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ASYMMETRIC SYNTHESIS OF FLINDERSIACHROMANONE USING LIPASE-CATALYZED REACTION

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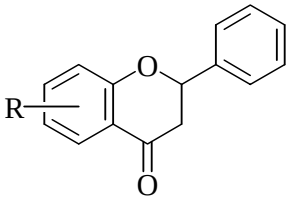
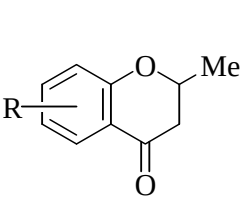
Abstract - The (*R*)- and (*S*)-enantiomers of flindersiachromanone (2-(2-phenylethyl)-4-chromanone) were synthesized from the enantiomerically pure 1-phenyl-5-hexen-3-ol obtained *via* the lipase-catalyzed enantioselective transesterification.

INTRODUCTION

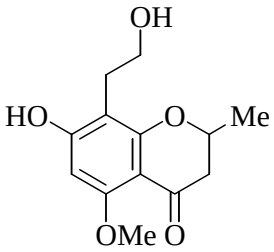
A variety of 2-substituted 4-chromanones (2-substituted 2,3-dihydro-4*H*-benzopyran-4-ones) are present in nature,[1] and it is known that many of these compounds including non-natural products possess biological and pharmacological activities.[1a] Several 2-substituted 4-chromanones are exemplified below.[2] Flavanones (**1**) are the representative compounds and have been isolated from plants.[3] The flavanone with a 7-methoxy group (**1b**) was found to be a potent inhibitor of MCF-7 breast cancer cell growth.[4] As other examples, **2b** is among compounds that show some fly killing activity,[5] and a weak anthelmintic activity has been demonstrated for **2c**.[6]



1a: R=H
1b: R=7-OMe
1c: R=5-OH and 7-OMe



2a: R=H
2b: R=6-Me
2c: R=7-OH



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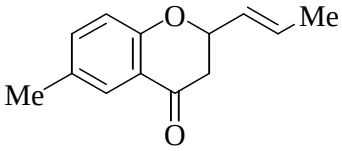

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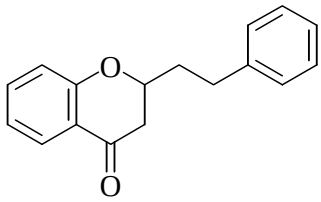

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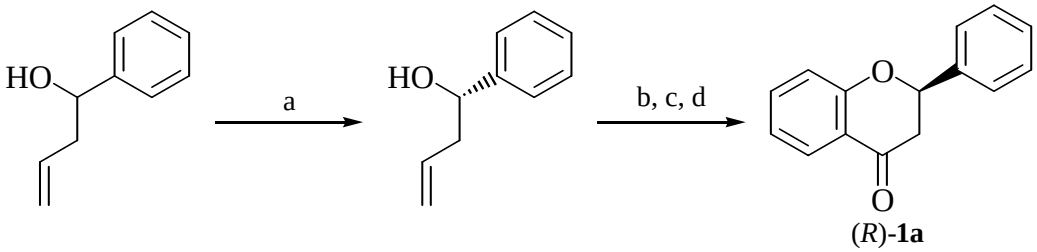
Despite this interesting potential of the 2-substituted 4-chromanones, there are few reports on their asymmetric synthesis. Both enantiomers of **1a** and **2a** were prepared *via* the ring-opening reaction of chiral epoxides with a dithiane anion, followed by the intramolecular Mitsunobu reaction.[7] Hodgetts described two approaches to (*S*)-**1a** and (*R*)-**2a**.[8] One of the approaches utilized the oxidation of the preformed chiral 2-substituted chromans and another approach involved the intramolecular Mitsunobu reaction. The latter methodology was also used for the synthesis of (*S*)-**1c**. Other successful examples include the diastereoselective conjugated addition of cuprates to homochiral 3-(*p*-tolylsulfinyl)chromones[9] and an approach based on the Houben-Hoesch reaction.[10] We recently described the synthesis of both enantiomers of **1a** based on the intermolecular Mitsunobu reaction between phenol and chiral 1-phenyl-3-buten-1-ol prepared *via* a lipase-catalyzed kinetic resolution, followed by the oxidative cleavage of the double bond and subsequent intramolecular Friedel-Crafts acylation (Scheme 1).[11]



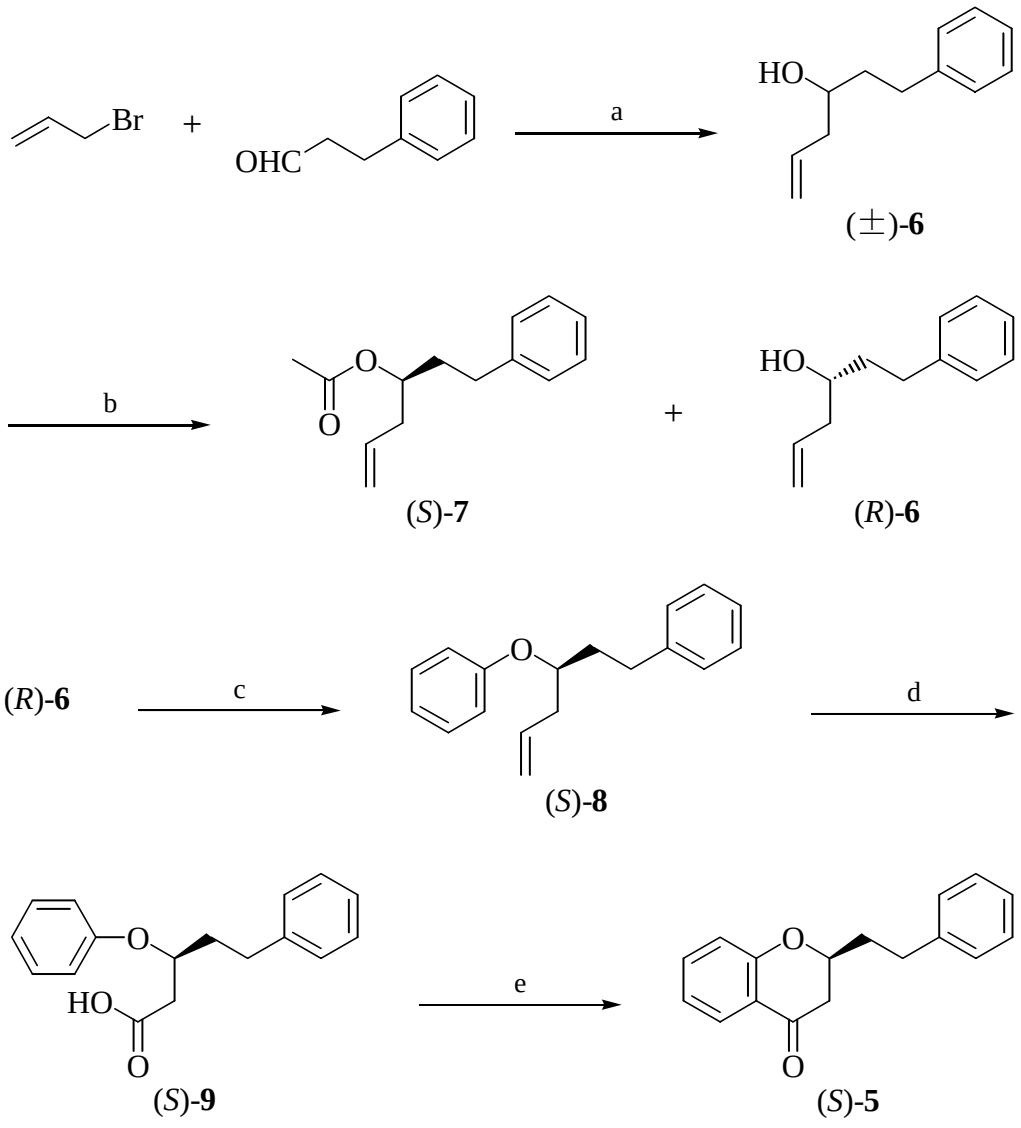
(*R*)-**1a**

Scheme 1: Reagents and conditions: a: lipase, vinyl acetate, isooctane, rt (40%, >99% ee); b: PhOH, PPh_3, diisopropyl azodicarboxylate, THF, rt (61%, 97% ee); c: $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O-*t*-BuOH, rt (67%); d: TFAA, TFA, CH_2Cl_2, rt (49%, 96% ee).

We now report an application of our methodology to the asymmetric synthesis of flindersiachromanone (**5**) isolated from the extracts of the bark of *Flindersia laevicarpa* by Picker *et al.*,[2g] and the determination of the absolute configuration of **5**.

RESULTS AND DISCUSSION

Compound ((*S*)-**5**) was synthesized according to the route shown in Scheme 2. The most important point of the present synthesis is to prepare the 1-phenyl-5-hexen-3-ol (**6**) in the highly enantiomerically active form. There are many reports for the asymmetric synthesis of **6**.[12] Significant results have been obtained using the catalytic enantioselective allylation of 3-phenylpropanal and a stoichiometric amount of allyl metal compounds bearing chiral ligands. Although Maruoka *et al*. reported the highly enantioselective catalytic allylation (>98% ee),[12i,12m] they have used organotin compound with potential toxicity. Therefore, we adopted our previously reported method that secondary alcohols structurally related to (±)-**6** could be resolved with a high enantioselectivity *via* the lipase-catalyzed transesterification.[11,13]



Scheme 2: Reagents and conditions: a: In, H_2O, rt (91%); b: lipase PS, vinyl acetate, rt (51% and 96% ee for (*S*)-**7**, 48% and >99% ee for (*R*)-**6**); c: PhOH, PPh_3, diisopropyl azodicarboxylate, toluene, 0^o-rt (76%, >99% ee); d: $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O-*t*-BuOH, rt (85%); e: TFAA, TFA, CH_2Cl_2, rt (94%, >99% ee).

The racemic secondary alcohol ((±)-**6**) was prepared from the purified 3-phenylpropanal and allyl bromide with indium in 91% yield. Six commercially available lipases from different origins were screened to obtain an efficient catalyst for the enantioselective acetylation of (±)-**6**. The obtained results are summarized in Table 1. While Amano AY, Meito ALC, and Meito PLC showed only a low activity (<20%, Entries 3, 5, and 6), Amano PS, Amano AK, and Novozym 435 showed high levels of activity (Entries 1, 2, and 4). These lipases followed the empirical rule for the enantiopreference of several lipases toward secondary alcohols,[14] and therefore, (*S*)-**6** was acetylated faster than (*R*)-**6**. However, the lipases showed a different degree of enantioselectivity. Among them, Amano PS produced the best enantioselectivity (E^{15}=747, Entry 1). This result agrees with the high enantioselectivity of this lipase observed in the discrimination of enantiomers of the secondary alcohols structurally related to (±)-**6**. [11,13]

Table 1. Lipase-catalyzed transesterification of (±)-**6** with vinyl acetate in hexane[a]

Entry	Lipase[b]	Time (h)	Conversion (%)[c]	(*S*)-**7** ee (%)	(*R*)-**6** ee (%)	E[c]
1	Amano PS	66	49	99	95	747
2	Amano AK	41	49	98	95	371
3	Amano AY	51	3[d]	-	-	-
4	Novozym 435	75	50	65	65	9
5	Meito ALC	51	1[d]	-	-	-
6	Meito PLC	51.5	16[d]	-	-	-

[a] Conditions: lipase (20 mg/ml), (±)-**6** (60 mM), vinyl acetate (120 mM), room temperature.

[b] Amano PS from *Burkholderia cepacia*, Amano AK from *Pseudomonas fluorecens*, Amano AY from *Candida rugosa*, Novozym 435 from *Candida antarctica*, Meito ALC from *Achromobacter* sp., Meito PLC from *Alcaligenes* sp.

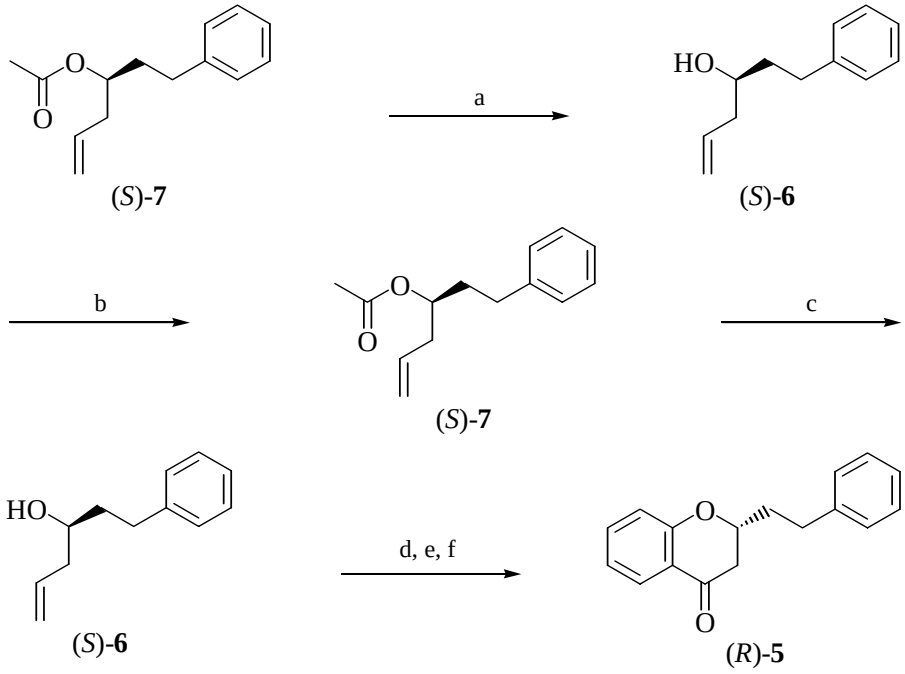
[c] Calculated from ees of (*S*)-**7** and (*R*)-**6**.[15]

[d] Determined by GC analysis.

On the basis of these results, we conducted the large scale resolution of (±)-**6** with the lipase PS as the asymmetric catalyst to obtain (*R*)-**6** with >99% ee {$[\alpha]^{23}_D$ +22.4° (*c* 1.2, $CHCl_3$); lit.,[12a] $[\alpha]^{20}_D$ -9.6° (*c* 4.2, $CHCl_3$), 48% ee, (*S*)} in 48% yield and (*S*)-**7** with 96% ee in 51% yield. The coupling of (*R*)-**6** with phenol by using of diisopropyl azodicarboxylate in the presence of triphenylphosphine gave the phenyl

ether ((*S*)-**8**) in 76% yield. The ^{1}H-NMR spectral data showed that (*S*)-**8c** was contaminated by the triphenylphosphine oxide.[16] However, the triphenylphosphine oxide did not interfere with the following reaction. The oxidative cleavage of the double bond of (*S*)-**8** with $KMnO_4$ and $NaIO_4$ afforded the corresponding acid ((*S*)-**9**) in 85% yield. The intramolecular Friedel-Crafts acylation of (*S*)-**9** using trifluoroacetic acid and trifluoroacetic anhydride afforded (*S*)-**5** with >99% ee {$[\alpha]^{24}_D$ -77.8° (*c* 1.2, MeOH); lit.,[2g] $[\alpha]_D$ -1.6° (*c* 5%, MeOH)} in 94% yield. Judging from the ee value, no racemization occurred during the conversion processes from (*R*)-**6** to (*S*)-**5**. The ^{1}H-NMR spectral data and the sign of the specific rotation were in agreement with the published data.[2g] Therefore, **5** isolated by Picker *et al*. has the (*S*)-configuration. However, the specific rotation was considerably higher than the published value. Such a discrepancy was observed with the simpler analogue (*S*)-2**b** by Hodgetts *et al*., who described the possibility of the partial racemization of the material isolated from a natural source *via* the reversible elimination of the pyran oxygen during isolation.[9a]

We also synthesized (*R*)-**5**, not a natural product, from (*S*)-**7** according to the route shown in Scheme 3. Because (*S*)-**7** did not have an ee (96%) high enough for use, we tried the hydrolysis of (*S*)-**7** to (*S*)-**6** to increase the ee with the lipase PS. Unfortunately, (*S*)-**6** with a higher ee could not be obtained. Therefore, (*S*)-**7** was hydrolyzed to (*S*)-**6** using NaOH and the resultant (*S*)-**6** was again subjected to the lipase PS-catalyzed transesterification to increase the ee. The obtained ester ((*S*)-**7**) was then hydrolyzed in a similar manner to give (*S*)-**6** with >99% ee, and (*S*)-**6** was converted to (*R*)-**5** with >99% ee {$[\alpha]^{24}_D$ +77.6° (*c* 1.1, MeOH)} according to the same route as that used to prepare (*S*)-**5**.



Scheme 3: Reagents and conditions: a: NaOH, EtOH-H_2O, rt (89%, 96% ee); b: lipase PS, vinyl acetate, hexane, rt (89%, >99% ee); c: NaOH, EtOH-H_2O, rt (90%, >99% ee); d: PhOH, PPh_3, diisopropyl azodicarboxylate, toluene, 0^o-rt (68%, >99% ee); e: $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O-*t*-BuOH, rt (89%); f: TFAA, TFA, CH_2Cl_2, rt (88%, >99% ee).

In conclusion, we have been able to easily synthesize the (*R*)- and (*S*)-enantiomers of **5**.

EXPERIMENTAL

All commercially available reagent chemicals were obtained from Aldrich, Nacalai Tesque, Tokyo Kasei and Wako Chemicals, and generally used without further purification. Toluene was distilled from Na/benzophenone under Ar. Benzene, hexane, dichloromethane, and pyridine were distilled from CaH_2 under Ar. Vinyl acetate was distilled from molecular sieves 4A under Ar. Amano PS and Amano AK were purchased from Amano Enzyme, Inc., and dried over P_2O_5. Amano AY, Meito ALC, Meito PLC, and Novozym 435 were generous gifts from Amano Enzyme, Inc., Meito Sangyo Co., Ltd., and Novozymes Japan, Inc. The ^{1}H-NMR spectra were recorded using a JEOL JNM-LA 400 spectrometer for solutions 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 spectrophotometer. The MS spectra were obtained using a JEOL JMS-GCmate spectrometer. The HRMS spectra 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 using a Shimadzu GC-14B with an 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 Chiralcel OJ (Daicel), 250 × 4.6 mm and Chiralcel OD-H (Daicel), 250 × 4.6 mm.

Purification of 3-phenylpropanal. Commercially available 3-phenylpropanal was dissolved in ether. The organic phase was washed with 10% Na_2CO_3 solution (three times) and a saturated Na_2SO_3 solution, and then dried over $MgSO_4$. After removal of the solvents, the residue was distilled under reduced pressure (73.0-78.0 °C/0.6 mm Hg).

1-Phenyl-5-hexen-3-ol ((±)-6). A mixture of 3-phenylpropanal (6.809 g, 50.75 mmol), allyl bromide (12.279 g, 101.50 mmol), and indium (11.675 g, 101.7 mmol) in water (400 mL) was stirred for 6 h at rt under Ar. The allyl bromide (3.425 g, 28.31 mmol) and indium (3.171 g, 27.62 mmol) were added to the mixture to completely consume the 3-phenylpropanal, and the resulting mixture was stirred overnight at rt under Ar. The reaction mixture was quenched at 0 °C with 6 M HCl (120 mL) and extracted three times with ether. The organic phase was washed with deionized water, a saturated $NaHCO_3$ solution and a saturated NaCl solution, then dried over Na_2SO_4. After removal of the solvents, the residue was chromatographed {silica gel, hexane-ethyl acetate 5:1 (v/v)} to give (±)-**6** (8.054 g, 91%) as a colorless oil. The ^{1}H-NMR spectral data of this sample were identical to those described in the literature.[12b]

1-(2-Phenylethyl)-3-butenyl acetate ((±)-7). Compound ((±)-**7**) was prepared as an authentic sample. To a solution of (±)-**6** (0.094 g, 0.53 mmol) and dry pyridine (0.212 g, 2.68 mmol) in dry benzene (3 mL) at 0 °C, acetyl chloride (0.101 g, 1.29 mmol) was slowly added. The reaction mixture was stirred overnight at rt and quenched at 0 °C with 1 M HCl. The resulting mixture was extracted with ether. The organic phase was washed in order with deionized water, a saturated $NaHCO_3$ solution, and a saturated NaCl solution, and then dried over Na_2SO_4. After removal of the solvents, the residue was chromatographed {silica gel, hexane-ethyl acetate 5:1 (v/v)} to give (±)-**7** (0.115 g, 99%) as a colorless oil; ^{1}H-NMR: 7.28 (2H, t, *J*=7.0), 7.16-7.20 (3H, m), 5.75 (1H, ddt, *J*=17.0, *J*=10.2, *J*= 7.1), 5.06-5.11 (2H, m), 4.97 (1H, quintet, *J*=6.2), 2.56-2.71 (2H, m), 2.34 (2H, t, *J*=6.7), 2.03 (3H, s), 1.85-1.91 (2H, m); IR (neat): 1738, 1643, 995, 919 cm^{-1}; MS *m/z* (%): 218 (M^+, 2), 159 (66), 158 (100), 129 (67), 118 (100), 117 (100), 105 (71), 104 (100), 92 (60), 91 (100), 65 (72); HRMS calcd for $C_{14}H_{18}O_2$ (M^+), 218.1307. Found: 218.1319; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.89; H, 8.23.

Resolution of (±)-6 (screening experiments). In a typical run, lipase PS (20 mg) was placed in a vial containing a 1 mL hexane solution of (±)-**6** (60 μmol) and the vinyl acetate (120 μmol). The resulting suspension was then magnetically stirred at rt. Samples were withdrawn from the vial and analyzed by gas chromatography (OV 101, 120 °C). The reaction was stopped by filtration of the lipase at about a 50% conversion, and the filtrate was 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 (*S*)-**7** and (*R*)-**6**. The *E* value and the conversion of the reaction were calculated from the ees of (*S*)-**7** and (*R*)-**6**.[15]

Conditions for the determination of the ees of (*S*)-**7** and (*R*)-**6** are as follows. Compound ((*S*)-**7**): HPLC (Chiralcel OJ), hexane:2-propanol = 40:1 (v/v), flow rate=0.5 mL/min, retention times: (*S*)-**7**, t=17 min; (*R*)-**7**, t=19 min; Compound ((*R*)-**6**): HPLC (Chiralcel OD-H), hexane:2-propanol = 10:1 (v/v), flow rate=0.5 mL/min, retention times: (*S*)-**6**, t=13 min; (*R*)-**6**, t=18 min.

Preparative resolution of (±)-6. Lipase PS (12.00 g) was added to a solution of (±)-**6** (4.002 g, 22.71 mmol) and vinyl acetate (5.975 g, 69.40 mmol) in dry hexane (400 mL). The mixture was stirred for 29 h at rt. 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*)-**7** and (*R*)-**6** as colorless oils.

Compound ((*S*)-**7**): yield: 2.485 g (51%); ee: 96%; The ^{1}H-NMR spectral data of this sample were identical to those of (±)-**7**.

Compound ((*R*)-**6**): yield: 1.898 g (48%); ee: >99%; $[\alpha]^{23}_{D}$: +22.4° (*c* 1.2, $CHCl_3$) {lit.,[12a] $[\alpha]^{20}_{D}$ -9.6° (*c* 4.2, $CHCl_3$), 48% ee, (*S*)}; The ^{1}H-NMR spectral data of this sample were identical to those of (±)-**6**.

6 M NaOH (3.6 mL, 22 mmol) was added to a solution of (*S*)-**7** (2.406 g, 11.02 mmol) obtained above in ethanol (15 mL). The mixture was stirred for 1.5 h at rt. After removal of the solvent, the residue was extracted three times with ether. The organic layer was washed with a saturated NaCl solution, then dried over Na_2SO_4 and concentrated. The residue was chromatographed {silica gel, hexane-ethyl acetate 3:1 (v/v)} to give (*S*)-**6** (1.723 g, 89%) as a yellow oil. The ^{1}H-NMR spectral data of this sample were identical to those of (±)-**6**.

According to the procedures described above, (*S*)-**6** obtained here was again subjected to the lipase PS-catalyzed transesterification with vinyl acetate to give the optically purer (*S*)-**7**; lipase PS (5.169 g), (*S*)-**6** (1.723 g, 9.776 mmol), vinyl acetate (2.764 g, 32.11 mmol), dry hexane (170 mL), reaction time (13 h), yield of (*S*)-**7** (1.882 g, 89%, >99% ee). The ^{1}H-NMR spectral data of this sample were identical to those of (±)-**7**.

Thus the obtained optically purer (*S*)-**7** was again hydrolyzed with NaOH to give (*S*)-**6**; (*S*)-**7** (1.864 g, 8.539 mmol), 6 M NaOH (3 mL, 18 mmol), ethanol (15 mL), reaction time (18 h), yield of (*S*)-**6** (1.365 g, 91%, >99% ee). The ^{1}H-NMR spectral data of this sample were identical to those of (±)-**6**.

Lipase-catalyzed hydrolysis of (*S*)-7. Amano PS (10.0 mg) was placed in a vial containing a suspension of (*S*)-**7** (10.0 mg, 45.8 μmol, 96% ee) in 0.07 M phosphate buffer (KH_2PO_4 and Na_2HPO_4, pH 7, 1 mL). The resulting suspension was then magnetically stirred for 43 h at rt. A sample was withdrawn from the vial and analyzed by GC (OV 101, 120 °C) and HPLC {(Chiralcel OD-H), hexane:2-propanol = 10:1 (v/v)}.

Phenyl (*S*)-1-(2-phenylethyl)-3-butenyl ether ((*S*)-8). A solution of diisopropyl azodicarboxylate (2.931 g, 14.49 mmol) in dry toluene (10 mL) was dropwise added to a mixture of (*R*)-**6** (1.684 g, 9.555 mmol, >99% ee), phenol (1.859 g, 20.14 mmol), and triphenylphosphine (4.101 g, 15.64 mmol) in dry toluene (20 mL) at 0 °C under Ar. The mixture was stirred overnight at rt. After evaporation of the toluene, a mixture of ether and hexane {1:1 (v/v)} was added to the viscous residue. The suspended solid was filtered with suction, and the filtrate was concentrated. Chromatography {silica gel, hexane-ethyl acetate 40:1 (v/v)} of the crude product provided (*S*)-**8** (1.826 g, 76%, >99% ee) as a colorless oil. The ^{1}H-NMR spectral data showed that (*S*)-**8c** was contaminated by triphenylphosphine oxide (0.449 g). The yield described here was estimated from the ^{1}H-NMR spectral analysis; ^{1}H-NMR: 7.25-7.29 (4H, m), 7.15-7.20 (3H, m), 6.87-6.95 (3H, m), 5.84 (1H, ddt, *J*=17.1, *J*=10.2, *J*=7.1), 5.07-5.13 (2H, m), 4.27-4.33 (1H, m), 2.78-2.85 (1H, m), 2.66-2.73 (1H, m), 2.38-2.51 (2H, m),

1.91-2.10 (2H, m); IR (neat): 1640, 1240, 1029, 998, 918 cm^{-1}; MS *m/z* (%): 252 (M^+, 10), 117 (34), 94 (33), 92 (11), 91 (100), 77 (12), 65 (23); HRMS calcd for $C_{18}H_{20}O$ (M^+), 252.1514. Found: 252.1521. The enantiomeric excess was determined by HPLC analysis on a Chiralcel OJ column {hexane:2-propanol = 10:1 (v/v)}, flow rate=0.5 mL/min, retention times: (*R*)-**8**, t=12 min; (*S*)-**8**, t=13 min.

(*S*)-3-Phenoxy-5-phenylpentanoic acid ((*S*)-9). A solution of $NaIO_4$ (14.370 g, 67.18 mmol) and $KMnO_4$ (0.704 g, 4.45 mmol) in deionized water (200 mL) was treated with a solution of K_2CO_3 (9.282 g, 67.16 mmol) in deionized water (100 mL), and then with *tert*-butyl alcohol (75 mL). To the mixture, a solution of (*S*)-**8** (1.876 g, 7.434 mmol) accompanied by triphenylphosphine oxide in *tert*-butyl alcohol (75 mL) was slowly added. The resulting purplish suspension was stirred for 15 min at rt. The suspension was treated with ethylene glycol (20 mL), stirred for 3 h, acidified to pH 4 with 1 M HCl (120 mL) at 0 °C, and extracted three times with ethyl acetate. The organic layer was washed with a saturated NaCl solution, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane-ethyl acetate 1:2 - hexane-acetone 1:1 (v/v)} to give (*S*)-**9** (1.702 g, 85%) as a colorless viscous oil; ^{1}H-NMR: 7.25-7.29 (4H, m), 7.15-7.22 (3H, m), 6.90-6.98 (3H, m), 4.71 (1H, quintet, *J*=6.1), 2.83 (1H, dd, *J*=15.6, *J*=6.1), 2.69-2.83 (2H, m), 2.64 (1H, dd, *J*=15.9, *J*=6.4), 1.99-2.14 (2H, m); IR (neat): 1712, 1237, 1038 cm^{-1}; MS *m/z* (%): 270 (M^+, 17), 176 (19), 117 (43), 94 (70), 91 (100), 65 (20); HRMS calcd for $C_{17}H_{18}O_3$ (M^+), 270.1256. Found: 270.1281; Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.46; H, 6.74.

Flindersiachromanone (2-(2-Phenylethyl)-4-chromanone) ((*S*)-5). To a solution of (*S*)-**9** (1.678 g, 6.208 mmol) in anhydrous CH_2Cl_2 (16 mL) was slowly added a mixture of trifluoroacetic acid (7.8 mL, 100 mmol) and trifluoroacetic anhydride (7.8 mL, 55 mmol). The mixture was stirred for 25 min at rt, poured onto crushed ice in a beaker, and K_2CO_3 was added to the resulting mixture until the evolution of CO_2 gas ceased. The mixture was extracted three times with CH_2Cl_2. The extract was washed with a saturated NaCl solution, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane-ethyl acetate 5: 1 (v/v)} to give (*S*)-**5** (1.466 g, 94%, >99% ee) as a colorless viscous oil; $[\alpha]^{24}_D$: -77.8° (*c* 1.2, MeOH); ^{1}H-NMR: 7.88 (1H, dd, *J*=8.0, *J*=1.7), 7.47-7.51 (1H, m), 7.19-7.32 (5H, m), 6.99-7.03 (2H, m), 4.40-4.47 (1H, m), 2.80-2.95 (2H, m), 2.65-2.77 (2H, m), 2.18-2.28 (1H, m), 1.95-2.04 (1H, m); IR (neat): 1692, 1607, 1577, 1227, 1031 cm^{-1}; MS *m/z* (%): 252 (M^+, 51), 161 (26), 160 (6), 148 (8), 147 (62), 121 (64), 120 (37), 117(12), 92 (69), 91 (100), 65 (38); HRMS calcd for $C_{17}H_{16}O_2$ (M^+), 252.1150. Found: 252.1153; Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.93. Found: C, 80.77; H, 6.46. The enantiomeric excess was determined by HPLC analysis

on a Chiralcel OD-H column {hexane:2-propanol = 2:1 (v/v)}, flow rate=0.5 mL/min, retention times: (*S*)-**5**, t=17 min; (*R*)-**5**, t=27 min.

2-(2-Phenylethyl)-4-chromanone ((*R*)-5). Compound ((*R*)-**5**) was prepared from (*S*)-**6** (>99% ee) in three steps according to the procedures described above; colorless viscous oil; 54% from (*S*)-**6**; >99% ee; $[\alpha]^{24}_{D}$: +77.6° (*c* 1.1, MeOH); The ^{1}H-NMR spectral data of this sample were identical to those of (*S*)-**5**.

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REFERENCES AND NOTES

1. a) G. P. Ellis, 'Chromenes, Chromanones and Chromones,' John Wiley & Sons, New York, 1977, pp. 331-348; b) S. T. Saengchantara and T. W. Wallace, *Nat. Prod. Rep.*, 1986, 465.
2. a) **1a**: E. J. Corey and R. B. Mitra, *J. Am. Chem. Soc.*, 1962, **84**, 2938; b) **1b**: F. Bohlmann and J. Jakupovic, *Phytochemistry*, 1979, **18**, 1189; c) **1c**: T. Jaipetch, V. Reutrakul, P. Tuntiwachwuttikul, and T. Santisuk, *Phytochemistry*, 1983, **22**, 625; d) **2**: Ref. 1a; e) **3**: I. M. Chandler, C. R. Mclntyre, and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2271; f) **4**: Ch. Tamm, B. Bohner, and W. Zurcher, *Helv. Chim. Acta*, 1972, **55**, 510; g) **5**: K. Picker, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, 1976, **29**, 2023.
3. J. B. Harborne, 'The Flavonoids: Advances in Research Since 1986,' Chapman & Hall, New York, 1993, pp. 406-419.
4. C. Pouget, F. Lauthier, A. Simon, C. Fagnere, J. -P. Basly, C. Delage, and A. -J. Chulia, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 3095.
5. O. Dann, G. Volz, and O. Huber, *Liebigs Ann. Chem.*, 1954, **587**, 16.
6. T. Ueda and T. Tsuji, *Pharm. Bull.*, 1954, **2**, 22 (*Chem. Abstr.*, 1956, **50**, 322).
7. Y. Noda and M. Watanabe, *Helv. Chim. Acta*, 2002, **85**, 3473.
8. K. J. Hodgetts, *Tetrahedron Lett.*, 2001, **42**, 3763.
9. a) K. J. Hodgetts, K. I. Maragkou, T. W. Wallace, and R. C. R. Wootton, *Tetrahedron*, 2001, **57**, 6793; b) G. Solladie, N. Gehrold, and J. Maignan, *Tetrahedron: Asymmetry*, 1999, **10**, 2739; c) S. T. Saengchantara and T. W. Wallace, *Tetrahedron*, 1990, **46**, 6553; d) S. T. Saengchantara and T. W.

Wallace, *J. Chem. Soc., Chem. Commun.*, 1986, 1592.

10. A. V. Rama Rao, A. S. Gaitonde, K. R. C. Prakash, and S. Prahlada Rao, *Tetrahedron Lett.*, 1994, **35**, 6347.
11. M. Kawasaki, H. Kakuda, M. Goto, S. Kawabata, and T. Kometani, *Tetrahedron: Asymmetry*, 2003, **14**, 1529.
12. For recent examples, see: a) J. -Y. Lee, J. J. Miller, S. S. Hamilton, and M. S. Sigman, *Org. Lett.*, 2005, **7**, 1837; b) J. Lu, S. -J. Ji, Y. -C. Teo, and T. -P. Loh, *Org. Lett.*, 2005, **7**, 159; c) Y. -C. Teo, K. -T. Tan, and T. -P. Loh, *Chem. Commun.*, 2005, 1318; d) J. Lu, M. -L. Hong, S. -J. Ji, and T. -P. Loh, *Chem. Commun.*, 2005, 1010; e) G. Xia, K. Shibatomi, and H. Yamamoto, *Synlett*, 2004, 2437; f) A. Yanagisawa, Y. Nakamura, and T. Arai, *Tetrahedron: Asymmetry*, 2004, **15**, 1909; g) A. V. Malkov, M. Bell, M. Orsini, D. Pernazza, A. Massa, P. Herrmann, P. Meghani, and P. Kocovsky, *J. Org. Chem.*, 2003, **68**, 9659; h) M. Wadamoto, N. Ozasa, A. Yanagisawa, and H. Yamamoto, *J. Org. Chem.*, 2003, **68**, 5593; i) H. Hanawa, D. Uraguchi, S. Konishi, T. Hashimoto, and K. Maruoka, *Chem. Eur. J.*, 2003, **9**, 4405; j) T. Tomoyasu, K. Tomooka, and T. Nakai, *Tetrahedron Lett.*, 2003, **44**, 1239; k) K. Kubota and J. L. Leighton, *Angew. Chem., Int. Ed.*, 2003, **42**, 946; l) H. Lachance, X. Lu, M. Gravel, and D. G. Hall, *J. Am. Chem. Soc.*, 2003, **125**, 10160; m) H. Hanawa, T. Hashimoto, and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 1708; n) M. Inoue, T. Suzuki, and M. Nakada, *J. Am. Chem. Soc.*, 2003, **125**, 1140.
13. K. Nakamura, M. Kawasaki, and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1079.
14. a) R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport, and L. A. Cuccia, *J. Org. Chem.*, 1991, **56**, 2656; b) D. Rotticci, F. Haeffner, C. Orrenius, T. Norin, and K. Hult, *J. Mol. Catal. B: Enzymatic*, 1998, **5**, 267; c) L. E. Janes and R. J. Kazlauskas, *Tetrahedron: Asymmetry*, 1997, **8**, 3719.
15. C. -S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294.
16. The yield described here was estimated from the ^{1}H-NMR spectral analysis.