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Asymmetric synthesis of 5,6-dehydrosenedigitalene using lipase-catalyzed highly enantioselective transesterification of a primary alcohol with vinyl 3-(4-trifluoromethylphenyl)propanoate

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Abstract—The highly enantioselective kinetic resolution of a racemic primary alcohol by lipase-catalyzed transesterification with vinyl 3-(4-trifluoromethylphenyl)propanoate afforded an enantiomerically pure primary alcohol. The versatility of this approach is shown in the asymmetric synthesis of 5,6-dehydrosenedigitalene (*R*)-**1**.
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1. Introduction

Lipase-catalyzed reactions play an important role in the resolution of the racemates of alcohols.[1] The lipase-catalyzed transesterification in organic solvents is particularly important in this field. In the presence of an acyl donor, one enantiomer of a racemic alcohol can be selectively transformed into the corresponding ester, while the other remains unreacted in an enantiomerically pure form. Although lipases can accept a wide range of alcohols, they do not always show a high enantioselectivity in the resolution. Secondary alcohols are frequently good targets, whereas the resolution of chiral primary alcohols is more difficult to achieve.[1]

During the transesterification, a lipase is initially acylated by an acyl donor such as a vinyl alkanoate and the acylated lipase then reacts enantioselectively with an alcohol.[2] Chen and Sih have proposed that because the acyl group of the acylated lipase exerts steric and/or stereoelectronic effects on the process during which the acylated lipase reacts with an alcohol, it is possible, in principle, to achieve highly enantioselective transesterification by the selection of suitable acyl donors.[2]

On the basis of this assumption, several studies have previously shown that the moderately enantioselective transesterifications of racemic alcohols with vinyl acetate, which is used most frequently as an acyl donor, were improved upon by using other vinyl esters.[3–7] Recently, we reported the highly enantioselective transesterification of 2-phenyl-1-propanol with a lipase (Amano PS from *Burkholderia cepacia*, formerly *Pseudomonas cepacia*) and vinyl 3-arylpropanoates.[3,5] Although the *E*-value[8] with vinyl acetate was 5, the value was 116 for vinyl 3-(4-iodophenyl)propanoate and 138 for vinyl 3-(4-trifluoromethylphenyl)propanoate.[3] This is the first example that shows the utility of vinyl esters having a bulky substituent for lipase-catalyzed transesterification. In the same paper, we also reported that vinyl 3-phenylpropanoate is an efficient reagent for the lipase-catalyzed transesterification of several 2-phenyl-1-alkanols.[3] In order to demonstrate the efficiency of vinyl 3-arylpropanoates for the lipase-catalyzed transesterification of 2-phenyl-1-alkanols, we applied this

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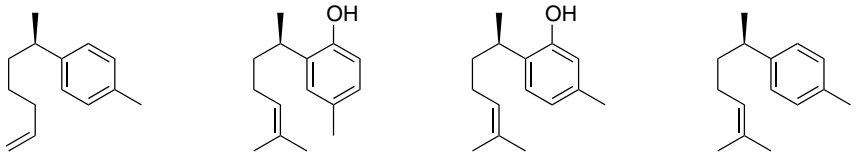
method to the asymmetric synthesis of 5,6-dehydrosene-digitalene (*R*)-**1**,[9] a member of the norsesquiterpenes. Lipase-catalyzed hydrolysis has been used for the asymmetric syntheses of sesquiterpenes such as elvirol (*R*)-**2**[10] and curcuphenol (*R*)-**3**;[11,12] the chiral primary alcohols, which were the synthetic intermediates, have been prepared by lipase-catalyzed hydrolysis.



(*R*)-**1** (*R*)-**2** (*R*)-**3** (*R*)-**4**

Compound (*R*)-**1** was isolated from the aerial parts of the South African *Senecio digitalifolius* by Bohlmann and Zdero in 1978[9] and is structurally related to (*R*)-**3** and α-curcumene (*R*)-**4**, constituents of a large number of essential oils.[13] It has been reported that (*R*)-**3** exhibits weak antibacterial activities against *Staphylococcus aureus* and *Vibrio anguillarum*,[14] while the (*S*)-enantiomer has potent antimicrobial activities against *Candida albicans* et al.[15] and inhibits the activity of gastric H^+, K^+-ATPase.[16] There are many reports on the asymmetric syntheses of **4**, which is quite structurally related to (*R*)-**1**. Chemical methods using stoichiometric chiral materials such as chiral sulfoximine,[17] citronellal,[18,19] 1,1-binaphthalene-8,8-diol,[20] *t*-leucinol,[21] zingiberene isolated from ginger,[22] chiral 5-trimethylsilyl-2-cyclohexenone,[23] chiral *N*,*N*-dimethyllactamide,[24] and D-mannitol[25] have been reported. Catalytic procedures, which are more practical, using asymmetric hydrovinylation,[26] reductive esterification,[27] boron reduction,[28] baker's yeast-mediated reduction,[29,30] Sharpless epoxidation,[31,32] cinchonidine-catalyzed Michael addition,[33] and Grignard cross-coupling[34] have also been reported. However, several reports of the catalytic procedures do not describe any enantiomeric excesses (ees) of **4** and the ee from the baker's yeast-mediated reduction approach, the most efficient procedure for achieving high enantiomeric excess in the final product, is 95%.[29] Although (*R*)-**1** is an analogue of (*R*)-**4**, there is no report on the asymmetric synthesis of (*R*)-**1**.[35] In addition, the absolute stereochemistry of (*R*)-**1** has not yet been confirmed by physical or chemical methods.

Herein, we report the asymmetric synthesis of (*R*)-and (*S*)-**1** from the chiral primary alcohols prepared by lipase PS-catalyzed transesterification with vinyl 3-(4-trifluoromethylphenyl)propanoate in a highly optically pure form (>99% ee).

2. Results and discussion

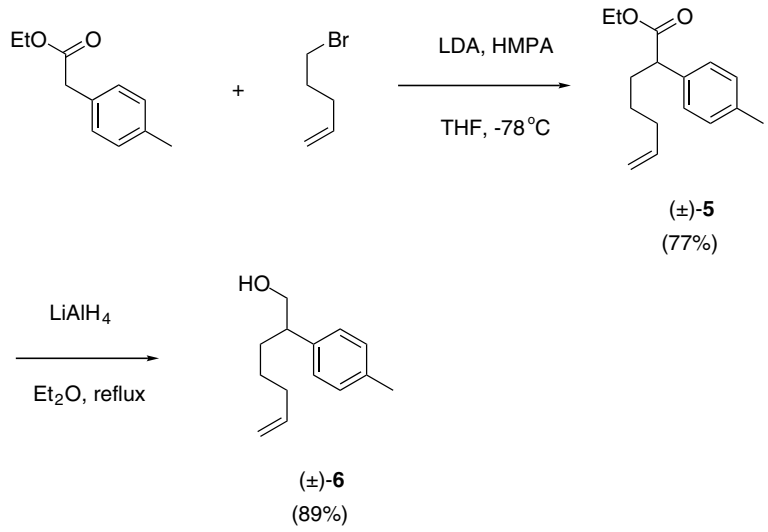
The first step in the sequence leading to (*R*)-**1** was the introduction of the 4-pentenyl group into the α-position of ethyl (4-methylphenyl)acetate, which is commercially available (Scheme 1). Deprotonation of ethyl (4-methylphenyl)acetate with LDA and the addition of 5-bromo-1-pentene provided ethyl 2-(4-methylphenyl)-6-heptenoate (±)-**5** in 77% yield. Treatment of (±)-**5** with $LiAlH_4$ produced the racemic primary alcohol, 2-(4-methylphenyl)-6-heptene-1-ol (±)-**6**, in 89% yield.

The most important point of the present synthesis is to prepare **6** in an optically active form. We successfully achieved this by using the Amano PS-catalyzed transesterification of (±)-**6** with vinyl 3-arylpropanoates. Initially, (±)-**6** was subjected to screening experiments (Table 1). While the lipase-catalyzed transesterification of (±)-**6** with vinyl acetate **7a** in cyclohexane had an *E*-value of 26 (entry 1), the reaction with vinyl 3-phenylpropanoate **7b** had a higher enantioselectivity ($E = 145$, entry 2). This result is consistent with our previous report on the resolution of 2-phenyl-1-propanol.[3,5] The absolute configuration of the enantiomer preferentially esterified by the lipase was thought to have the (*S*)-configuration on the basis of the empirical rule for the enantiopreference of the lipase.[36] We then investigated the effects of solvents on the enantioselectivity of the lipase (entries 2–8), because the enantioselectivity of the lipase was found to depend on the nature of the solvent.[37] As a result of the screening of solvents, we found that hexane was the most suitable regarding the enantioselectivity ($E = 235$) and reaction rate (entry 3). Finally, we tried vinyl 3-(4-trifluoromethylphenyl)propanoate **7c**, which is a very efficient acyl donor for the lipase-catalyzed transesterification of 2-phenyl-1-propanol, and obtained the best result ($E = 331$, entry 9).

On the basis of these results, we conducted a large scale resolution of (±)-**6** with the lipase PS as the asymmetric catalyst and **7c** as the acyl donor in hexane. As we wanted to obtain (*R*)-**6** with an ee as high as possible, we controlled the conversion of the reaction to exceed at least 34% (entry 9). With a rise of the conversion of the transesterification, the ee of (*R*)-**6** becomes higher theoretically, while the ee of (*S*)-**8** becomes lower.[8] Thus, we obtained (*R*)-**6** with >99% ee $\{[\alpha]_D^{24} = -12.6$ (*c* 0.8, $CHCl_3$)$\}$ in 40% yield and (*S*)-**8c** with 79% ee in 49% yield.[†]

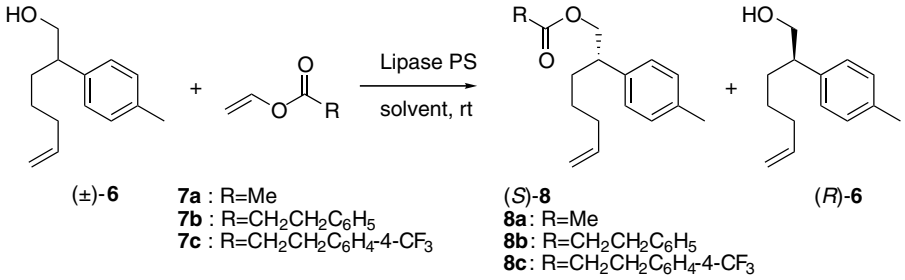
The enantiomerically pure (*R*)-**6** obtained above was converted to the corresponding methanesulfonate (*R*)-**9**

[†] ^1H NMR spectra data of (*S*)-**8c** showed that (*S*)-**8c** was contaminated by **7c**. The yields described here was estimated from the ^1H NMR analysis.



Scheme 1.

Table 1. Lipase-catalyzed kinetic resolution of (±)-**6**[a]



Entry	Acyl donor	Solvent	Time (h)	Conversion (%)[b]	(*S*)-**8** ee (%)	(*R*)-**6** ee (%)	*E*[b]
1	**7a**[c]	Cyclohexane	5.5	50	82	83	26
2	**7b**	Cyclohexane	3.5	52	93	99	145
3	**7b**	Hexane	4.5	49	97	94	235
4	**7b**	Isooctane	1.5	54	86	99	69
5	**7b**	Toluene	23.5	46	96	81	123
6[d]	**7b**	Acetone	18.5	34	98	50	163
7[d]	**7b**	THF	21	42	97	70	138
8	**7b**	1,4-Dioxane	4.5	<1[e]	—	—	—
9	**7c**	Hexane	4.5	34	99	51	331

[a] Conditions: Lipase PS (20 mg/ml), (±)-**6** (60 mM), acyl donor (60 mM), room temperature. All the solvents except isooctane were dried.
[b] Calculated from ees of (*S*)-**8** and (*R*)-**6**.
[c] **7a** (300 mM).
[d] Lipase PS (40 mg/ml).
[e] Determined by GC analysis.

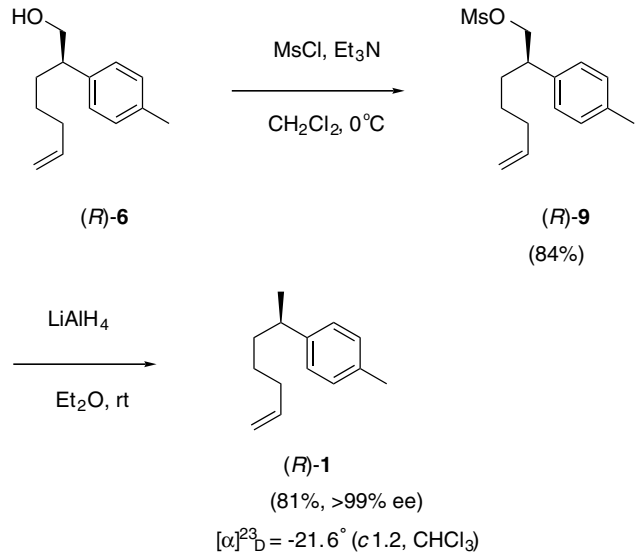
with methanesulfonyl chloride and triethylamine in 84% yield (Scheme 2). The synthesis of (*R*)-**1** was finally accomplished by the reaction of (*R*)-**9** with $LiAlH_4$ in 81% yield and >99% ee $\{[\alpha]_D^{23} = -21.6$ (*c* 1.2, $CHCl_3$)$\}$.[‡]

The ^1H NMR spectroscopic data were identical to those of the natural product isolated by Bohlmann and Zdero.[9]

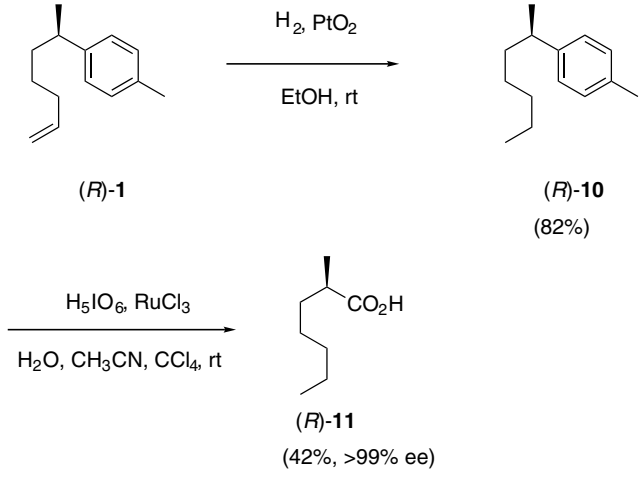
The absolute configuration of (*R*)-**1** was determined according to Scheme 3. Compound (*R*)-**1** was hydrogenated with a catalytic amount of PtO_2 at 1 atm of hydrogen to give (*R*)-**10**. The treatment of (*R*)-**10** with $RuCl_3$ and H_5IO_6 gave (*R*)-**11** with >99% ee $\{[\alpha]_D^{23} = -14.9$ (*c* 1.2, EtOH), Lit.:[38] $[\alpha]_D = -15.6$ (*c* 0.55, EtOH), 93% ee (*R*)$\}$.

We also synthesized (*S*)-**1**, not a natural product, from (*S*)-**8c** according to Scheme 4. As (*S*)-**8c** did not have an enantiomeric excess high enough for use, (*S*)-**8c** was

[‡] Bohlmann and Zdero did not mention the value of the specific rotation of (*R*)-**1** in their paper. However, they stated that they assumed the absolute configuration of (*R*)-**1** by the comparison of the specific rotation of (*R*)-**1** with that of (*R*)-**4**. They also assumed the absolute configuration of a structurally closely related norsesquiterpene having an (*R*)-configuration by a similar method. The norsesquiterpene had a specific rotation of −32.6 (*c* 1.38, $CHCl_3$).[9] Therefore, we judged that (*R*)-**1** had a specific rotation with a negative sign.



Scheme 2.



Scheme 3.

hydrolyzed to (*S*)-**6** with NaOH and (*S*)-**6** again subjected to the lipase-catalyzed transesterification to increase the ee. The obtained ester (*S*)-**8c** was then hydrolyzed in a similar manner to give (*S*)-**6** with >99% ee $\{[\alpha]_D^{24} = +16.0$ (*c* 1.1, $CHCl_3)\}$ and (*S*)-**6** was converted to (*S*)-**1** with >99% ee $\{[\alpha]_D^{24} = +23.0$ (*c* 1.1, $CHCl_3)\}$ according to the same route we used to prepare (*R*)-**1**.

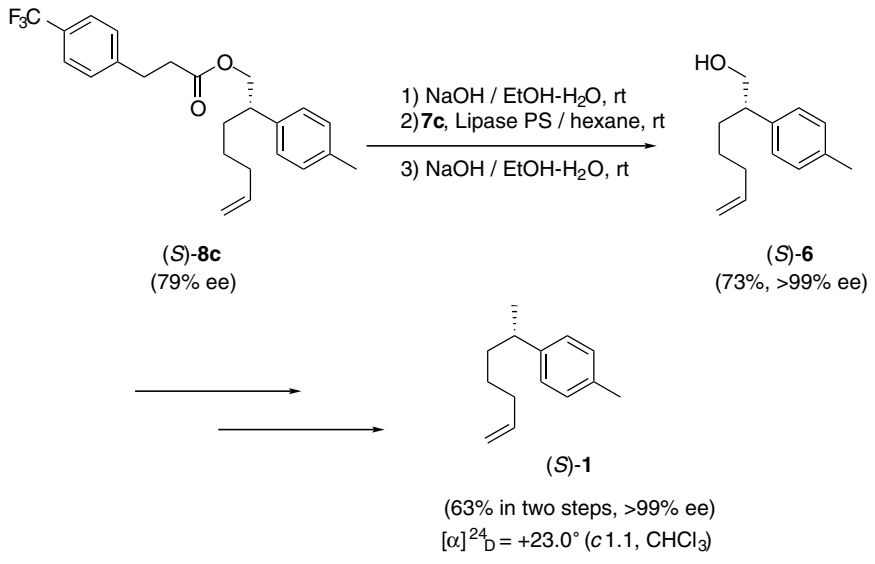
3. Conclusion

We have been able to synthesize optically active 5,6-dehydrosenedigitalene (*R*)-**1** and its enantiomer, not a natural product, from the chiral intermediates obtained via the lipase-catalyzed transesterification of (±)-**6** with **7c**. We firmly believe in the utility of vinyl 3-arylpropanoates in the lipase-catalyzed kinetic resolution of 2-aryl-1-alkanols and are now synthesizing other natural products from chiral primary alcohols prepared via our method.

4. Experimental

4.1. General

All commercially available reagent chemicals were obtained from Aldrich, Nacalai Tesque, Tokyo Kasei, and Wako Chemicals, and generally used without further purification. Compounds **7b** and **7c** were prepared according to the reported procedure.[3] Ether, benzene, 1,4-dioxane, and THF were distilled from Na/benzophenone under Ar. Cyclohexane, hexane, toluene, dichloromethane, pyridine, triethylamine, and diisopropylamine were distilled from CaH_2. Acetone and vinyl acetate were distilled from molecular sieves 3 Å. HMPA was distilled from CaH_2 under reduced pressure (70.1–72.1 °C/0.5 mmHg). Lipase PS was purchased from Amano Enzyme, Inc., and dried over P_2O_5. The ^1H NMR spectra were



Scheme 4.

recorded using a Jeol JNM-LA 400 spectrometer for solution in $CDCl_3$ with TMS as the internal standard, and the J values are given in hertz. The IR spectra were obtained using a Jasco FT/IR-410 spectrometer. The mass spectra (MS) were obtained using a Jeol JMS-GCmate spectrometer. The high-resolution mass spectra (HRMS) were obtained using a Jeol JMS-AX505HAD spectrometer and the electron ionization method. The optical rotations were measured with a Horiba SEPA-300 polarimeter. The gas chromatograms were recorded on a Shimazu GC-14B with GAMMA DEX™ 120 capillary column (Supelco), 30 m × 0.25 mm and OV 101 bonded capillary column (GL Sciences), 17 m × 0.25 mm. The HPLC analyses were carried out on a Hitachi L-6250 intelligent pump with a Hitachi L-4000 UV detector using a Chiralcel OJ (Daicel), 250 × 4.6 mm.

4.2. Ethyl 2-(4-methylphenyl)-6-heptenoate (±)-5

Anhydrous THF (15 ml) and anhydrous diisopropylamine (2.532 g, 25.02 mmol) were added to a three-necked, round-bottomed flask and maintained under an Ar atmosphere. After cooling the mixture to 0 °C, *n*-butyl lithium in hexane solution (16 ml of 1.6 M, 26 mmol) was added via a syringe over a period of 10 min. The mixture was stirred for 15 min at 0 °C and cooled to −78 °C. Ethyl 2-(4-methylphenyl)acetate (4.453 g, 24.99 mmol) was added via a syringe over a period of 10 min. After stirring for 45 min, 5-bromo-1-pentene (3.720 g, 24.96 mmol) dissolved in dry HMPA (4.467 g, 24.93 mmol) was added over the period of 15 min at −78 °C. After stirring overnight at room temperature, the mixture was treated with 1 M HCl (50 ml) at 0 °C and extracted three times with ether. The ether solution was washed with deionized water, saturated aqueous sodium chloride, and dried with sodium sulfate. The solvent was evaporated and the residue was chromatographed (silica gel, hexane–acetone 10:1 (v/v)) to give (±)-**5** as a colorless oil (4.698 g, 77%); ^{1}H NMR: 7.19 (2H, d, $J = 8.0$), 7.12 (2H, d, $J = 8.3$), 5.76 (1H, ddt, $J = 16.8$, $J = 10.3$, $J = 6.7$), 4.98 (1H, dd, $J = 17.2$, $J = 1.6$), 4.93 (1H, dd, $J = 10.1$, $J = 1.3$), 4.03–4.18 (2H, m), 3.48 (1H, t, $J = 7.7$), 2.32 (3H, s), 2.05 (2H, q, $J = 7.7$), 2.01–2.10 (1H, m), 1.71–1.80 (1H, m), 1.29–1.41 (2H, m), 1.20 (3H, t, $J = 7.1$); IR (neat): 1640, 1732, 993, 911 cm^{-1}; MS (*m*/*z*) 246 (M^+); HRMS calcd for $C_{16}H_{22}O_2$ (M^+), 246.1620. Found: 246.1602.

4.3. 2-(4-Methylphenyl)-6-heptene-1-ol (±)-6

To a suspension of $LiAlH_4$ (0.720 g, 19.0 mmol) in dry ether (25 ml) at room temperature under an Ar atmosphere was slowly added a solution of (±)-**5** (4.615 g, 18.73 mmol) in dry ether (35 ml). The reaction mixture was refluxed overnight and quenched at 0 °C with 6 M HCl (20 ml). The resulting mixture was extracted three times with ether. The organic phase was washed with a saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvents, the residue was chromatographed (silica gel, hexane–ethyl acetate 2:1 (v/v)) to give (±)-**6** as a colorless oil (3.417 g, 89%); ^{1}H NMR: 7.15 (2H, d, $J = 8.3$), 7.10 (2H, d, $J = 8.0$), 5.74 (1H, ddt, $J = 17.1$, $J = 10.1$, $J = 6.8$), 4.96 (1H, dd, $J = 17.1$, $J = 1.4$), 4.91 (1H, dd, $J = 10.3$, $J = 1.2$), 3.66–3.77 (2H, m), 2.71–2.78 (1H, m), 2.33 (3H, s), 1.97–2.07 (2H, m), 1.65–1.73 (1H, m), 1.51–1.61 (1H, m), 1.26–1.37 (2H, m); IR (neat): 3350, 1640, 994, 910 cm^{-1}; MS (*m*/*z*) 204 (M^+); HRMS calcd for $C_{14}H_{20}O$ (M^+), 204.1514. Found: 204.1528.

4.4. 2-(4-Methylphenyl)-6-hepten-1-yl acetate (±)-8a

Compound (±)-**8a** was prepared as an authentic sample. To a solution of (±)-**6** (0.104 g, 0.509 mmol) and dry pyridine (0.243 g, 3.07 mmol) in dry benzene (10 ml) at 0 °C, acetyl chloride (0.138 g, 1.76 mmol) was slowly added. The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with 1 M HCl (10 ml). The resulting mixture was extracted with ethyl acetate. The organic phase was washed with deionized water, a saturated sodium hydrogen carbonate solution, and a saturated sodium chloride solution, then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed (silica gel, hexane–ethyl acetate 5:1 (v/v)) to give (±)-**8a** as a colorless oil (0.107 g, 86%); ^{1}H NMR: 7.12 (2H, d, $J = 8.0$), 7.07 (2H, d, $J = 8.3$), 5.73 (1H, ddt, $J = 17.1$, $J = 10.2$, $J = 6.6$), 4.95 (1H, dd, $J = 17.2$, $J = 2.1$), 4.91 (1H, dd, $J = 10.3$, $J = 1.9$), 4.12–4.21 (2H, m), 2.83–2.90 (1H, m), 2.33 (3H, s), 1.99 (3H, s), 1.96–2.05 (2H, m), 1.68–1.77 (1H, m), 1.53–1.63 (1H, m), 1.25–1.32 (2H, m); IR (neat): 1741, 1640, 990, 911 cm^{-1}; MS (*m*/*z*) 246 (M^+); HRMS calcd for $C_{16}H_{22}O_2$ (M^+), 246.1620. Found: 246.1487.

4.5. 2-(4-Methylphenyl)-6-hepten-1-yl 3-phenylpropanoate (±)-8b

Compound (±)-**8b** was prepared as an authentic sample. To a solution of (±)-**6** (0.100 g, 0.489 mmol), 3-phenylpropanoic acid (0.076 g, 0.51 mmol), and 4-dimethylaminopyridine (0.059 g, 0.48 mmol) in dry dichloromethane (10 ml) at 0 °C, *N*,*N*′-dicyclohexylcarbodiimide (0.102 g, 0.494 mmol) was slowly added. The reaction mixture was stirred overnight at room temperature and filtered. The filtrate was washed with 0.5 M HCl (two times), and a saturated sodium hydrogen carbonate solution (two times), and then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed [silica gel, hexane–ethyl acetate 5:1 (v/v)] to give (±)-**8b** as a colorless oil (0.113 g, 69%); ^{1}H NMR: 7.12–7.30 (5H, m), 7.10 (2H, d, $J = 7.8$), 7.04 (2H, d, $J = 8.0$), 5.72 (1H, ddt, $J = 17.1$, $J = 10.2$, $J = 6.8$), 4.99–4.98 (2H, m), 4.16 (2H, dd, $J = 7.0$, $J = 3.3$), 2.88 (2H, t, $J = 7.8$), 2.82–2.90 (1H, m), 2.57 (2H, t, $J = 7.9$), 2.32 (3H, s), 1.96–2.03 (2H, m), 1.63–1.70 (1H, m), 1.53–1.60 (1H, m), 1.23–1.31 (2H, m); IR (neat): 1736, 1639, 992, 911 cm^{-1}; MS (*m*/*z*) 336 (M^+); HRMS calcd for $C_{23}H_{28}O_2$ (M^+), 336.2089. Found: 336.2074.

4.6. 2-(4-Methylphenyl)-6-hepten-1-yl 3-(4-trifluoromethylphenyl)propanoate (±)-8c

Compound (±)-**8c** as an authentic sample was prepared from (±)-**6** (0.094 g, 0.46 mmol), 3-(4-trifluoromethylphenyl)propanoic acid (0.121 g, 0.555 mmol) with 4-

dimethylaminopyridine (0.046 g, 0.38 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (0.094 g, 0.46 mmol) in dry dichloromethane (5 ml) according to the procedure for the preparation of (±)-**8b**. Chromatography [silica gel, hexane–ethyl acetate 5:1 (v/v)] of the crude product provided (±)-**8c** as a colorless oil (0.096 g, 49%); ^{1}H NMR: 7.51 (2H, d, $J = 8.3$), 7.23 (2H, d, $J = 8.1$), 7.11 (2H, d, $J = 7.8$), 7.03 (2H, d, $J = 8.0$), 5.72 (1H, ddt, $J = 17.1$, $J = 10.2$, $J = 6.8$), 4.89–4.98 (2H, m), 4.17 (2H, dd, $J = 7.0$, $J = 3.3$), 2.92 (2H, t, $J = 76$), 2.82–2.86 (1H, m), 2.58 (2H, t, $J = 7.6$), 2.32 (3H, s), 1.96–2.03 (2H, m), 1.62–1.69 (1H, m), 1.50–1.60 (1H, m), 1.23–1.31 (2H, m); IR (neat): 1737, 1640, 1326, 993, 912 cm^{-1}; MS (*m*/*z*) 404 (M^+); HRMS calcd for $C_{24}H_{27}F_3O_2$ (M^+), 404.1963. Found: 404.1978.

4.7. Resolution of (±)-6 (screening experiments)

In a typical run, lipase PS (20 mg) was placed in a vial containing a 1 ml solution of (±)-**6** (60 μmol) and vinyl ester (60 μmol). The resulting suspension was then magnetically stirred at room temperature. Samples were withdrawn from the vial and analyzed by gas chromatography (OV 101). The reaction was stopped by the filtration of the lipase at about a 40% conversion, and the filtrate concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane–ethyl acetate 10:1–5:1 (v/v)) with a short column (10 mm × 80 mm) to give (*R*)-**6** and (*S*)-**8**. The *E*-value and the conversion of the reaction were calculated from the ees of (*R*)-**6** and (*S*)-**8**.[8] As the ee of (*S*)-**8b** could not be determined by either GC or HPLC, (*S*)-**8b** was hydrolyzed to (*S*)-**6** according to the procedure in Section 4.8.

Conditions for the determination of the ee of (*R*)-**6**, (*S*)-**8a**, and (*S*)-**8c** are as follows. Compound (*R*)-**6**: HPLC (Chiralcel OJ), hexane–2-propanol = 10:1 (v/v); (*S*)-**8a**: HPLC (Chiralcel OJ), hexane–2-propanol = 10:1 (v/v); (*S*)-**8c**: HPLC (Chiralcel OJ), hexane–2-propanol = 30:1 (v/v).

4.8. Preparative resolution of (±)-6

Lipase PS (5.699 g) was added to a solution of (±)-**6** (3.417 g, 16.73 mmol) and **7c** (4.090 g, 16.75 mmol) in dry hexane (280 ml). The mixture was stirred for 29 h at room temperature. The reaction was quenched by filtration and the filtrate was concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane–ethyl acetate 5:1–2:1 (v/v)) to give (*S*)-**8c** and (*R*)-**6** as colorless oils.

Compound (*S*)-**8c**: yield 3.304 g (49%), accompanied by **7c** of 0.52 g; ee = 79%; ^{1}H NMR spectra data of this sample were identical with those of (±)-**8c**.

Compound (*R*)-**6**: yield 1.355 g (40%); ee >99%; $[\alpha]_D^{24} = -12.6$ (*c* 0.8, $CHCl_3$); ^{1}H NMR spectra data of this sample were identical to those of (±)-**6**.

NaOH (6 M, 3 ml) was added to a solution of (*S*)-**8c** (3.276 g, 8.100 mmol) accompanied by **7c** (0.514 g) in ethanol (15 ml). The mixture was stirred overnight at room temperature. After removal of the solvent, the residue was extracted three times with ether. The organic layer was washed with brine, then dried over sodium sulfate, and concentrated. The residue was chromatographed (silica gel, hexane–ethyl acetate 5:1 (v/v)) to give (*S*)-**6** (1.609 g, 98%) as a yellow oil. ^{1}H NMR spectra data of this sample were identical to those of (±)-**6**.

According to the procedures described above, the (*S*)-**6** obtained here was again subjected to the lipase PS-catalyzed transesterification with **7c** to give the enantiomerically pure (*S*)-**8c**: lipase PS (1.250 g), (*S*)-**6** (1.581 g, 7.739 mmol), **7c** (2.861 g, 11.72 mmol), dry hexane (125 ml), reaction time (24.5 h), yield of (*S*)-**8c** (2.372 g, 76%). Compound (*S*)-**8c** was accompanied by 1.031 g of **7c**.

Thus, the obtained enantiomerically pure (*S*)-**8c** was again hydrolyzed with NaOH to give (*S*)-**6**: (*S*)-**8c** (2.359 g, 5.832 mmol) accompanied by **7c** (1.026 g), 6 M NaOH (3.5 ml), ethanol (15 ml), reaction time 1 h, yield of (*S*)-**6** {1.158 g, 97%, >99% ee, $[\alpha]_D^{24} = +16.0$ (*c* 1.1, $CHCl_3$)}. ^{1}H NMR spectra data of this sample were identical to those of (±)-**6**.

4.9. (*R*)-2-(4-Methylphenyl)-6-hepten-1-yl methanesulfonate (*R*)-9

To a solution of (*R*)-**6** (1.335 g, 6.535 mmol) and dry Et_3N (1.872 g, 18.50 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C was slowly added methanesulfonyl chloride (0.959 g, 8.37 mmol). The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with 1 M HCl (20 ml). The resulting mixture was then extracted twice with ether. The organic phase was washed with deionized water, a saturated sodium hydrogen carbonate solution, and a saturated sodium chloride solution in this order, then dried over sodium sulfate. After removal of the solvents, the residue was chromatographed [silica gel, hexane–ethyl acetate 2:1 (v/v)] to give (*R*)-**8** as a colorless oil (1.540 g, 84%); ^{1}H NMR: 7.14 (2H, d, $J = 8.0$), 7.08 (2H, d, $J = 8.3$), 5.72 (1H, ddt, $J = 16.8$, $J = 10.2$, $J = 6.8$), 4.90–4.98 (2H, m), 4.28 (2H, d, $J = 6.8$), 2.91–2.98 (1H, m), 2.76 (3H, s), 2.32 (3H, s), 1.95–2.09 (2H, m), 1.74–1.83 (1H, m), 1.57–1.67 (1H, m), 1.24–1.34 (2H, m); IR (neat): 1640, 1356, 1175, 974 cm^{-1}; MS (*m*/*z*) 282 (M^+); HRMS calcd for $C_{15}H_{22}O_3S$ (M^+), 282.1290. Found: 282.1306.

4.10. 5,6-Dehydrosenedigitalene [(*R*)-6-(4-Methylphenyl)-1-heptene] (*R*)-1

To a suspension of $LiAlH_4$ (1.280 g, 33.73 mol) in dry ether (45 ml) at room temperature under an Ar atmosphere was slowly added a solution of (*R*)-**8** (1.460 g, 5.170 mmol) in dry ether (14 ml). The reaction mixture was stirred overnight at room temperature and quenched at 0 °C with 2 M HCl (70 ml). The resulting mixture was extracted three times with ether. The organic phase was washed with a saturated sodium hydrogen carbonate solution and a saturated sodium chloride solution, then dried over sodium sulfate. After removal of the solvents,

the residue was chromatographed (silica gel, hexane) to give (*R*)-**1** as a colorless oil (0.785 g, 81%, >99% ee); $[\alpha]_D^{23} = -21.6$ (*c* 1.2, $CHCl_3$); ^1H NMR: 7.10 (2H, d, $J = 8.0$), 7.07 (2H, d, $J = 8.3$), 5.76 (1H, ddt, $J = 17.1$, $J = 10.2$, $J = 6.8$), 4.96 (1H, dd, $J = 17.1$, $J = 2.2$), 4.91 (1H, dd, $J = 10.2$, $J = 1.5$), 2.64 (1H, sextet, $J = 7.1$), 2.32 (3H, s), 2.01 (2H, dt, $J = 7.3$, $J = 6.8$), 1.53–1.59 (2H, m), 1.24–1.39 (2H, m), 1.21 (3H, d, $J = 7.1$); IR (neat): 1640, 995, 909 cm^{-1}; MS (*m/z*) 188 (M^+); HRMS calcd for $C_{14}H_{20}$ (M^+), 188.1565. Found: 188.1547. The enantiomeric excess was determined by GC analysis on a GAMMA DEX™ 120 capillary column (95 °C).

4.11. (*R*)-2-(4-Methylphenyl)heptane (*R*)-10

A solution of (*R*)-**1** (0.500 g, 2.66 mmol) in EtOH (10 ml) was hydrogenated overnight over PtO_2 (10.3 mg) at room temperature under an atmospheric pressure of hydrogen. The reaction was quenched by filtration, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane) to give (*R*)-**10** as a colorless oil (0.413 g, 82%); ^1H NMR: 7.10 (2H, d, $J = 8.3$), 7.07 (2H, d, $J = 8.3$), 2.63 (1H, sextet, $J = 7.1$), 2.32 (3H, s), 1.46–1.59 (2H, m), 1.21 (3H, d, $J = 6.8$), 1.13–1.30 (6H, m), 0.85 (3H, t, $J = 6.8$).

4.12. (*R*)-2-Methylheptanoic acid (*R*)-11

A round-bottom flask was charged with (*R*)-**10** (0.371 g, 1.95 mmol), CCl_4 (3.7 ml), acetonitrile (3.7 ml), deionized water (5.6 ml), and H_5IO_6 (6.339 g, 27.81 mmol). The flask contents were stirred until both phases became clear. To the flask was slowly added $RuCl_3$ (27.2 mg, 0.132 mmol) at 0 °C, and the reaction mixture was vigorously stirred for 4 h at room temperature. The reaction mixture was cooled to 0 °C, and ether (7.5 ml) then added with vigorous stirring for 15 min. The organic phase was separated and the aqueous phase extracted two times with ether. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was diluted with ether and extracted with 0.3 M NaOH (3 × 5 ml). The aqueous extract was acidified with hydrochloric acid to pH 3, then extracted three times with ether. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was distilled (158–190 °C/0.8 mmHg) to give (*R*)-**11** (0.117 g, 42%, >99% ee) as a colorless oil; $[\alpha]_D^{23} = -14.9$ (*c* 1.2, EtOH), Lit.:[38] $[\alpha]_D = -15.6$ (*c* 0.55, EtOH), 93% ee, (*R*); ^1H NMR spectra data of this sample were identical to those of a commercially available authentic sample (racemate). The enantiomeric excess was determined by GC analysis on a GAMMA DEX™ 120 capillary column (120 °C).

4.13. (*S*)-6-(4-Methylphenyl)-1-heptene (*S*)-1

Compound (*S*)-**1** was prepared from (*S*)-**6** in two steps according to the procedures described in Sections 4.9 and 4.10. Colorless oil (63% from (*S*)-**6**, >99% ee); $[\alpha]_D^{24} = +23.0$ (*c* 1.1, $CHCl_3$); ^1H NMR spectra data of this sample were identical with those of (*R*)-**6**.

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