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Journal of Molecular Catalysis B: Enzymatic 54 (2008) 93–102
JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC
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Asymmetric synthesis of 2-substituted 4-chromanones using enzyme-catalyzed reactions

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Received 8 November 2007; received in revised form 20 December 2007; accepted 21 December 2007
Available online 4 January 2008

Abstract

2-Substituted 4-chromanones were synthesized in their optically active forms. The chiral intermediates were obtained via lipase-catalyzed enantioselective reactions. Lipase and esterase were also used for the hydrolysis of ester moieties of the precursors of the target compounds under mild conditions.

Keywords: Asymmetric synthesis; Chromanones; Enzyme; Hydrolysis; Resolution

1. Introduction

2-Substituted 4-chromanone (2-substituted 2,3-dihydro-4H-benzopyran-4-one) compounds are widespread in nature and found in a variety of forms (Fig. 1) [1]. Flavanones (**1a–d**) are compounds representing the 2-substituted 4-chromanones [2]. Many of the 2-substituted 4-chromanones possess biological and pharmacological activities [**1a**]. 7-Methoxyflavanone (**1a**) was found to be a potent inhibitor of MCF-7 breast cancer cell growth [3] and 4′-hydroxy-7-methoxyflavanone (**1c**) was found to be a more potent aromatase inhibitor than aminoglutethimide, the first clinically used aromatase inhibitor [4]. As other examples, 2,6-dimethyl-4-chromanone (**2a**) is among the compounds that show some fly killing activity [5], and a bronchus dilation activity [6] was demonstrated by 7-methoxy-2-methyl-4-chromanone (**2b**), not a natural product.

Despite this interesting potential of the 2-substituted 4-chromanones, there are few reports on their asymmetric synthesis [7]. Recently, Biddle et al. reported the asymmetric synthesis of some flavanones from α-substituted chalcones by an intramolecular conjugated addition reaction catalyzed by chiral thioureas [7h]. We previously described the synthesis of both enantiomers of **1d**, **2c** and 2-(2-phenylethyl)-4-chromanone (flindersiachromanone) [8]. It is a characteristic of our method to obtain their chiral intermediates by lipase-catalyzed reactions. However, the 2-substituted 4-chromanones, which we synthesized, are compounds with an extremely simple structure that have no substituent groups on the benzene rings. We now report an application of our methodology to the asymmetric synthesis of other 2-methyl-4-chromanones and flavanones.

2. Results and discussion

2.1. Asymmetric synthesis of 2-methyl-4-chromanones

We synthesized the optically active **2a** and **2b** based on the route similar to that which we adopted for the asymmetric synthesis of **2c** (Scheme 1) [8a]. The chromanone (*S*)-**2a** was isolated from the roots of *Leontopodiun alpinum* [9] and (*R*)-**2b** was used for the synthesis of the chiral chromanol moiety of calanolide A possessing an impressive anti-HIV activity [7c].

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doi:10.1016/j.molcatb.2007.12.022

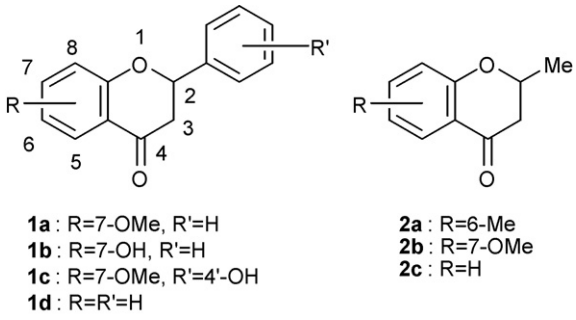
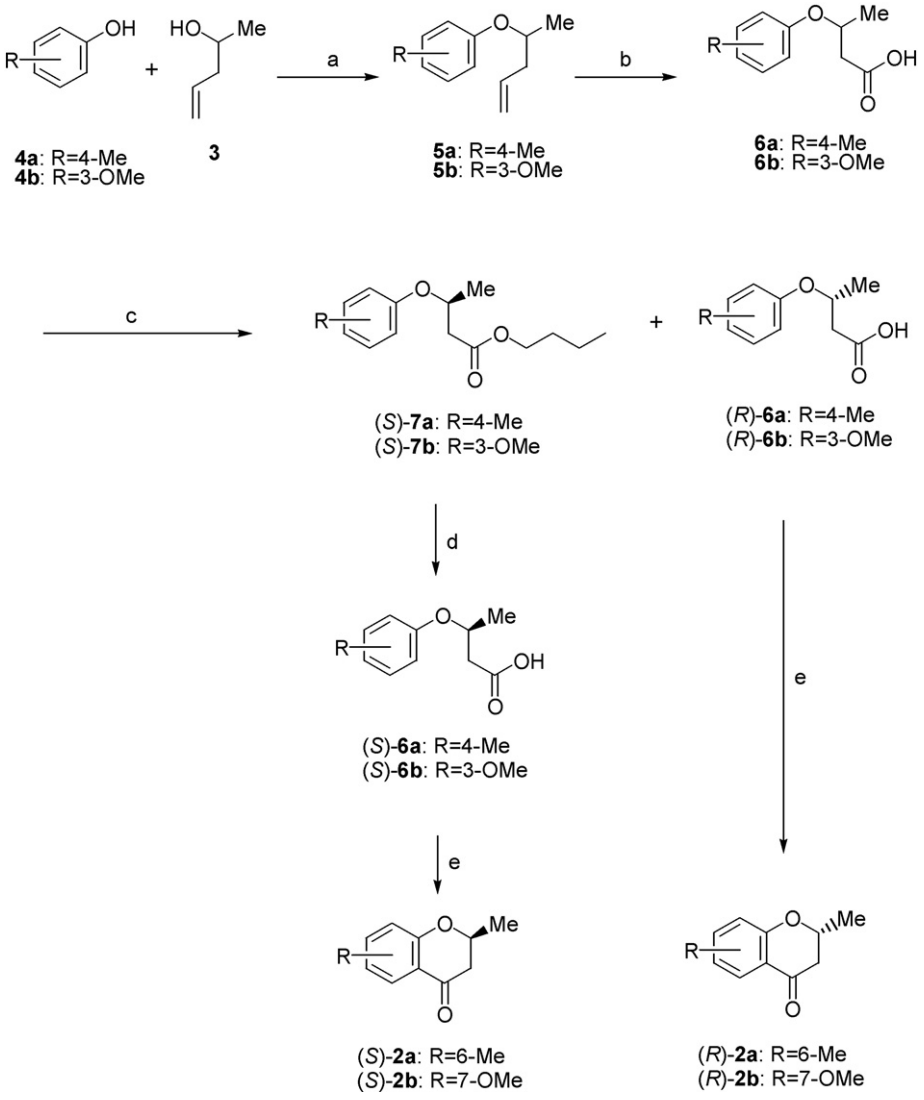


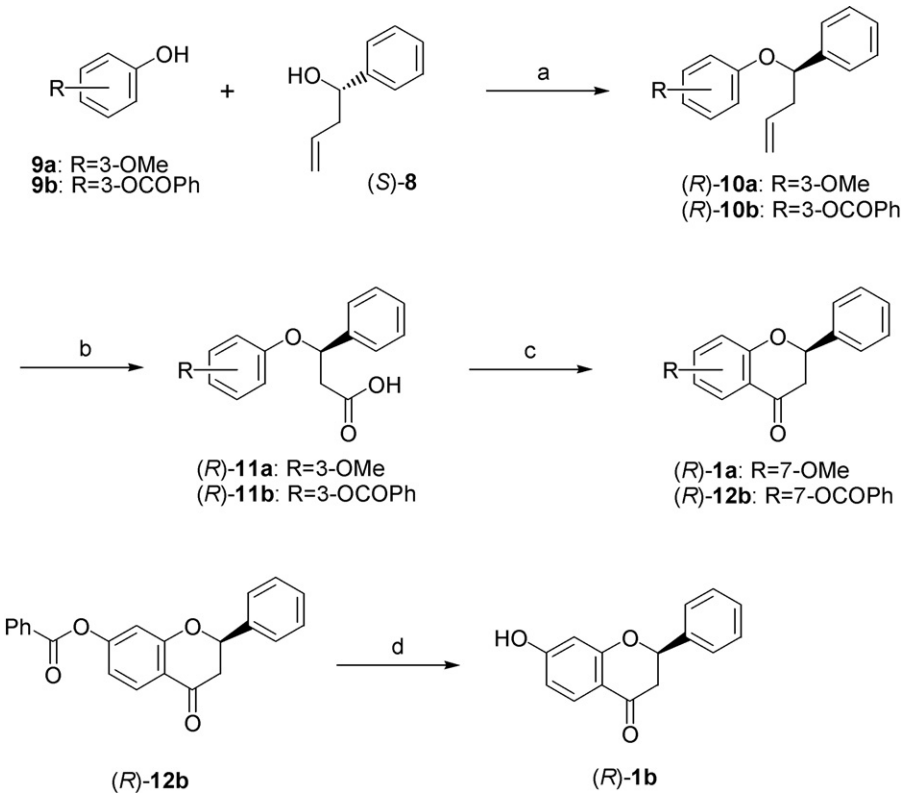
Fig. 1. 2-Substituted 4-chromanones.

The separate coupling reaction of the commercially available 4-penten-2-ol (**3**) with 4-methylphenol (**4a**) and 3-methoxyphenol (**4b**) using diisopropyl azodicarboxylate (DIAD) in the presence of triphenylphosphine gave the aryl ethers, **5a** in 70% and **5b** in 62%, respectively. The oxidative cleavage of the double bonds of the ethers afforded the corresponding acids, **6a** in 85% and **6b** in 68%. The acids **6a** and **6b** were separately subjected to the lipase (Chirazyme L-1 from *Burkholderia cepacia*)-catalyzed esterification with 1-butanol in hexane containing anhydrous Na_2SO_4 to remove the water produced during the reaction. (*R*)-3-(4-Methylphenoxy)butanoic acid ((*R*)-**6a**) (98% e.e., 44%) and the butyl ester ((*S*)-**7a**) (98% e.e., 47%) were obtained from **6a** and (*R*)-3-(3-methoxyphenoxy)butanoic acid ((*R*)-**6b**) (98% e.e., 37%) and the butyl ester ((*S*)-**7b**) (99% e.e., 42%) from **6b**. Both the esterifications took place with extremely enantioselectivity ($E > 400$). Varadharaj et al. reported the lipase-catalyzed highly enantioselective ($E > 50$) hydrolysis of the racemic methyl 3-phenylbutanoate, an analogue of **6a** and **6b** [10]. Our result is consistent with that of Varadharaj et al.

It is reported that lipase from *Candida rugosa*, one of the most popular lipases, can be an enantioselective catalyst for the esterification of methyl branched carboxylic acids with their stereocenters remotely located from the carboxyl groups which are reaction centers [11]. However, our result indicates that Chi-



Scheme 1. (a) DIAD, PPh_3, THF, rt; (b) $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O/*t*-BuOH, rt; (c) 1-butanol, Chirazyme L-1, Na_2SO_4, hexane, rt; (d) lipase PS, buffer (pH 7), rt; (e) trifluoroacetic acid, trifluoroacetic anhydride, CH_2Cl_2, rt.



Scheme 2. (a) DIAD, PPh_3, THF or toluene, rt; (b) $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O/*t*-BuOH, rt; (c) trifluoroacetic acid, trifluoroacetic anhydride, CH_2Cl_2, rt; (d) lipase MY, buffer (pH 7), rt.

razyme L-1 showed a higher enantioselectivity than CRL for the β-branched carboxylic acids.

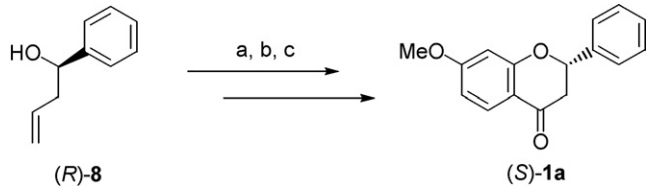
The intramolecular cyclization of (*R*)-**6a** and (*R*)-**6b** using trifluoroacetic acid and trifluoroacetic anhydride afforded (*R*)-**2a** with 98% e.e. $\{[\alpha]_D^{24} = +69.4^\circ$ (*c* 1.2, MeOH); lit. [7f], $[\alpha]_D^{20} = -68^\circ \pm 4^\circ$ (*c* 1.0, MeOH) (*S*)$\}$ in 79% and (*R*)-**2b** with 97% e.e. $\{[\alpha]_D^{23} = +42.4^\circ$ (*c* 1.1, MeOH); lit. [7c] $[\alpha]_D = +53.2^\circ$ (*c* 1, MeOH) (*R*)$\}$ in 61%, respectively. The butyl esters (*S*)-**7a** and (*S*)-**7b** were hydrolyzed to the corresponding acids (*S*)-**6a** with >99% e.e. in 53% and (*S*)-**6b** with 99% e.e. in 52% with another lipase, lipase PS from *Burkholderia cepacia*. We have reported that when butyl (*S*)-3-phenoxybutanoate, the intermediate of (*S*)-**2c**, was subjected to hydrolysis with NaOH in water–methanol, elimination of the phenol mainly resulted [8a]. Therefore, we applied the lipase-catalyzed hydrolysis under very mild conditions. The carboxylic acids (*S*)-**6a** and (*S*)-**6b** were also converted into (*S*)-**2a** with >99% e.e. $\{[\alpha]_D^{21} = -64.4^\circ$ (*c* 1.1, MeOH); lit. [7f], $[\alpha]_D^{20} = -68^\circ \pm 4^\circ$ (*c* 1.0, MeOH) (*S*)$\}$ in 83% and (*S*)-**2b** with 99% e.e. $\{[\alpha]_D^{23} = -46.6^\circ$ (*c* 1.2, MeOH); lit. [7c] $[\alpha]_D = +53.2^\circ$ (*c* 1, MeOH) (*R*)$\}$ in 66%, respectively.

2.2. Asymmetric synthesis of flavanones

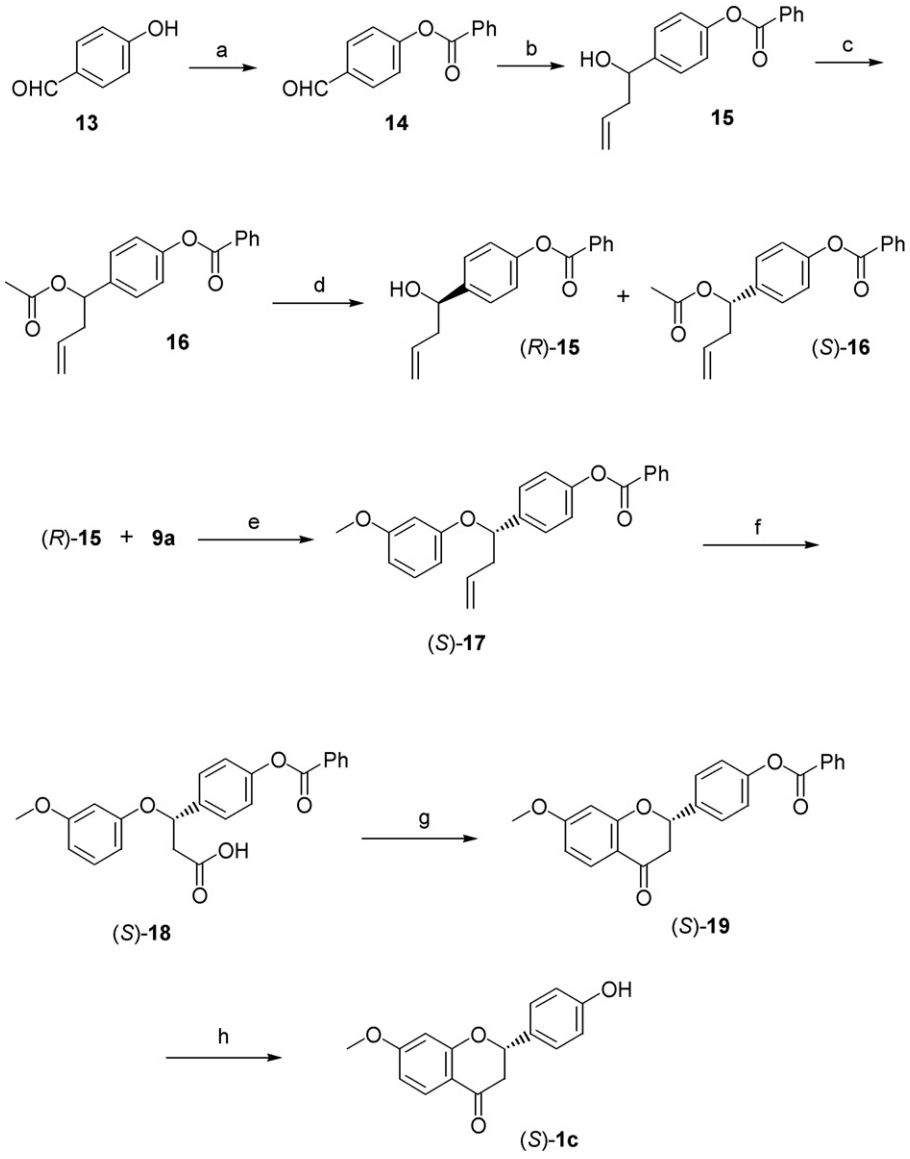
We synthesized the optically active (*R*)-**1a**, (*S*)-**1a**, (*R*)-**1b** and (*S*)-**1c** according to the route similar to that which we adopted for the asymmetric synthesis of **1d** (Schemes 2–4) [8a]. The flavanones (*S*)-**1a**, (*R*)-**1b** and (*S*)-**1c** were isolated from *Flourensia heterolepis* [12], *Platymiscium praecox* [13] and *Bauhinia manca* [14], respectively.

3-Methoxyphenol (**9a**) and (*S*)-**8** (>99% e.e.) prepared by the lipase PS-catalyzed enantioselective transesterification of the racemic **8** [8a] were treated with DIAD and triphenylphosphine in THF to give the ether ((*R*)-**10a**) with 96% e.e. in 56% yield with inversion of the configuration which caused a slight racemization (Scheme 2). The ether (*R*)-**10a** was converted into (*R*)-**1a** with 96% e.e. $\{[\alpha]_D^{26} = +86.3^\circ$ (*c* 1.1, EtOH); lit. [7h] $[\alpha]_D^{20} = +58.5^\circ$ (*c* 0.5, EtOH), 89% e.e. (*R*)$\}$ via oxidation ((*R*)-**10a** to (*R*)-**11a**) in 79% and subsequent cyclization ((*R*)-**11a** to (*R*)-**1a**) in 59%. Although Biddle recently reported the asymmetric synthesis of (*R*)-**1a** [7h], the e.e. of theirs (89% ee.) was lower than ours. The flavanone (*S*)-**1a** (95% e.e., 16% yield in three steps) was also synthesized from (*R*)-**8** with >99% e.e. [8a] by a similar method (Scheme 3).

Next, we synthesized (*R*)-**1b** (Scheme 2). The combination of (*S*)-**8a** (>99% e.e.) [8a] and 3-benzoyloxyphenol (**9b**) was



Scheme 3. (a) **9a**, DIAD, PPh_3, THF, rt; (b) $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O/*t*-BuOH, rt; (c) trifluoroacetic acid, trifluoroacetic anhydride, CH_2Cl_2, rt.



Scheme 4. (a) PhCOCl, pyridine, THF, rt; (b) allyl bromide, In, DMF/H_2O, rt; (c) AcCl, pyridine, THF, rt; (d) lipase PS, buffer (pH 7), rt; (e) DIAD, PPh_3, toluene, rt; (f) $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O/t-BuOH, rt; (g) trifluoroacetic acid, trifluoroacetic anhydride, CH_2Cl_2, rt; (h) esterase SNSM-87, buffer (pH 7), rt.

carried out in toluene instead of THF as the solvent to afford (*R*)-**10b** (58%, 98% e.e.). The application of toluene as an organic solvent reduced the lowering of the e.e. of (*R*)-**10b**. The ether (*R*)-**10b** was converted into (*R*)-**12b** (97% ee., 42% in two steps) according to the synthetic route described for (*R*)-**1a**. Because of the possible partial racemization of the 2-substituted 4-chromanones via the reversible elimination of the pyran oxygen [7f] (*R*)-**12b** had to be hydrolyzed under mild conditions to afford (*R*)-**1b**. We screened seven lipases (lipase AP4, AP6, F-AP15, M-AP10, MY, OF, PS) and three proteases (protease M, N, S) for the hydrolysis of (*R*)-**12b** in buffer at pH 7. Lipase MY and OF, which originated from *Candida rugosa*, exhibited hydrolysis activity. However, when we tried to extract a product from the reaction mixture including lipase OF, an emulsification occurred. Therefore, we used lipase MY as the catalyst for the preparative scale hydrolysis of (*R*)-**12b** and obtained (*R*)-**1b** with 97% e.e. $\{[\alpha]_D^{26} = +63.8^\circ$ (*c* 0.14, MeOH); lit. [15] $[\alpha]_D^{23} = -85.3^\circ$ (*c* 1.2, MeOH) (*S*)$\}$ in 58% yield.

Finally, we synthesized (*S*)-**1c** according to Scheme 4. 4-Benzoyloxybenzaldehyde (**14**) was prepared from 4-hydroyloxybenzaldehyde (**13**) and benzoyl chloride in 99% yield. The racemic alcohol (**15**) was synthesized in 99% yield from **14** and allyl bromide with indium in water. The racemic alcohol **15** was acetylated with acetyl chloride to afford the racemic ester (**16**) in 97% yield. The intermediates **14** and **15** were used for the next steps without being purified. The optically active (*R*)-**15** (>99% e.e., 34%) and (*S*)-**16** (>99% e.e., 36%) were obtained by the lipase PS-catalyzed enantioselective hydrolysis of the acetyl group of the racemic **16**. The hydrolysis took place with extremely high enantioselectivity ($E > 1000$). Similar to the benzoate moiety of (*R*)-**12b**, **15** could also not be hydrolyzed by the lipase PS. The optically active alcohol

(*R*)-**15** was converted into (*S*)-**19** (96% e.e., 16% in three steps via (*S*)-**17** and (*S*)-**18**) in a similar manner as described for the synthesis of (*R*)-**12b**. Because lipase PS could not hydrolyze the benzoate moiety of **15**, it was postulated that the lipase also could not hydrolyze the benzoate moiety of (*S*)-**19**. The benzoate moiety of (*S*)-**19** could be hydrolyzed by esterase SNSM-87 from *Klebsiella oxytoca* to afford (*S*)-**1c** with 93% e.e. $\{[\alpha]_D^{22} = -52.0^\circ$ (*c* 1.0, MeOH); lit. [14] $[\alpha]_D^{21} = -33.0^\circ$ (*c* 0.10, MeOH) (*S*)$\}$ in 54% yield. A lowering of the e.e. was observed during the conversion of (*S*)-**19** to (*S*)-**1c**. For the 2-substituted 4-chromanones, there is the possible partial racemization via the reversible pyran oxygen elimination which causes ring-opening into the chalcones [7e,f]. The electron-donating hydroxyl group at the 4′ position is suggested to facilitate the racemization.

3. Experimental

3.1. Materials and methods

All commercially available reagent chemicals were obtained from Aldrich, Kanto Kagaku, Nacalai Tesque, Tokyo Kasei, and Wako Chemicals, and generally used without further purification. THF and toluene were distilled from Na/benzophenone under Ar. Dichloromethane, hexane and pyridine were distilled from CaH_2 under Ar. The vinyl acetate was distilled from molecular sieves 4A under Ar. Lipase AP4, AP6, F-AP15, M-AP10, PS and protease M, N, S were purchased from Amano Enzyme, Inc. Lipase MY and OF were purchased from Meito Sangyo Co. Ltd. Chirazyme L-1 and esterase SNSM-87 were generous gifts from Roche Diagnostics K.K. and Nagase & Co. Ltd., respectively. Lipase PS and Chirazyme L-1 were used after drying over P_2O_5 for 1 day. The NMR spectra were recorded using a JEOL JNM-LA 400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer for the solutions in $CDCl_3$ unless otherwise indicated 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 by a Horiba SEPA-300 polarimeter. The melting points were measured by a Yanaco MP-S3 micro-melting point apparatus. The HPLC analyses were carried out using a Hitachi L-6250 intelligent pump with a Hitachi L-4000 UV detector and CHIRALCEL OJ, CHIRALPAK AD-H, CHIRALPAK AS-H, CHIRALCEL OB-H and CHIRALCEL OD-H (all columns from Daicel, 250 mm × 4.6 mm).

3.2. Experimental procedures for the synthesis of (R)-2a and (S)-2a

3.2.1. Synthesis of 5a

A solution of diisopropyl azodicarboxylate (7.279 g, 36.00 mmol) in dry THF (20 mL) was dropwise added to a mixture of **3** (2.564 g, 27.77 mmol), **4a** (3.590 g, 33.20 mmol) and triphenylphosphine (8.704 g, 33.19 mmol) in dry THF (40 mL) at 0 °C under Ar. The mixture was then stirred overnight at room temperature. After evaporation of the solvent, hexane was added to the resulting viscous residue. The suspended solid was filtered with suction, and the filtrate was concentrated. Chromatography {silica gel, hexane/ethyl acetate = 20:1 (v/v)} of the crude product provided **5a** (3.640 g, 70%) as a colorless oil; ^{1}H-NMR: 7.07 (2H, d, *J* = 8.5), 6.80 (2H, d, *J* = 9.2), 5.86 (1H, dddd, *J* = 17.2, *J* = 12.8, *J* = 5.1, *J* = 5.1), 5.06–5.14 (2H, m), 4.36 (1H, sextet, *J* = 6.1), 2.46–2.52 (1H, m), 2.30–2.36 (1H, m), 2.28 (3H, s), 1.29 (3H, d, *J* = 6.1); ^{13}C-NMR: 134.39, 129.97, 129.95, 117.37, 116.13, 115.17, 73.58, 40.62, 20.50, 19.48; IR (neat) (cm^{-1}): 1642, 1240; Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15; Found: C, 81.91; H, 8.87.

3.2.2. Synthesis of 6a

A solution of $NaIO_4$ (53.02 g, 247.9 mmol) and $KMnO_4$ (2.670 g, 16.89 mmol) in deionized water (1060 mL) was treated with a solution of K_2CO_3 (41.250 g, 298.46 mmol) in deionized water (120 mL), and then with *tert*-butyl alcohol (75 mL). To the mixture, a solution of **5a** (4.800 g, 27.23 mmol) in *tert*-butyl alcohol (200 mL) was slowly added. The resulting purplish suspension was stirred for 2 h at room temperature. The suspension was treated with ethylene glycol (40 mL), stirred overnight, acidified to pH 4 with 2 M HCl (320 mL) at 0 °C and extracted three times with ethyl acetate. The organic layer was washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane/ethyl acetate = 1:2 (v/v)} to give **6a** (4.491 g, 85%) as a colorless viscous oil; ^{1}H-NMR: 7.08 (2H, d, *J* = 8.3), 6.83 (2H, d, *J* = 8.6), 4.76 (1H, sextet, *J* = 6.3), 2.84 (1H, dd, *J* = 15.9, *J* = 6.8), 2.59 (1H, dd, *J* = 15.7, *J* = 6.0), 2.29 (3H, s), 1.37 (3H, d, *J* = 6.1); ^{13}C-NMR: 177.01, 155.06, 130.76, 130.01, 116.44, 70.74, 41.30, 20.51, 19.74; IR (neat) (cm^{-1}): 1713, 1237; MS *m*/*z* (%): 194 (*M*$^+$, 8), 108 (100); HRMS: Calcd for $C_{11}H_{14}O_3$ 194.0943; Found 194.0945.

3.2.3. Synthesis of 7a

Compound **7a** was prepared as an authentic sample. To a solution of **6a** (0.350 g, 1.80 mmol), 1-butanol (0.198 g, 2.67 mmol), and 4-dimethylaminopyridine (0.226 g, 1.85 mmol) in dry dichloromethane (30 ml) at 0 °C, *N*,*N*′-dicyclohexylcarbodiimide (0.401 g, 1.94 mmol) was slowly added. The reaction mixture was stirred for 23 h at room temperature and filtered. The filtrate was washed with 0.5 M HCl, and a saturated sodium hydrogen carbonate solution, and then dried over sodium sulfate. After removal of the solvent, the residue was chromatographed {silica gel, hexane/ethyl acetate = 5:1 (v/v)} to give 7**a** (0.270 g, 60%) as a colorless oil; ^{1}H-NMR: 7.07 (2H, d, *J* = 8.6), 6.82 (2H, d, *J* = 8.8), 4.76 (1H, sextet, *J* = 6.3), 4.08 (2H, t, *J* = 6.7), 2.79 (1H, dd, *J* = 15.1, *J* = 6.8), 2.51 (1H, dd, *J* = 15.3, *J* = 6.2), 2.28 (3H, s), 1.55–1.62 (2H, m), 1.31–1.40 (2H, m), 1.35 (3H, d, *J* = 6.1), 0.91 (3H, t, *J* = 7.4); ^{13}C-NMR: 171.17, 155.29, 130.51, 129.94, 116.34, 71.10, 64.48, 41.69, 30.60, 20.49, 19.90, 19.09, 13.67; IR (neat) (cm^{-1}): 1736, 1237; MS *m*/*z* (%): 250 (*M*$^+$, 15), 108 (100); HRMS: Calcd for $C_{15}H_{22}O_3$ 250.1569; Found 250.1578.

*3.2.4. Lipase-catalyzed esterification of **6a***

Carboxylic acid **6a** (3.040 g, 15.65 mmol) and 1-butanol (3.450 g, 46.55 mmol) were dissolved in dry hexane (250 mL). Na_2SO_4 (2.620 g) and dry Chirazyme L-1 (0.615 g) were then added, and the mixture was stirred for 17 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 = 5:1–1:2 (v/v)) to give (*S*)-**7a** {1.824 g, 47%, 98% e.e., $[\alpha]_D^{24} = +7.4^\circ$ (*c* 0.99, $CHCl_3$)} as a colorless oil and (*R*)-**6a** {1.328 g, 44%, 98% e.e., $[\alpha]_D^{23} = -20.3^\circ$ (*c* 1.0, $CHCl_3$)} as a colorless viscous oil. ^{1}H-NMR spectral data of (*S*)-**7a** and (*R*)-**6a** were identical to those of **7a** prepared as an authentic sample and racemic **6a**, respectively. The e.e.s of (*S*)-**7a** and (*R*)-**6a** were determined by HPLC {CHIRALCEL OB-H, hexane/2-propanol/trifluoroacetic acid = 195:5:0.2 (v/v/v)}.

*3.2.5. Synthesis of (R)-**2a***

To a solution of (*R*)-**6a** (1.261 g, 6.493 mmol) in anhydrous CH_2Cl_2 (25 mL) was slowly added a mixture of trifluoroacetic acid (8.5 mL) and trifluoroacetic anhydride (8.5 mL). The mixture was stirred for 1 h at room temperature, 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 brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane/ethyl acetate = 3:1 (v/v)} to give (*R*)-**2a** (0.902 g, 79%, 98% e.e.) as a white solid. The spectroscopic data (^{1}H-NMR and IR) agreed with those in the lit. [7f]. The e.e. was determined by HPLC {CHIRALCEL OB-H, hexane/2-propanol = 100:1 (v/v)}; mp 78.0–80.5 °C (lit. [7f] 76 °C); $[\alpha]_D^{24} = +69.4^\circ$ (*c* 1.2, MeOH) {lit. [7f] $[\alpha]_D^{20} = -68^\circ \pm 4^\circ$ (*c* 1.0, MeOH) (*S*)}.

*3.2.6. Lipase-catalyzed hydrolysis of (S)-**7a***

A 0.07 M phosphate buffer (pH 7) as the reaction medium was prepared by mixing a 0.07 M KH_2PO_4 solution and 0.07 M Na_2HPO_4 solution in the ratio of 2:3.

To a suspension of (*S*)-**7a** (1.730 g, 6.911 mmol) in the buffer (170 mL) was added lipase PS (1.700 g). The mixture was then stirred for 7 h at room temperature. The suspended solid was filtered with suction. The filtrate was extracted three times with ether/hexane (2:1). The organic layer was washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane–ethyl acetate 1:2 (v/v)} to give (*S*)-**6a** (0.706 g, 53%, >99% e.e.) as a colorless viscous liquid. The spectroscopic data (^{1}H-NMR and IR) agreed with those of (*R*)-**6a**. The e.e. was determined by HPLC {CHIRALCEL OB-H, hexane/2-propanol/trifluoroacetic acid = 195:5:0.2 (v/v/v)}.

*3.2.7. Synthesis of (S)-**2a***

Compound (*S*)-**2a** was prepared from (*S*)-**6a** in 83% yield and >99% e.e. according to the procedure described in Section 3.2.5. The spectroscopic data (^{1}H-NMR and IR) agreed with those of (*R*)-**2a**. The e.e. was determined by HPLC {CHIRALCEL OB-H, hexane/2-propanol = 100:1 (v/v)}; mp 79.5–81.5 °C (lit. [7f] 76 °C); $[\alpha]_D^{21} = -64.4^\circ$ (*c* 1.1, MeOH) {lit. [7f] $[\alpha]_D^{20} = -68^\circ \pm 4^\circ$ (*c* 1.0, MeOH) (*S*)}.

*3.3. Experimental procedures for the synthesis of (R)-**2b** and (S)-**2b***

*3.3.1. Synthesis of **5b***

Compound **5b** was prepared from **3** and **4b** in 62% yield according to the procedure described in Section 3.2.1. Chromatography {silica gel, hexane/ethyl acetate = 20:1 (v/v)} of the crude product afforded **5b** as a colorless liquid; ^{1}H-NMR: 7.17 (1H, t, *J* = 8.1), 6.46–6.51 (3H, m), 5.86 (1H, dddd, *J* = 17.2, *J* = 12.8, *J* = 5.1, *J* = 5.1), 5.07–5.15 (2H, m), 4.41 (1H, sextet, *J* = 6.1), 3.78 (3H, s), 2.47–2.54 (1H, m), 2.30–2.37 (1H, m), 1.31 (3H, d, *J* = 6.1); ^{13}C-NMR: 160.87, 159.15, 134.22, 129.85, 117.46, 108.01, 106.23, 102.38, 73.25, 55.24, 40.56, 19.42; IR (neat) (cm^{-1}): 1642, 1264; MS *m/z* (%): 192 (M^+, 78), 124 (100); HRMS: Calcd for $C_{12}H_{16}O_2$ 192.1150; Found 192.1104.

*3.3.2. Synthesis of **6b***

Compound **6b** was prepared from **5b** in 68% yield according to the procedure described in Section 3.2.2. Chromatography {silica gel, hexane/ethyl acetate = 1:2 (v/v)} of the crude product afforded **6b** as a colorless viscous liquid; ^{1}H-NMR: 7.18 (1H, t, *J* = 8.2), 6.48–6.54 (3H, m), 4.81 (1H, sextet, *J* = 6.2), 3.78 (3H, s), 2.85 (1H, dd, *J* = 15.9, *J* = 6.8), 2.59 (1H, dd, *J* = 15.6, *J* = 6.1), 1.39 (3H, d, *J* = 6.1); ^{13}C-NMR: 176.85, 160.87, 158.47, 129.97, 108.20, 106.97, 102.65, 70.36, 55.26, 41.24, 19.73; IR (neat) (cm^{-1}): 1713, 1265; MS *m/z* (%): 210 (M^+, 16), 124 (100); HRMS: Calcd for $C_{11}H_{14}O_4$ 210.0892; Found 210.0928.

*3.3.3. Synthesis of **7b***

Compound **7b** as an authentic sample was prepared from **6b** and 1-butanol in 60% yield according to the procedure described in Section 3.2.3. Chromatography {silica gel, hexane/ethyl acetate = 5:1 (v/v)} of the crude product afforded **7b** as a colorless liquid; ^{1}H-NMR: 7.17 (1H, t, *J* = 8.2), 6.48–6.53 (3H, m), 4.81 (1H, sextet, *J* = 6.3), 4.09 (2H, t, *J* = 6.7), 3.78 (3H, s), 2.80 (1H, dd, *J* = 15.4, *J* = 6.6), 2.52 (1H, dd, *J* = 15.4, *J* = 6.3), 1.55–1.62 (2H, m), 1.30–1.41 (2H, m), 1.37 (3H, d, *J* = 6.1), 0.90 (3H, t, *J* = 7.4); ^{13}C-NMR: 171.03, 160.86, 158.68, 129.90, 108.12, 106.77, 102.52, 70.72, 64.52, 55.25, 41.64, 30.60, 19.87, 19.09, 13.66; IR (neat) (cm^{-1}): 1736, 1265; MS *m/z* (%): 266 (M^+, 18), 124 (100); HRMS: Calcd for $C_{15}H_{22}O_4$ 266.1518; Found 266.1530.

*3.3.4. Lipase-catalyzed esterification of **6b***

The Chirazyme L-1-catalyzed esterification of **6b** was carried out to afford (*S*)-**7b** {42%, 99% e.e., $[\alpha]_D^{26} = +13.5^\circ$ (*c* 1.1, $CHCl_3$)} and (*R*)-**6b** {37%, 98% e.e., $[\alpha]_D^{26} = -31.2^\circ$ (*c* 0.63, $CHCl_3$)} according to the procedure described in Section 3.2.4. The spectroscopic data (^{1}H-NMR and IR) of (*S*)-**7b** and (*R*)-**6b** agreed with those of **7b** prepared as an authentic sample and the racemic **6b**, respectively. The e.e.s of (*S*)-**7b** and (*R*)-**6b** were determined by HPLC {CHIRALCEL OD-H, hexane/2-propanol/trifluoroacetic acid = 95:5:0.1 (v/v/v)}.

*3.3.5. Synthesis of (R)-**2b***

Compound (*R*)-**2b** with 97% e.e. was prepared from (*R*)-**6b** in 61% yield according to the procedure described in Section 3.2.5. Chromatography {silica gel, hexane/ethyl acetate = 2:1 (v/v)} of the crude product afforded (*R*)-**2b** as a white solid. The e.e. of (*R*)-**2b** was determined by HPLC {CHIRALCEL OB-H, hexane/2-propanol = 10:1 (v/v)}; mp 81.3–81.7 °C (lit. [7c] 69.5 °C); $[\alpha]_D^{23} = +42.4°$ (*c* 1.1, MeOH) {lit. [7c] $[\alpha]_D = +53.2°$ (*c* 1, MeOH) (*R*)}; ^{1}H-NMR (C_6D_6): 7.65 (1H, d, *J* = 8.6), 5.91–5.94 (2H, m), 3.44–3.53 (1H, m), 2.63 (3H, s), 1.63–1.76 (2H, m), 0.49 (3H, d, *J* = 6.4); ^{13}C-NMR (C_6D_6): 189.66, 166.00, 163.81, 129.05, 115.55, 109.77, 101.14, 74.64, 54.93, 44.30, 20.70; IR (CCl_4) (cm^{-1}): 1686, 1268; MS *m*/*z* (%): 192 (M^+, 44), 150 (100); HRMS: Calcd for $C_{11}H_{12}O_3$ 192.0787; Found 192.0810.

*3.3.6. Lipase-catalyzed hydrolysis of (S)-**7b***

The lipase PS-catalyzed hydrolysis of (*S*)-**7b** was carried out to afford (*S*)-**6b** (52%, 99% e.e.) according to the procedure described in Section 3.2.6. The spectroscopic data (^{1}H-NMR and IR) of (*S*)-**6b** agreed with those of (*R*)-**6b**. The e.e. of (*S*)-**6b** was determined by HPLC {CHIRALCEL OD-H, hexane/2-propanol/trifluoroacetic acid = 95:5:0.1 (v/v/v)}.

*3.3.7. Synthesis of (S)-**2b***

Compound (*S*)-**2b** with 99% e.e. was prepared from (*S*)-**6b** in 66% yield according to the procedure described in Section 3.2.5. Chromatography {silica gel, hexane/ethyl acetate = 10:1 (v/v)} of the crude product afforded (*S*)-**2b** as a white solid. The spectroscopic data (^{1}H-NMR and IR) of (*S*)-**2b** agreed with those of (*R*)-**2b**. The e.e. of (*S*)-**2b** was determined by HPLC {CHIRALCEL OB-H, hexane/2-propanol = 10:1 (v/v)}; mp 80.0–81.7 °C (lit. [7c] 69.5 °C); $[\alpha]_D^{23} = -46.6°$ (*c* 1.2, MeOH) {lit. [7c] $[\alpha]_D = +53.2°$ (*c* 1, MeOH) (*R*)}.

*3.4. Experimental procedures for the synthesis of (R)- and (S)-**1a***

*3.4.1. Synthesis of (R)-**10a***

Compound (*R*)-**10a** with 96% e.e. was prepared from (*S*)-**8** (>99% e.e. [8a]) and **9a** in 56% yield according to the procedure described in Section 3.2.1. Chromatography {silica gel, hexane/ether = 20:1 (v/v)} of the crude product afforded (*R*)-**10a** as a colorless viscous oil. The e.e. of (*R*)-**10a** was determined by HPLC {CHIRALCEL OJ, hexane/2-propanol = 20:1 (v/v)}; $[\alpha]_D^{26} = -8.6°$ (*c* 0.96, $CHCl_3$); ^{1}H-NMR: 7.22–7.36 (5H, m), 7.04–7.09 (1H, m), 6.42–6.44 (3H, m), 5.86 (1H, dddd, *J* = 17.2, *J* = 12.7, *J* = 5.1, *J* = 5.1), 5.05–5.15 (2H, m), 3.72 (3H, s), 2.71–2.79 (1H, m), 2.54–2.61 (1H, m); ^{13}C-NMR: 160.63, 159.35, 141.39, 134.14, 129.67, 128.53. 127.57, 126.02, 117.52, 108.19, 106.35, 102.41, 79.86, 55.17, 42.83; IR (neat) (cm^{-1}): 1642, 1263; MS *m*/*z* (%): 254 (M^+, 8), 130 (100); HRMS: Calcd for $C_{17}H_{18}O_2$ 254.1307; Found 254.1339.

*3.4.2. Synthesis of (R)-**11a***

Compound (*R*)-**11a** was prepared from (*R*)-**10a** in 79% yield according to the procedure described in Section 3.2.2. Chromatography {silica gel, hexane/acetone = 1:1 (v/v)} of the crude product afforded (*R*)-**11a** as a colorless viscous oil; $[\alpha]_D^{23} = +4.5°$ (*c* 0.093, $CHCl_3$); ^{1}H-NMR: 7.19–7.43 (5H, m), 7.05–7.09 (1H, m), 6.44–6.47 (3H, m), 5.61 (1H, dd, *J* = 9.3, *J* = 4.2), 3.72 (3H, s), 3.08 (1H, dd, *J* = 15.9, *J* = 9.0), 2.82 (1H, dd, *J* = 16.1, *J* = 4.4); ^{13}C-NMR: 175.81, 160.61, 158.75, 140.05, 129.73, 128.85, 128.17, 125.95, 108.33, 106.94, 102.63, 76.36, 55.18, 43.44; IR (neat) (cm^{-1}): 1714, 1264; MS *m*/*z* (%): 272 (M^+, 6), 124 (100); HRMS: Calcd for $C_{16}H_{16}O_4$ 272.1049; Found 272.1045.

*3.4.3. Synthesis of (R)-**1a***

Compound (*R*)-**1a** with 96% e.e. was prepared from (*R*)-**11a** in 59% yield according to the procedure described in Section 3.2.5. Chromatography {silica gel, hexane/ethyl acetate = 5:1 (v/v)} of the crude product afforded (*R*)-**1a** as a white solid. When the reaction time exceeded 10 min, the yield of (*R*)-**1a** was significantly reduced. The spectroscopic data (^{1}H-NMR and IR) of (*R*)-**1a** agreed with those of the racemic **1a** purchased from Aldrich. The e.e. of (*R*)-**1a** was determined by HPLC {CHIRALCEL OD-H, hexane/2-propanol = 1:1 (v/v)}; mp 89.7–90.9 °C; $[\alpha]_D^{26}$: +86.3° (*c* 1.1, EtOH) {lit. [7h] $[\alpha]_D^{20} = +58.5°$ (*c* 0.5, EtOH), 89% e.e. (*R*)}.

*3.4.4. Synthesis of (S)-**1a***

Compound (*S*)-**1a** with 95% e.e. was prepared from (*R*)-**8** (>99% e.e. [8a]) in 16% via three steps according to the procedures described in Sections 3.2.1, 3.2.2 and 3.2.5. The spectroscopic data (^{1}H-NMR and IR) of (*S*)-**1a** agreed with those of the racemic **1a** purchased from Aldrich. The e.e. of (*S*)-**1a** was determined by HPLC {CHIRALCEL OD-H, hexane/2-propanol = 1:1 (v/v)}; white solid; mp 89.9–91.3 °C; $[\alpha]_D^{26} = -84.0°$ (*c*, EtOH) {lit. [7h] $[\alpha]_D^{20} = +58.5°$ (*c* 0.5, EtOH), 89% e.e. (*R*)}.

*3.5. Experimental procedures for the synthesis of (R)-**1b***

*3.5.1. Synthesis of (R)-**10b***

Compound (*R*)-**10b** with 98% e.e. was prepared in 58% yield from (*S*)-**8** (>99% e.e. [8a]) and **9b** according to the procedure described in Section 3.2.1. Toluene was used as the solvent instead of THF. Chromatography {silica gel, hexane/ethyl acetate = 100:1 (v/v)} of the crude product afforded (*R*)-**10b** as a pale yellow viscous oil. The e.e. of (*R*)-**10b** was determined by HPLC {CHIRALCEL OJ, hexane/2-propanol = 5:1 (v/v)}; $[\alpha]_D^{24} = +6.6°$ (*c* 0.63, $CHCl_3$); ^{1}H-NMR: 8.16 (2H, d, *J* = 8.4), 7.63 (1H, t, *J* = 7.4), 7.50 (2H, t, *J* = 7.8), 7.24–7.37 (5H, m), 7.20 (1H, t, *J* = 8.4), 6.73–6.75 (3H, m), 5.85 (1H, dddd, *J* = 17.1, *J* = 12.7, *J* = 5.1, *J* = 5.1), 5.16 (1H, dd, *J* = 7.6, *J* = 5.2), 5.06–5.09 (2H, m), 2.72–2.79 (1H, m), 2.56–2.62 (1H, m); ^{13}C-NMR: 159.10, 141.00, 133.96, 133.55, 130.23, 130.17, 129.71, 128.63, 128.60, 128.55, 127.71, 126.04, 119.27, 117.71, 114.07, 113.37, 109.94, 80.13, 42.84; IR (neat) (cm^{-1}): 1737, 1642, 1248; MS *m*/*z* (%): 344 (M^+, 1), 105 (100); HRMS: Calcd for $C_{23}H_{20}O_3$ 344.1413; Found 344.1421.

*3.5.2. Synthesis of (R)-**11b***

Compound (*R*)-**11b** (pale yellow viscous oil) was prepared in 71% yield from (*R*)-**10b** according to the procedure described in Section 3.2.2 and used for the next reaction step without purification; $[\alpha]_D^{25} = +4.8^\circ$ (*c* 1.2, $CHCl_3$); ^{1}H-NMR: 8.16 (2H, d, *J* = 8.4), 7.63 (1H, t, *J* = 7.6), 7.50 (2H, t, *J* = 7.7), 7.19–7.42 (6H, m), 6.74–6.79 (3H, m), 5.65 (1H, dd, *J* = 9.2, *J* = 4.3), 3.09 (1H, dd, *J* = 16.1, *J* = 9.3), 2.84 (1H, dd, *J* = 16.1, *J* = 4.4); ^{13}C-NMR: 175.36, 165.05, 158.57, 151.68, 139.76, 133.63, 130.19, 129.79, 129.49, 128.86, 128.58, 128.29, 126.02, 114.63, 113.50, 110.20, 43.50, 31.00; IR (neat) (cm^{-1}): 1732, 1715, 1250; MS *m/z* (%): 362 (M^+, 1), 105 (100); HRMS: Calcd for $C_{22}H_{18}O_5$ 362.1154; Found 362.1143.

*3.5.3. Synthesis of (R)-**12b***

Compound (*R*)-**12b** with 97% e.e. was prepared in 59% yield from (*R*)-**11b** according to the procedure described in Section 3.2.5. Chromatography {silica gel, hexane/ethyl acetate = 10:1 (v/v)} of the crude product afforded (*R*)-**12b** as a pale yellow solid. The e.e. of (*R*)-**12b** was determined by HPLC {CHIRALPAK AD-H, hexane/2-propanol = 2:1 (v/v)}; $[\alpha]_D^{26} = -45.4^\circ$ (*c* 0.047, $CHCl_3$); mp 108.0–120.0 °C; ^{1}H-NMR: 8.19 (2H, d, *J* = 8.2), 8.02 (2H, d, *J* = 8.5), 7.67 (1H, t, *J* = 7.4), 7.38–7.55 (7H, m), 6.99 (1H, s), 6.95 (1H, d, *J* = 8.6), 5.55 (1H, dd, *J* = 13.4, *J* = 2.9), 3.12 (1H, dd, *J* = 16.8, *J* = 13.4), 2.92 (1H, dd, *J* = 17.0, *J* = 3.1); ^{13}C-NMR: 190.93, 164.36, 162.54, 156.97, 138.46, 134.55, 134.00, 130.59, 130.30, 128.89, 128.71, 128.59, 126.16, 118.91, 115.85, 111.38, 80.03, 44.46; IR (CCl_4) (cm^{-1}): 1748, 1697, 1235; MS *m/z* (%): 344 (M^+, 3), 130 (100); HRMS: Calcd for $C_{22}H_{16}O_4$ 344.1049; Found 344.1088.

*3.5.4. Enzyme-catalyzed hydrolysis of (R)-**12b** (screening experiment)*

As a typical procedure, to a solution of lipase MY (50 mg) in 0.07 M phosphate buffer (pH 7, 2 mL) was added a solution of (*R*)-**12b** (0.010 g, 0.029 mmol) in acetonitrile (1 mL). The suspension was then stirred for 24 h at 30 °C. A sample was withdrawn and analyzed by TLC {hexane/ethyl acetate = 5:1 (v/v)}.

*3.5.5. Lipase MY-catalyzed hydrolysis of (R)-**12b***

To a solution of lipase MY (3.100 g) in 0.07 M phosphate buffer (pH 7, 200 mL) was then added a solution of (*R*)-**12b** (1.000 g, 2.904 mmol) in acetonitrile (70 mL). The suspension was stirred for 48 h at 30 °C and extracted three times with ethyl acetate. The organic layer was washed with 10% $NaHCO_3$ solution, brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane/ethyl acetate = 1:1 (v/v)} to give (*R*)-**1b** (58%, 97% e.e.) as a pale yellow solid. The spectroscopic data {^{1}H-NMR and IR (CCl_4)} agreed with those of the racemic **1b** purchased from Tokyo Kasei. The e.e. was determined by HPLC {CHIRALPAK AS-H, hexane/2-propanol = 3:1 (v/v)}; $[\alpha]_D^{26} = +63.8^\circ$ (*c* 0.14, MeOH) {lit. [15] $[\alpha]_D^{23} = -85.3^\circ$ (*c* 1.2, MeOH) (*S*)}; mp 178.0–179.8 °C.

*3.6. Experimental procedures for the synthesis of (S)-**1c***

*3.6.1. Synthesis of **14***

To a solution of **13** (3.662 g, 29.99 mmol) and dry pyridine (4.817 g, 60.90 mmol) in dry THF (30 mL) at 0 °C, benzoyl chloride (4.494 g, 31.97 mmol) was slowly added. The reaction mixture was stirred for 19 h at room temperature under Ar and quenched at 0 °C with 1 M HCl (50 mL). The resulting mixture was extracted with toluene. The organic phase was washed in order with deionized water, a saturated $NaHCO_3$ solution, brine, and then dried over Na_2SO_4. After removal of the solvents, **14** was obtained as a white solid in 99% yield. The spectroscopic data {^{1}H-NMR and IR ($CHCl_3$)} agreed with the literature values [16]; mp 89.0–90.2 °C (lit. [16] 93–95 °C).

*3.6.2. Synthesis of **15***

A mixture of crude **14** (13.146 g, 58.112 mmol), allyl bromide (30 mL, 347 mmol), indium (13.380 g, 116.6 mmol) in DMF (60 mL) and water (500 mL) was stirred for 49 h at room temperature under Ar. The reaction mixture was quenched at 0 °C with 3 M HCl (60 mL) and extracted three times with ether. The organic phase was washed with deionized water and subsequently with brine, and then dried over Na_2SO_4. After removal of the solvents, **15** was obtained as a white solid in 99% yield; mp 53.2–54.0 °C; ^{1}H-NMR: 8.21 (2H, d, *J* = 8.5), 7.65 (1H, t, *J* = 7.4), 7.52 (2H, t, *J* = 7.7), 7.44 (2H, d, *J* = 8.8), 7.21 (2H, d, *J* = 8.3), 5.79–5.89 (1H, m), 5.16–5.21 (1H, m), 4.77–4.80 (1H, m), 2.51–2.56 (2H, m); ^{13}C-NMR: 165.24, 150.21, 141.54, 134.29, 133.63, 130.18, 129.51, 128.59, 126.97, 121.64, 118.64, 72.79, 43.89; IR (CCl_4) (cm^{-1}): 3415, 1641, 1736; MS *m/z* (%): 269 (M^++1, 1), 105 (100); HRMS: Calcd for $C_{17}H_{17}O_3$ (M^++1) 269.1178; Found 269.1152.

*3.6.3. Synthesis of **16***

To a solution of crude **15** (10.662 g, 39.739 mmol) and dry pyridine (15.732 g, 198.9 mmol) in dry THF (160 mL) at 0 °C, acetyl chloride (9.567 g, 121.9 mmol) was slowly added. The reaction mixture was stirred for 45 h at room temperature and quenched at 0 °C with 1 M HCl (100 mL). The resulting mixture was extracted three times with ether. The organic phase was washed in order with deionized water, a saturated $NaHCO_3$ solution, and brine, and then dried over Na_2SO_4. After removal of the solvents, the residue was chromatographed {silica gel, hexane/ethyl acetate = 3:1 (v/v)} to give **16** (11.920 g, 97%) as a colorless oil; ^{1}H-NMR: 8.20 (2H, d, *J* = 7.1), 7.65 (1H, t, *J* = 7.4), 7.52 (2H, t, *J* = 7.7), 7.41 (2H, d, *J* = 8.5), 7.21 (2H, d, *J* = 8.8), 5.82–5.86 (1H, m), 5.67–5.77 (1H, m), 5.06–5.12 (2H, m), 2.54–2.71 (2H, m), 2.08 (3H, s); ^{13}C-NMR: 170.18, 165.09, 150.53, 137.70, 133.66, 133.15, 130.18, 129.46, 128.60, 127.83, 121.69, 118.24, 74.56, 40.70, 21.21; IR (neat) (cm^{-1}): 1739, 1643; MS *m/z* (%): 310 (M^+, 2), 105 (100); HRMS: Calcd for $C_{19}H_{18}O_4$ 310.1205; Found 310.1198.

*3.6.4. Lipase-catalyzed hydrolysis of **16***

To a suspension of **16** (5.447 g, 17.55 mmol) in 0.07 M phosphate buffer (pH 7, 300 mL) was added lipase PS (5.500 g). The mixture was stirred for 88 h at room temperature. The sus-

pended solid was filtered with suction. The filtrate was extracted three times with ether. The organic layer was washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed {silica gel, hexane/ethyl acetate = 3:1 (v/v)} to give (*R*)-**15** {1.599 g, 34%, >99% e.e., $[\alpha]_D^{26} = +38.6^\circ$ (*c* 0.98, $CHCl_3$)} as a white solid and (*S*)-**16** {1.922 g, 36%, >99% e.e., $[\alpha]_D^{26} = -50.7^\circ$ (*c* 0.97, $CHCl_3$)} as a colorless oil. The spectroscopic data (^{1}H-NMR and IR) of (*R*)-**15** and (*S*)-**16** agreed with those of the racemic **15** and **16**, respectively. The e.e.s of (*R*)-**15** and (*S*)-**16** were determined by HPLC {CHIRALCEL OD-H, hexane/2-propanol = 20:1 (v/v)}.

3.6.5. Synthesis of (S)-*17*

Compound (*S*)-**17** with 96% e.e. was prepared in 42% yield from (*R*)-**15** with >99% e.e. and **9a** according to the procedure described in Section 3.2.1. Toluene was used as the solvent instead of THF. Chromatography {silica gel, hexane/ethyl acetate = 5:1 (v/v)} of the crude product afforded (*S*)-**17** as a pale yellow viscous oil. The e.e. of (*S*)-**17** was determined by HPLC {CHIRALPAK AD-H, hexane/2-propanol = 10:1 (v/v)}; $[\alpha]_D^{26} = -2.8^\circ$ (*c* 1.3, $CHCl_3$); ^{1}H-NMR: 8.19 (2H, d, *J* = 7.1), 7.64 (1H, t, *J* = 7.5), 7.51 (2H, t, *J* = 7.9), 7.42 (2H, d, *J* = 8.8), 7.19 (2H, d, *J* = 8.6), 7.08 (1H, t, *J* = 8.4), 6.44–6.46 (3H, m), 5.82–5.92 (1H, m), 5.08–5.19 (3H, m), 3.74 (3H, s), 2.73–2.80 (1H, m), 2.56–2.63 (1H, m); ^{13}C-NMR: 165.09, 160.71, 159.23, 150.26, 139.02, 133.96, 133.65, 130.17, 129.79, 129.52, 128.61, 127.17, 121.81, 117.79, 108.21, 106.51, 102.51, 79.38, 55.21, 42.82; IR (neat) (cm^{-1}): 1736, 1641, 1265; MS *m*/*z* (%): 374 (M^+, 1), 105 (100); HRMS: Calcd for $C_{24}H_{22}O_4$ 374.1518; Found 374.1503.

3.6.6. Synthesis of (S)-*18*

Compound (*S*)-**18** was prepared in 92% yield from (*S*)-**17** according to the procedure described in Section 3.2.2. Chromatography {silica gel, ether/acetone = 2:1 (v/v)} of the crude product afforded (*S*)-**18** as a pale yellow viscous oil; $[\alpha]_D^{26} = -30.1^\circ$ (*c* 0.19, $CHCl_3$); ^{1}H-NMR: 8.18 (2H, d, *J* = 6.8), 7.64 (1H, t, *J* = 7.4), 7.51 (2H, t, *J* = 7.8), 7.45 (2H, d, *J* = 8.8), 7.21 (2H, d, *J* = 8.8), 7.09 (1H, t, *J* = 8.4), 6.46–6.49 (3H, m), 5.66 (1H, dd, *J* = 8.6, *J* = 4.4), 3.74 (3H, s), 3.10 (1H, dd, *J* = 16.0, *J* = 9.2), 2.85 (1H, dd, *J* = 16.0, *J* = 4.4); ^{13}C-NMR: 176.09, 165.07, 160.67, 158.63, 150.66, 137.69, 133.71, 130.19, 129.83, 129.38, 128.62, 127.21, 122.16, 108.36, 107.08, 102.73, 75.87, 55.22, 43.46; IR (neat) (cm^{-1}): 1742, 1708, 1262; MS *m*/*z* (%): 392 (M^+, 1), 105 (100); HRMS: Calcd for $C_{23}H_{20}O_6$ 392.1260; Found 392.1239.

3.6.7. Synthesis of (S)-*19*

Compound (*S*)-**19** of 96% e.e. was prepared in 40% yield from (*S*)-**18** according to the procedure described in Section 3.2.5. Chromatography {silica gel, hexane/ethyl acetate = 2:1 (v/v)} of the crude product afforded (*S*)-**19** as a pale yellow solid. The e.e. of (*S*)-**19** was determined by HPLC {CHIRALPAK AS-H, hexane/2-propanol = 1:2 (v/v)}; $[\alpha]_D^{23} = -110.0^\circ$ (*c* 0.060, $CHCl_3$); mp 122.0–124.0 °C; ^{1}H-NMR: 8.22 (2H, d, *J* = 7.3), 7.89 (1H, d, *J* = 8.8), 7.66 (1H, t, *J* = 7.4), 7.51–7.57 (4H, m), 7.30 (2H, d, *J* = 8.3), 6.64 (1H, dd, *J* = 8.8, *J* = 2.4), 6.52 (1H, d, *J* = 2.4), 5.52 (1H, dd, *J* = 13.3, *J* = 2.8), 3.85 (3H, s), 3.05 (1H, dd, *J* = 17.1, *J* = 13.2), 2.87 (1H, dd, *J* = 16.7, *J* = 3.1); ^{13}C-NMR: 190.39, 166.25, 165.07, 163.42, 151.12, 136.45, 133.75, 130.22, 129.33, 128.80, 128.63, 127.42, 122.17, 114.82, 110.38, 100.93, 79.45, 55.69, 44.37; IR (CCl_4) (cm^{-1}): 1728, 1673, 1257; MS *m*/*z* (%): 374 (M^+, 12), 105 (100); HRMS: Calcd for $C_{23}H_{18}O_5$ 374.1154; Found 374.1147.

3.6.8. Synthesis of (S)-*1c*

To a solution of esterase SNSM-87 (0.390 g) in 0.07 M phosphate buffer (pH 7, 16 mL) was added a solution of (*S*)-**19** (0.332 g, 0.887 mmol) in acetone (16 mL). The mixture was stirred for 23 h at room temperature and then poured into deionized water in a beaker. The resultant mixture was stored overnight in a refrigerator then filtered with suction. The filtrate was dissolved in acetone and any insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was recrystallized from ethyl acetate–hexane to afford (*S*)-**1c** (0.128 g, 54%, 93% e.e.) as a white solid. The spectroscopic data {^{1}H-NMR (acetone-d_6) and IR ($CHCl_3$)} agreed with the literature values [14]. The e.e. was determined by HPLC {CHIRALCEL OD-H, hexane/2-propanol = 3:1 (v/v)}; mp 165–169 °C (lit. [14] 150–152 °C); $[\alpha]_D^{22} = -52.0^\circ$ (*c* 1.0, MeOH) {lit. [14] $[\alpha]_D^{21} = -33.0^\circ$ (*c* 1.0, MeOH,) (*S*)}.

4. Conclusion

We successfully synthesized several 2-substituted 4-chromanones in optically active forms using several enzymes complementarily. The Chirazyme L-1 was suitable as a catalyst for the enantioselective esterification of the 3-aryloxybutanoic acids. Lipase PS selectively hydrolyzed the acetate moiety coexisting with the benzoate moiety which was hydrolyzed by lipase MY, OF and esterase SNSM-87.

Acknowledgments

The authors thank Roche Diagnostics K.K. and Nagase & Co. Ltd., for kindly providing the enzymes. The authors also thank the researchers at the Biotechnology Research Center, Toyama Prefectural University, for their generous support regarding the NMR spectroscopic and optical rotation measurements.

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