3.31 (1H, dd, J = 7.2, 8.8 Hz), 3.73 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 4.04–4.11 (1H, m), 5.92 (1H, d, J = 15.6 Hz), 6.71(1H, d, J = 1.6 Hz), 6.75 (1H, dd, J = 8.4, 1.6 Hz), 6.83 (1H, d, J = 8.4 Hz), 7.27 (1H, dd, J = 8.8, 15.6 Hz); ^{13}C NMR: δ 23.5, 24.2, 53.8, 54.5, 58.6, 72.6, 114.0, 126.0, 131.1, 131.4, 132.8, 133.1, 151.3, 157.6, 169.9; IR: 3500, 1714, 1652 1621, 1261, 1241, 1027 cm^{-1}. HR-EI-MS calcd for $C_{15}H_{20}O_5$: 280.1311; found: 280.1312; HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 20/1, flow rate; 1.0 mL/ min, detection; 254 nm, (4*R*,5*R*)-**1g**; t_R = 32.4 min, (4*S*,5*S*)-**1g**; t_R = 28.1 min.

(4*R*,5*R*)-**9g**: $[\alpha]_D^{27}$ = −11.2 (*c* 1.07, $CHCl_3$); Lit.[11] $[\alpha]_D^{24}$ = +10.5 (*c* 1.77, $CHCl_3$, (4*S*,5*S*)-**9g**, 99%ee); ^{1}H NMR: δ 1.13 (3H, d, J = 6.4 Hz), 2.05 (3H, s), 3.47 (1H, dd, J = 8.0, 8.4 Hz), 3.72 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 5.22 (1H, qd, J = 6.4, 8.0 Hz), 5.84 (1H, d, J = 15.6 Hz), 6.70 (1H, d, J = 2.0 Hz), 6.76 (1H, dd, J = 2.0, 8.0 Hz), 6.84 (1H, d, J = 8.0 Hz), 7.14 (1H, dd, J = 8.4, 15.6 Hz); ^{13}C NMR: δ 18.4, 21.0, 51.3, 53.6, 55.7, 55.7, 72.2, 110.9, 111.3, 120.3, 122.4, 131.1, 147.5, 148.1, 149.1 166.4, 170.2; IR: 1722, 1654, 1622, 1517, 1237 cm^{-1}; HR-EI-MS calcd for $C_{17}H_{22}O_6$: 322.1416; found: 322.1421. Ee of **9g** was determined by HPLC analysis after **9g** was converted to **1g** by methanolysis using K_2CO_3.

4.2.9. Resolution of *rac*-methyl 5-hydroxy 4-(3′,4′-dimethoxyphenyl)hex-2(*E*)-enoate 1h

From *rac*-**1h** (940 mg, 3.16 mmol) to (4*S*,5*S*)-**1h** (460 mg, 50%) and (4*R*,5*R*)-methyl 5-acetoxy-4-(2-methoxy-5-methylphenyl) hex-2(*E*)-enoate (4*R*,5*R*)-**9h** (498 mg, 46%). (4*S*,5*S*)-**1h**: $[\alpha]_D^{14}$ = +10.5 (*c* 1.36, $CHCl_3$); ^{1}H NMR: δ 1.12 (3H, d, J = 6.0 Hz), 2.20 (3H, s), 3.70(3H, s), 3.72–3.78 (1H, m), 3.78 (3H, s), 4.18 (1H, qd, J = 6.0, 8.4 Hz), 5.90 (1H, d, J = 15.6 Hz), 6.64 (1H, s), 6.71 (1H, s), 7.36 (1H, dd, J = 8.4, 15.6 Hz); ^{13}C NMR: δ 16.0, 21.2, 50.8, 51.3, 55.5, 56.1, 69.5, 111.6, 114.4, 122.6, 126.0, 126.1, 148.6, 150.4, 151.7, 166.9; IR: 1722, 1654, 1622, 1517, 1237 cm^{-1}; HR-EI-MS calcd for $C_{16}H_{22}O_5$: 294.1467; found: 294.1460; Chiralcel AD-H, *n*-hexane/*i*-PrOH = 20/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**1h**; t_R = 27.5 min, (4*S*,5*S*)-**1h**; t_R = 33.5 min.

(4*R*,5*R*)-**9h**: $[\alpha]_D^{14}$ = −5.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR: δ 1.12 (3H, d, J = 7.2 Hz), 2.03 (3H, s), 2.20 (3H, s), 3.70 (3H, s), 3.77 (6H, s), 3.95 (1H, t, J = 8.4 Hz), 5.32 (1H, qd, J = 7.2, 8.4 Hz), 5.84 (1H, d, J = 15.6 Hz), 6.60 (1H, s), 6.70 (1H, s), 7.18 (1H, dd, J = 8.4, 15.6 Hz); ^{13}C NMR: δ 16.1, 18.4, 21.1, 47.5, 51.3, 56.0, 56.0, 71.9, 111.4, 114.4, 122.3, 124.7, 126.4, 147.8, 150.6, 151.7, 166.7, 170.4; IR: 1725, 1655, 1505, 1237, 1210 cm^{-1}. HR-EI-MS calcd for $C_{18}H_{24}O_6$: 336.1573; found: 336.1575; HPLC analysis: Chiralcel AD-H, *n*-hexane/*i*-PrOH = 20/1, flow rate; 1.0 mL/min, detection; 254 nm, (4*R*,5*R*)-**9h**; t_R = 8.5 min, (4*S*,5*S*)-**9h**; t_R = 10.5 min.

4.3. Brosylation of 1

4-Bromobenzenesulfonylchloride (2.5 equiv) was added to a solution of **1** (1.2 mmol) in pyridine (1.5 mL) at 0 °C and the mixture was stirred for 6 h at rt. The mixture was poured into water and extracted with ethyl acetate. The organic layer was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel 30 g, *n*-hexane/AcOEt = 6/1) to afford **13.**

4.3.1. (4*S*,5*S*)-Methyl 5-(4-bromobenzenesulfonyloxy)-4-(4-methoxyphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-13a

From (4*S*,5*S*)-**1a** (5.00 g, 20.0 mmol) to (4*S*,5*S*)-**13a** (8.31 g, 17.8 mmol, 89%). $[\alpha]_D^{23}$ = +22.1 (*c* 1.13, $CHCl_3$); ^{1}H NMR: δ 1.29 (3H, d, J = 6.2 Hz), 3.48 (1H, t, J = 8.2 Hz), 3.72 (3H, s), 3.75 (3H, s), 4.86 (1H, qd, J = 8.2, 6.2 Hz), 5.76 (1H, d, J = 15.4 Hz), 6.79 (2H, d, J = 8.7 Hz), 6.95 (1H, dd, J = 8.2, 15.4 Hz), 6.98 (2H, d, J = 8.7 Hz), 7.60 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 8.4 Hz); ^{13}C NMR: δ 19.9, 51.6, 53.3, 55.2, 82.2, 114.3 (2C), 123.7, 128.6, 129.1 (2C), 129.1 (2C), 129.6, 132.4 (2C), 135.8, 145.8, 159.0, 166.1; IR: 1732, 1657, 1610, 1575, 1515, 1274, 1185, 904 cm^{-1}; HR-EI-MS calcd for $C_{20}H_{21}O_6SBr$: 468.0242, 470.0222; found: 468.0223 (100%), 470.0234 (99.2%).

(4*R*,5*R*)-**13a**: From (4*R*,5*S*)-**1a** (14.0 g, 56.0 mmol) to (4*R*,5*R*)-**13a** (22.3 g, 47.7 mmol, 85.2%). $[\alpha]_D^{23}$ = −19.4 (*c* 1.04, $CHCl_3$).

4.3.2. (4*S*,5*S*)-Methyl 5-(4-bromophenylsulfonyloxy)-4-(4-methoxy-2-methylphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-13b

From (4*S*,5*S*)-**1b** (300 mg, 1.14 mmol) to (4*S*,5*S*)-**13b** (377 mg, 0.782 mmol, 69%). $[\alpha]_D^{23}$ = +16.4 (*c* 4.80, $CHCl_3$); ^{1}H NMR: δ 1.31 (3H, d, J = 6.0 Hz), 2.03 (3H, s), 3.70 (3H, s), 3.70–3.78 (1H, m), 3.76 (3H, s), 4.89 (1H, dq, J = 8.0, 6.0 Hz), 5.70 (1H, d, J = 15.6 Hz), 6.65–6.70 (2H, m), 6.85–6.92 (2H, m), 7.62 (2H, d, J = 8.0 Hz) 7.68 (2H, d, J = 8.0 Hz); ^{13}C NMR: δ 19.8, 19.9, 48.7, 51.5, 55.1, 82.0, 111.9, 116.4, 123.1, 128.0, 128.4, 128.6, 129.1 (2C), 132.3 (2C), 135.7, 137.1 146.3, 158.4, 166.1; IR: 1719, 1655, 1608, 1576, 1504, 1185, 1173, 894 cm^{-1}; HR-EI-MS calcd for $C_{21}H_{23}O_6SBr$: 482.0399, 484.0378; found: 482.0353 (97.4%), 484.0377 (100%).

4.3.3. (4*S*,5*S*)-Methyl 5-(4-bromobenzenesulfonyloxy)-4-(2-methoxy-4-methylphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-13c

From (4*S*,5*S*)-**1c** (140 mg, 0.56 mmol) to (4*S*,5*S*)-**13c** (252 mg, 0.525 mmol, 94%). $[\alpha]_D^{23} = +3.7$ (*c* 2.96, $CHCl_3$); ^{1}H NMR: δ 1.35 (3H, d, *J* = 6.0 Hz), 2.32 (3H, s), 3.71 (6H, s), 3.71–3.81 (1H, m), 5.01 (1H, dq, *J* = 6.4, 6.0 Hz), 5.77 (1H, d, *J* = 15.8 Hz), 6.55 (1H, s), 6.63 (1H, d, *J* = 8.0 Hz), 6.85 (1H, d, *J* = 8.0 Hz), 7.04 (1H, dd, *J* = 8.2, 15.8 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 7.66 (2H, d, *J* = 8.4 Hz); ^{13}C NMR: δ 20.1, 21.4, 48.5, 51.5, 55.1, 81.0, 111.6, 121.2, 123.1, 123.8, 128.3, 129.0, 129.1 (2C), 132.0 (2C), 135.4, 138.9, 145.3, 156.0, 166.2. IR: 1732, 1657, 1610, 1575, 1515, 1274, 1185, 904 cm^{-1}. HR-EI-MS calcd for $C_{21}H_{23}O_6SBr$: 482.0399, 484.0378; found: 482.0226 (94.7%), 484.0234 (100%).

4.3.4. (4*S*,5*S*)-Methyl 5-(4-bromobenzenesulfonyloxy)-4-(4-methoxy-3-methylphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-13d

From (4*S*,5*S*)-**1d** (350 mg, 1.33 mmol) to (4*S*,5*S*)-**13d** (452 mg, 1.18 mmol, 89%). $[\alpha]_D^{23} = +22.6$ (*c* 1.62, $CHCl_3$); ^{1}H NMR: δ 1.31 (3H, d, *J* = 6.4 Hz), 2.15 (3H, s), 3.44 (1H, dd, *J* = 9.0, 8.4 Hz), 3.71 (3H, s), 3.79 (3H, s), 4.86 (1H, dq, *J* = 8.4, 6.4 Hz), 5.76 (1H, d, *J* = 15.4 Hz), 6.68 (1H, d, *J* = 8.0 Hz), 6.81 (1H, d, *J* = 2.0 Hz), 6.85 (1H, dd, *J* = 2.0, 8.0 Hz), 6.96 (1H, dd, *J* = 9.0, 15.4 Hz), 7.58 (2H, d, *J* = 8.4 Hz), 7.63 (2H, d, *J* = 8.4 Hz); ^{13}C NMR: δ 16.2, 19.9, 51.5, 53.3, 55.2, 82.3, 110.0, 123.4, 126.3, 137.2, 128.5, 129.0 (2C), 129.2, 130.0, 132.2 (2C), 135.7, 146.0, 157.1, 166.1; IR: 1720, 1655, 1609, 1576, 1505, 1254, 1186, 1174, 904 cm^{-1}; HR-EI-MS calcd for $C_{21}H_{23}O_6SBr$: 482.0399, 484.0378; found: 482.0296 (97.7%), 484.0249 (100%).

4.3.5. (4*S*,5*S*)-Methyl 5-(4-bromobenzenesulfonyloxy)-4-(2-methoxy-5-methylphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-13e

From (4*S*,5*S*)-**1e** (382 mg, 1.25 mmol) to (4*S*,5*S*)-**13e** (555 mg, 1.15 mmol, 92%). $[\alpha]_D^{23} = -5.5$ (*c* 1.23, $CHCl_3$); ^{1}H NMR: δ 1.31 (3H, d, *J* = 6.4 Hz), 2.17 (3H, s), 2.29 (3H, s), 3.69 (6H, s), 3.71–3.77 (1H, m), 5.02 (1H, dq, *J* = 6.4, 6.8 Hz), 5.74 (1H, d, *J* = 15.6 Hz), 6.62 (1H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 2.0 Hz), 6.95 (1H, dd, *J* = 2.0, 8.0 Hz), 7.21 (1H, dd, *J* = 8.8, 15.6 Hz), 7.51 (2H, d, *J* = 8.4 Hz) 7.53 (2H, d, *J* = 8.4 Hz); ^{13}C NMR: δ 20.2, 21.0, 48.9, 51.5, 55.3, 81.2, 110.7, 123.9, 125.9 128.5, 128.9, 129.0 (2C), 129.9, 130.0, 132.1 (2C), 135.6, 146.0, 154.2, 166.3; IR: 1723, 1654, 1576, 1505, 1187 cm^{-1}. HR-EI-MS calcd for $C_{21}H_{23}O_6SBr$: 482.0188, 484.0378; found: 482.0321 (96.7%), 484.0187 (100%).

4.3.6. (4*S*,5*S*)-Methyl 5-(4-bromobenzenesulfonyloxy)-4-(2,4-dimethoxyphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-13f

From (4*S*,5*S*)-**1f** (366 mg, 1.20 mmol) to (4*S*,5*S*)-**13f** (425 mg, 0.853 mmol, 71%). $[\alpha]_D^{24} = -0.5$ (*c* 2.26, $CHCl_3$); ^{1}H NMR: δ 1.33 (3H, d, *J* = 6.4 Hz), 3.69 (3H, s), 3.70 (3H, s), 3.70 (3H, s), 3.76 (1H, dd, *J* = 6.8, 9.6 Hz), 5.02 (1H, dq, *J* = 6.4, 6.8 Hz), 5.76 (1H, d, *J* = 15.6 Hz), 6.50 (1H, d, *J* = 2.8 Hz), 6.66 (1H, d, *J* = 8.8 Hz), 6.69 (1H, dd, *J* = 2.8, 8.8 Hz), 6.98 (1H, dd, *J* = 9.6, 15.6 Hz), 7.53 (2H, d, *J* = 8.8 Hz) 7.56 (2H, d, *J* = 8.8 Hz); ^{13}C NMR: δ 20.3, 48.8, 51.6, 55.6, 55.8, 81.1, 111.6, 112.3, 116.0, 124.2, 127.3, 128.5, 129.1 (2C), 132.2 (2C), 135.6, 144.9, 150.5, 153.5, 166.2. IR: 1720, 1655, 1577, 1499, 1225, 1186 cm^{-1}. HR-EI-MS calcd for $C_{21}H_{23}O_7SBr$: 498.0348, 500.0327; found; 498.0342 (100%), 500.0321 (99.7%).

4.3.7. (4*S*,5*S*)-Methyl 5-(4-bromobenzenesulfonyloxy)-4-(2,4-dimethoxyphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-13g

From (4*S*,5*S*)-**1g** (303 mg, 0.99 mmol) to (4*S*,5*S*)-**13g** (360 mg, 0.722 mmol, 73%). $[\alpha]_D^{23} = +19.2$ (*c* 1.04, $CHCl_3$); ^{1}H NMR: δ 1.31 (3H, d, *J* = 6.0 Hz), 3.47 (1H, dd, *J* = 7.2, 9.2 Hz), 3.80 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 4.88 (1H, dq, *J* = 7.2, 6.0 Hz), 5.79 (1H, d, *J* = 15.6 Hz), 6.57 (1H, d, *J* = 1.6 Hz), 6.62 (1H, dd, *J* = 1.6, 8.2 Hz), 6.75 (1H, d, *J* = 8.2 Hz), 6.98 (1H, dd, *J* = 9.2, 15.6 Hz), 7.61 (2H, d, *J* = 8.8 Hz) 7.65 (2H, d, *J* = 8.8 Hz); ^{13}C NMR: δ 20.6, 52.3, 54.4, 57.5, 57.6, 82.8, 111.8, 112.1, 120.9, 124.5, 129.4, 129.7 (2C), 130.8, 133.0 (2C), 137.5, 146.3, 149.3, 149.9, 166.8. IR: 1720, 1655, 1518, 1244, 1186 cm^{-1}; HR-EI-MS calcd for $C_{21}H_{23}O_7SBr$: 498.0348, 500.0327; found: 498.0338 (100%), 500.0323 (98.1%).

4.3.8. (4*S*,5*S*)-Methyl 5-(4-bromobenzenesulfonyloxy)-4-(2,5-dimethoxy-4-methylphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-13h

From (4*S*,5*S*)-**1h** (4.33 g, 14.7 mmol) to (4*S*,5*S*)-**13h** (6.32 mg, 12.3 mmol, 84%). $[\alpha]_D^{23} = -0.6$ (*c* 1.03, $CHCl_3$) ^{1}H NMR: δ 1.35 (3H, d, *J* = 6.4 Hz), 2.19 (3H, s), 3.69 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 3.72–3.80 (1H, m), 5.04 (1H, dq, *J* = 7.2, 6.4 Hz), 5.79 (1H, d, *J* = 15.6 Hz), 6.42 (1H, s), 6.57 (1H, s), 6.98 (1H, dd, *J* = 9.2, 15.6 Hz), 7.54 (2H, d, *J* = 9.2 Hz) 7.57 (2H, d, *J* = 9.2 Hz); ^{13}C NMR: δ 16.3, 20.2, 51.6, 55.8, 56.1, 81.3, 113.7, 114.0, 123.8, 124.0, 126.9, 128.5, 129.1 (2C), 132.1 (2C), 135.7, 145.3, 150.0, 151.7, 166.3; IR: 1721, 1656, 1576, 1508, 1212, 1187 cm^{-1} HR-EI-MS calcd for $C_{22}H_{25}O_7SBr$: 512.0504, 514.0484; found: 512.0518 (100%), 514.0490 (99.2%).

4.4. Solvolysis of 13

A solution of **13** (0.6 mmol) in water-saturated nitromethane (30 mL) was stirred for 2 days [6 h for (4*S*,5*S*)-**13b**, 35 h for (4*S*,5*S*)-**13c**] at 50 °C. To the reaction mixture was added saturated aq $NaHCO_3$ (1 mL) and the resulting mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel 15 g, *n*-hexane/AcOEt = 4/1) to afford **3**. The results are listed in Table 2.

4.4.1. (4*S*,5*S*)-Methyl 4-hydroxy-5-(4-methoxyphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-3a

From (4*S*,5*S*)-**13a** (311 mg, 0.665 mmol) to (4*S*,5*S*)-**3a** (153 mg, 0.613 mmol, 92%) and (4*S*,5*S*)-**1a** (12.0 mg, 0.048 mmol, 7.2%). $[\alpha]_D^{23} = -12.9$ (*c* 1.01, $CHCl_3$); Lit.[2] $[\alpha]_D^{20} = -14.7$ (*c* 1.00, $CHCl_3$, (4*S*,5*S*)-**3a**); ^{1}H NMR: δ 1.26 (3H, d, *J* = 7.2 Hz), 2.90 (1H, dq, *J* = 6.4,, 7.2 Hz), 3.68 (3H, s), 3.76 (3H, s), 4.31 (1H, br) 4.33 (1H, ddd, *J* = 1.6, 4.8, 6.4 Hz), 5.97 (1H, dd, *J* = 1.6, 15.6 Hz), 6.83 (2H, d, *J* = 8.6 Hz), 6.87 (1H, dd, *J* = 4.8, 15.8 Hz), 7.10 (2H, d, *J* = 8.6 Hz); ^{13}C NMR: δ 15.5, 44.3, 51.5, 55.2, 75.3, 113.9 (2C), 120.5, 128.8 (2C), 134.4, 148.8, 158.4, 166.9; IR: 3473, 1723, 1658, 1611, 1583, 1513, 1248 cm^{-1}; HPLC analysis: Chiralcel OD-H, *n*-hexane/EtOH = 50/1, flow rate; 0.3 mL/min, detection; 254 nm, (4*S*,5*S*)-**3a**; t_R = 39.0 min, (4*R*,5*R*)-**3a**; t_R = 47.2 min.

4.4.2. (4*R*,5*R*)-Methyl 4-hydroxy-5-(4-methoxyphenyl)hex-2(*E*)-enoate (4*R*,5*R*)-3a

From (4*R*,5*R*)-**13a** (312 mg, 0.667 mmol) to (4*R*,5*R*)-**3a** (157 mg, 0.626 mmol, 94%) and (4*R*,5*R*)-**1a** (9.2 mg, 0.037 mmol, 5.5%). $[\alpha]_D^{23} = +13.2$ (*c* 1.01, $CHCl_3$).

4.4.3. (4*S*,5*S*)-Methyl 4-hydroxy-5-(4-methoxy-2-methylphenyl) hex-2(*E*)-enoate (4*S*,5*S*)-3b

From (4*S*,5*S*)-**13b** (294 mg, 0.61 mmol) to (4*S*,5*S*)-**3b** (42.0 mg, 0.159 mmol, 26%) and (4*S*,5*S*)-**1b** (119 mg, 0.451 mmol, 74%). $[\alpha]_D^{20} = -11.7$ (*c* 1.40, $CHCl_3$); ^{1}H NMR: δ 1.24 (3H, d, *J* = 7.2 Hz), 1.92 (1H, br), 2.27 (3H, s), 3.15 (1H, dq, *J* = 6.0, 7.2 Hz), 3.70 (3H, s), 3.75 (3H, s), 4.31–4.36 (1H, m), 6.02 (1H, dd, *J* = 1.6, 15.8 Hz), 6.67–6.73 (2H, m), 6.89 (1H, dd, *J* = 4.4, 15.8 Hz), 7.12 (1H, d, *J* = 8.2 Hz); ^{13}C NMR: δ 15.4, 20.0, 39.2, 51.5, 55.1, 74.4, 111.3, 116.2, 120.3, 127.5, 133.1, 137.1, 149.0, 157.9, 166.9; IR: 3446, 1720, 1654, 1608, 1577, 1558, 1504, 1253 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1363.

4.4.4. (4*S*,5*S*)-Methyl 4-hydroxy-5-(2-methoxy-4-methylphenyl) hex-2(*E*)-enoate (4*S*,5*S*)-3c

From (4*S*,5*S*)-**13c** (252 mg, 0.52 mmol) to (4*S*,5*S*)-**3c** (55.2 mg, 0.209 mmol, 40%) and (4*S*,5*S*)-**1c** (80.0 mg, 0.303 mmol, 58%). $[\alpha]_D^{20} = +25.1$ (*c* 0.53, $CHCl_3$); Lit $[\alpha]_D^{22} = +18.5$ (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 1.22 (3H, d, *J* = 7.2 Hz), 2.15 (1H, br s), 2.32 (3H, s), 3.43 (1H, dq, *J* = 4.4, 7.2 Hz), 3.70 (3H, s), 3.80 (3H, s), 4.46–4.48 (1H, m), 6.01 (1H, d, *J* = 15.6 Hz), 6.68 (1H, s), 6.70 (1H, d, *J* = 8.0 Hz), 6.39 (1H, dd, *J* = 4.2, 15.6 Hz), 7.03 (1H, d, *J* = 8.0 Hz); ^{13}C NMR: δ 13.6, 21.4, 37.7, 51.5, 55.3, 74.1, 111.5, 120.1, 121.3, 127.6, 128.0, 137.8, 149.2, 156.6, 167.0; IR: 3464, 1721, 1654, 1612, 1507, 1264 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1357.

4.4.5. (4*S*,5*S*)-Methyl 4-hydroxy-5-(4-methoxy-3-methylphenyl) hex-2(*E*)-enoate (4*S*,5*S*)-3d

From (4*S*,5*S*)-**13d** (300 mg, 0.623 mmol) to (4*S*,5*S*)-**3d** (155 mg, 0.589 mmol, 94%) and (4*S*,5*S*)-**1d** (1.6 mg, 0.6 μmol, 0.3%). $[\alpha]_D^{21} = -8.4$ (*c* 1.00, $CHCl_3$); ^{1}H NMR: δ 1.25 (3H, d, *J* = 6.4 Hz), 2.18 (3H, s), 2.25 (1H, br s), 2.86 (1H, dq, *J* = 6.0, 6.4 Hz), 3.69 (3H, s), 3.80 (3H, s), 4.31–4.35 (1H, m), 6.01 (1H, dd, *J* = 1.6, 15.6 Hz), 6.74 (1H, d, 7.2 Hz), 6.89 (1H, dd, *J* = 4.4, 15.6 Hz), 6.95–6.99 (2H, m); ^{13}C NMR: δ 15.4, 16.2, 44.3, 51.4, 55.2, 75.2, 109.9, 120.4, 125.9, 126.6, 130.1, 134.0, 148.9, 156.6, 166.9; IR: 3502, 1719, 1654, 1609, 1545, 1506, 1254 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1366.

4.4.6. (4*S*,5*S*)-Methyl 4-hydroxy 5-(2-methoxy-5-methylphenyl) hex-2(*E*)-enoate (4*S*,5*S*)-3e

From (4*S*,5*S*)-**13e** (299 mg, 0.62 mmol) to (4*S*,5*S*)-**3e** (43.3 mg, 0.164 mmol, 26%) and (4*S*,5*S*)-**1e** (99.5 mg, 0.377 mmol, 61%). $[\alpha]_D^{21} = 0$ (*c* 0.78, $CHCl_3$); ^{1}H NMR: δ 1.22 (3H, d, *J* = 7.2 Hz), 2.15 (1H, br s), 2.26 (3H, s), 3.42 (1H, dq, *J* = 4.4, 7.2 Hz), 3.70 (3H, s), 3.78 (3H, s), 4.49 (1H, dt, *J* = 2.0, 4.4 Hz), 6.02 (1H, dd, *J* = 2.0, 15.6 Hz), 6.75 (1H, d, *J* = 8.2 Hz), 6.93 (1H, dd, *J* = 4.4, 15.6 Hz), 6.96 (1H, d, 2.0 Hz), 6.99 (1H, dd, *J* = 2.0, 8.2 Hz); ^{13}C NMR: δ 13.5, 20.6, 38.1, 51.4, 55.5, 74.0, 110.6, 120.1, 128.0, 129.0, 129.9, 130.5, 149.2, 154.7, 167.0; IR: 3481, 1719, 1654, 1504, 1242 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1363.

4.4.7. (4*S*,5*S*)-Methyl 4-hydroxy-5-(2,5-dimethoxyphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-3f

From (4*S*,5*S*)-**13f** (423 mg, 0.848 mmol) to (4*S*,5*S*)-**3f** (101 mg, 0.313 mmol, 37%) and (4*S*,5*S*)-**1f** (168 mg, 0.522 mmol, 67%). $[\alpha]_D^{21} = -4.1$ (*c* 0.60, $CHCl_3$); ^{1}H NMR: δ 1.24 (3H, d, *J* = 7.2 Hz), 2.34 (1H, br s), 3.54 (1H, dq, *J* = 4.4, 7.2 Hz), 3.72 (3H, s), 3.76 (3H, s), 3.79 (3H, s), 4.48–4.52 (1H, m), 6.04 (1H, dd, *J* = 1.6, 15.6 Hz), 6.73 (1H, dd, *J* = 2.8, 8.8 Hz), 6.77 (1H, d, *J* = 2.8 Hz), 6.81 (1H, d, *J* = 8.8 Hz), 6.94 (1H, dd, *J* = 4.4, 15.6 Hz); ^{13}C NMR: δ 13.6, 38.1, 51.5, 55.6, 55.9, 74.0, 111.4, 111.4, 115.0, 120.3, 132.1, 149.0, 151.0, 153.7, 167.0; IR: 3481, 1721, 1657, 1498, 1282, 1217, 1175 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_5$: 280.1311; found: 280.1313.

4.4.8. (4*S*,5*S*)-Methyl 4-hydroxy-5-(3,4-dimethoxyphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-3g

From (4*S*,5*S*)-**13g** (266 mg, 0.534 mmol) to (4*S*,5*S*)-**3g** (130 mg, 0.484 mmol, 87%) and (4*S*,5*S*)-**1g** (15.7 mg, 0.056 mmol, 11%). $[\alpha]_D^{23} = -12.1$ (*c* 1.21, $CHCl_3$); ^{1}H NMR: δ 1.30 (3H, d, *J* = 7.2 Hz), 1.98 (1H, br s), 2.94 (1H, dq, *J* = 5.6, 7.2 Hz), 3.72 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 4.36–4.42 (1H, m), 6.01 (1H, dd, *J* = 1.6, 15.6 Hz), 6.74 (1H, d, *J* = 2.0 Hz), 6.77 (1H, dd, *J* = 2.0, 8.4 Hz), 6.83 (1H, d, *J* = 8.4 Hz), 6.93 (1H, dd, *J* = 5.6, 15.6 Hz); ^{13}C NMR: δ 15.4, 44.8, 51.5, 55.8, 55.8, 75.2, 111.2, 111.2, 119.8, 120.6, 134.8, 147.9, 148.6, 148.9, 166.8; IR: 3493, 1720, 1516, 1261, 1237, 1145, 1026 cm^{-1}; HR-EI-MS calcd for $C_{15}H_{20}O_5$: 280.1311; found: 280.1321.

4.4.9. (4*S*,5*S*)-Methyl 4-hydroxy-5-(2,5-dimethoxy-4-methylphenyl)hex-2(*E*)-enoate (4*S*,5*S*)-3h

From (4*S*,5*S*)-**13h** (315 mg, 0.615 mmol) to (4*S*,5*S*)-**3h** (81.5 mg, 0.554 mmol, 45%) and (4*S*,5*S*)-**1h** (75.5 mg, 0.514 mmol, 42%). $[\alpha]_D^{23} = -5.8$ (*c* 1.22, $CHCl_3$); ^{1}H NMR: δ 1.25 (3H, d, *J* = 7.6 Hz), 2.24 (3H, s) 2.34 (1H, d, *J* = 4.0 Hz), 2.94 (1H, dq, *J* = 5.6, 7.2 Hz), 3.72 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 4.36–4.42 (1H, m), 6.01 (1H, dd, *J* = 1.6, 15.6 Hz), 6.74 (1H, d, *J* = 2.0 Hz), 6.77 (1H, dd, *J* = 2.0, 8.4 Hz), 6.83 (1H, d, *J* = 8.4 Hz), 6.93 (1H, dd, *J* = 5.6, 15.6 Hz); ^{13}C NMR: δ 13.9, 16.1, 38.2, 51.4, 56.1, 56.1, 74.2, 111.2, 114.1, 120.2, 125.7, 128.4, 149.1, 150.1, 151.8, 167.0; IR: 3467, 2951, 1722, 1658, 1505, 1209, 1046 cm^{-1}; HR-EI-MS calcd for $C_{16}H_{22}O_5$: 294.1467; found: 294.1460.

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