Lipase-Catalyzed Transesterification of 2-Hydroxy-2-(pentafluorophenyl)acetonitrile Leading to (1*R*,2*R*)- and (1*S*,2*S*)-Bis(pentafluorophenyl)ethane-1,2-diol

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Optically pure (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis(pentafluorophenyl)ethane-1,2-diol (**1**) were synthesized from key intermediates (*R*)- and (*S*)-2-hydroxy-2-(pentafluorophenyl)acetonitrile (**2**), both of which were prepared by the lipase LIP-catalyzed transesterification ($E = 465$). The absolute configuration of (*S*)-**2** was determined by X-ray structural analysis after transformation into (*S*)-α-cyano-2,3,4,5,6-pentafluorobenzyl (*S*)-6-methoxy-α-methyl-2-naphthaleneacetate (*S*,*S*)-**9**. In addition, the crystal structure of (*S*,*S*)-**9** has an interesting well-ordered packing pattern which shows face-to-face stacking interactions and end-to-end parallel contacts between the pentafluorophenyl and 6-methoxynaphthyl groups of the adjacent molecules.

Introduction

Optically active 1,2-diphenylethane-1,2-diol and its derivatives have attracted much attention owing to the versatile utilities as chiral ligands[1] and chiral auxiliaries[1a,2] in asymmetric syntheses. The stereoselectivity of the reactions with these compounds are generally controlled by the steric interaction of phenyl groups. On the other hand, perfluorophenyl group is known to construct the face-to-face stacking arrangement with phenyl group[3] due to the favorable electrostatic interaction between the aromatic rings (Figure 1a).[4−7] Recently, such stacking interactions have been utilized in the stereocontrolled photochemical reactions in the crystalline state,[8] in supramolecular systems,[9,10] and in the design of fluorinated drugs.[11] Moreover, the electron-withdrawing property of perfluorophenyl group (Figure 1b) has been utilized for enhancing the Lewis acidity of boranes[12−15]

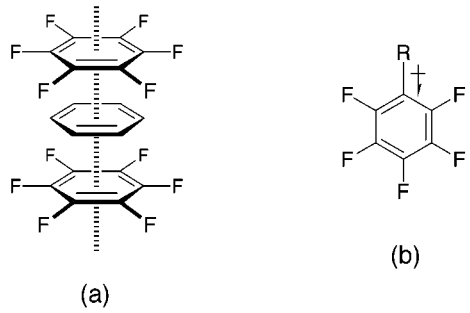

Figure 1. Features of the perfluorophenyl group. (a) Stacking ability with phenyl group. (b) Electron-withdrawing property.

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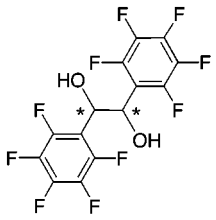
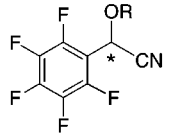
and for promoting Diels−Alder[16] and Baylis−Hillman[17] reactions. Despite their useful properties, only a few examples of perfluorophenyl-containing chiral compounds[1c,d,18] have been reported so far.



(1*R*,2*R*)- and (1*S*,2*S*)-**1**



(*R*)- and (*S*)-**2**: R = H
(*R*)- and (*S*)-**3**: R = TBS

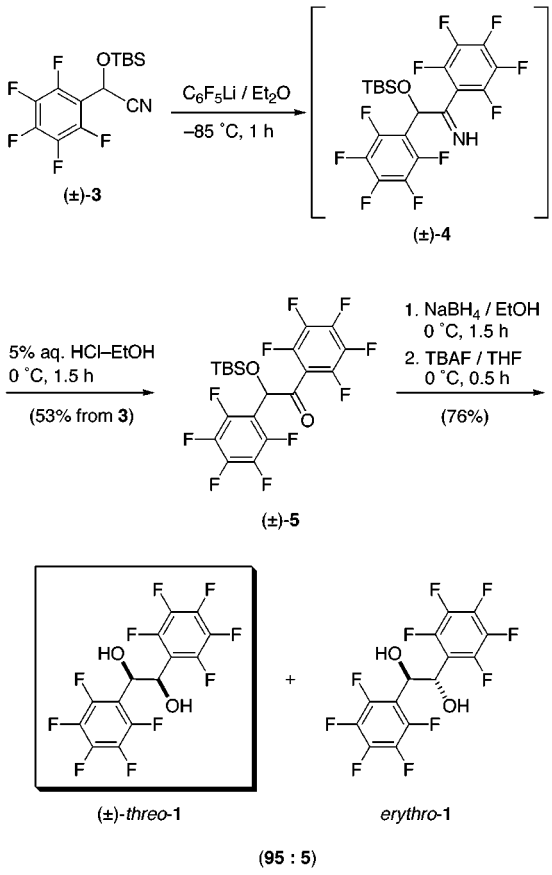
In this paper, we report the synthesis of both enantiomers of (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis(pentafluorophenyl)-ethane-1,2-diol, (1*R*,2*R*)- and (1*S*,2*S*)-**1**, as new entries of pentafluorophenyl-containing optically active compounds through key intermediates of (*R*)- and (*S*)-2-hydroxy-2-(pentafluorophenyl)acetonitrile, (*R*)- and (*S*)-**2**, respectively. We expected that introduction of pentafluorophenyl groups into chiral 1,2-diols will endow new potentialities in asymmetric syntheses and lead to interesting advanced materials reflecting the stacking interaction and the electron-withdrawing property.

In our preceding papers,[19] enantiomerically pure (1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-bis(pentafluorophenyl)-ethanol[19a] were synthesized from racemic (±)-2-(*tert*-butyldimethylsilyloxy)-2-(pentafluorophenyl)acetonitrile (**3**) through chemical resolutions with D-camphorsulfonic acid. Quite recently, we have reported the synthesis of optically pure (*S*)-**3**[19c] by the lipase-catalyzed enantioselective hydrolysis of racemic propanoate of **2** followed by TBS protection. In this paper, we successfully prepared both (*R*)- and (*S*)-**2** by the lipase-catalyzed transesterification with improved yields and optical purities. The absolute configuration of (*S*)-**2** was determined by X-ray structural analysis of its naproxen ester. Noteworthy is a well-ordered packing structure of the naproxen ester, where the pentafluorophenyl and the 6-methoxynaphthyl groups construct face-to-face stacking interactions and end-to-end parallel contacts.

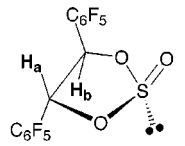
Results and Discussion

Diastereoselective Synthesis of Racemic 1,2-Diol (±)-1. Prior to the synthesis of optically active diols (1*R*,2*R*)-**1** and (1*S*,2*S*)-**1**, we first established the diastereoselective pathway for the racemic (±)-*threo*-**1**, which was prepared from racemic *tert*-butyldimethylsilyl (TBS) ether of cyanohydrin (±)-**3** as a key intermediate in three steps (Scheme 1). Thus, the reaction of (±)-**3** with 1.6 equiv of (pentafluorophenyl)lithium (prepared from bromopentafluorobenzene−*n*-BuLi in ether, −78 °C) gave imine (±)-**4**. Subsequent hydrolysis with 5% aqueous HCl−EtOH furnished the TBS ether of ketone (±)-**5** (53% yield). Attempts of chromatographic purification of (±)-**4** rather contaminated it with unidentified compounds. Reduction of (±)-**5** with $NaBH_4$ in ethanol followed by desilylation with tetra-*n*-butylammonium fluoride (TBAF) in THF gave (±)-*threo*-**1** together with a small amount of *erythro*-**1** [threo/erythro = 95:5 (85% yield)], which were easily separated chromatographically.

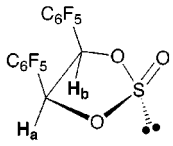
Scheme 1



The relative stereochemistry of (±)-*threo*-**1** was determined by ^1H NMR analysis after transformation ($SOCl_2$−Et_3N) into the corresponding cyclic sulfite **6**. The ^1H NMR spectrum for *trans*-**6** showed two doublets at δ 5.96 and 6.49 (J_{vic} = 10.2 Hz) assignable to chemically nonequivalent vicinal methine protons (H_a and H_b). On the other hand, *cis*-**6** similarly prepared from *erythro*-**1** exhibits one singlet at δ 6.52 assignable to the equivalence of H_a and H_b.



(±)-*trans*-**6**
from (±)-*threo*-**1**



cis-**6**
from *erythro*-**1**

The diastereoselectivity in $NaBH_4$ reduction of (±)-**5** can be rationalized by the Felkin−Anh model[20] (Scheme

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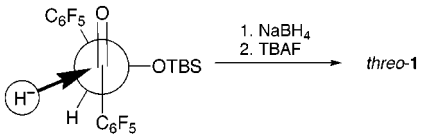
Scheme 2



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2). The silyloxy (OTBS) group seems to be bulkier than the pentafluorophenyl group. Consequently, the OTBS group locates in the least sterically hindered site and hydride attacks the carbonyl group from a direction antiperiplanar to the OTBS group.

Lipase-Catalyzed Transesterification of Cyanohydrin (±)-2. If optically active TBS ethers (*R*)- and (*S*)-**3** are available, both enantiomers of optically active diols (1*R*,2*R*)- and (1*S*,2*S*)-**1** would be prepared. For this purpose, we now prepared racemic cyanohydrin precursor (±)-**2**, a new compound itself, and then subjected it to the lipase-catalyzed transesterification in an organic solvent. Cyanohydrin (±)-**2** could be prepared by two new methods (Scheme 3) via its acetate (±)-**7** (method A) or its trimethylsilyl (TMS) ether (±)-**8** (method B),[21] both of which were readily prepared from pentafluorobenzaldehyde.[22] In method A, hydrolysis of acetate (±)-**7** was successfully carried out only by using lipase A6-catalyzed reaction in a phosphate buffer (pH 5.6)-acetone system (75% yield), although both $LiAlH_4$ reduction and alkaline saponification of (±)-**7** resulted in decomposed compounds. In the case of method B, hydrolysis of TMS ether (±)-**8** was achieved by using 3% aqueous HCl, giving (±)-**2** (98% yield).

The lipase-catalyzed transesterifications of (±)-**2** were carried out with vinyl acetate in dry diisopropyl ether at 30 °C (Scheme 4). Several commercially available lipases were examined as shown in Table 1. Among them, lipase PS showed the highest enantioselectivity ($E > 227$), while the reaction rate was slow (72 h for 8% conversion). In contrast, lipase PS immobilized on Toyonite-DM[23] remarkably accelerated the reaction rate (6.5 h for 35% conversion) while the enantioselectivity ($E = 18$) was decreased. The best choice was lipase LIP, which gave a good enantioselectivity ($E = 113$) with enhanced reaction rate (1.5 h for 44% conversion). We have previously reported the suitability of lipase LIP for the resolution of pentafluorophenyl-containing compounds such as the propanoate of (±)-**2** ($E = 211$) in hydrolysis[19c] and 3-hydroxy-3-(pentafluorophenyl)propionitrile ($E > 1057$) in transesterification.[19b]

Further optimization of the enantioselectivity ($E > 427$) was attained by lowering the reaction temperature to 0 °C. The plot of ln *E* vs 1/*T* in the lipase LIP-catalyzed transesterification (Figure 2) showed the linear correlation by changing the reaction temperature from 45 to 0 °C.[25]

Table 1. Screening of Lipases for the Enantioselective Transesterification of (±)-2[a]

lipase	time (h)	conversion[b] (%)	(*S*)-**7** (% ee[c])	(*R*)-**2** (% ee[d])	*E* value[e]
lipase AK[f]	26	32	61	48	6
lipase PS[g]	72	8	20	20	>227
lipase PS[h]	6.5	35	85	47	18
lipase LIP[i]	1.5	44	96	79	113

[a] Conditions: lipase (100 mg), (±)-**2** (50 mg, 0.224 mmol), vinyl acetate (0.448 mmol), dry diisopropyl ether (2.5 mL), 30 °C. [b] Determined by GC analysis. [c] Determined by ^{1}H NMR spectra (200 MHz) in the presence of Eu(hfc)$_3$. [d] Determined by ^{1}H NMR spectra (200 MHz) after transformation into MTPA ester. [e] Calculated from $E = \ln [1 - c[1 + \mathbf{7}(ee)]]/\ln[1 - c[1 - \mathbf{7}(ee)]]$, $c = \mathbf{2}(ee)/[\mathbf{7}(ee) + \mathbf{2}(ee)]$ according to ref 24. [f] *Pseudomonas fluorescens* lipase. [g] *Pseudomonas cepacia* lipase. [h] *Pseudomonas cepacia* lipase immobilized on Toyonite-DM. [i] *Pseudomonas aeruginosa* lipase immobilized on Hyflo Super-Cel.

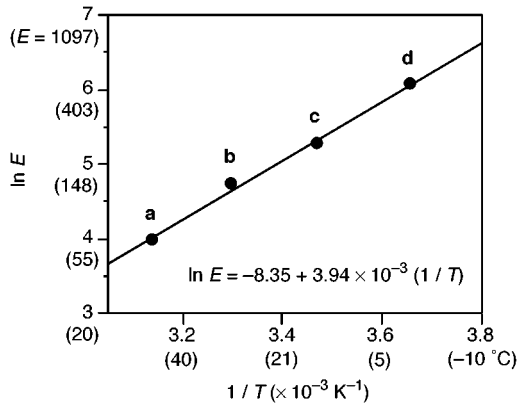

Figure 2. Correlation between the ln *E* in the lipase LIP-catalyzed transesterifications of (±)-**2** and 1/*T*. Conditions: lipase LIP (100 mg), (±)-**2** (50 mg), vinyl acetate (2 equiv), in dry *i*-Pr_2O (2.5 mL). Reaction temperature (*E* value, reaction time, conversion): (a) 45 °C (53, 1.0 h, 47%), (b) 30 °C (113, 1.5 h, 48%), (c) 15 °C (197, 2.3 h, 44%), (d) 0 °C (>427, 4.0 h, 44%).

By using the optimized conditions, transesterification on a preparative scale [(±)-**2** (2 g), lipase LIP (2 g), vinyl acetate (4 equiv) in dry diisopropyl ether, 0 °C, 23 h] gave optically active (*S*)-**7** (50% yield, 98% ee) and its antipodal alcohol (*R*)-**2** (46% yield, 96% ee) with high enantioselectivity ($E = 465$). Moreover, lipase LIP was reusable to give both enantiomers with retention of the enantioselectivity [(*S*)-**7**: 50% yield, 98% ee; (*R*)-**2**: 47% yield, 94% ee, $E = 356$]. The optical purity of (*R*)-**2** was increased up to >99% ee by one recrystallization from petroleum ether−CH_2Cl_2.

Absolute Configuration of Cyanohydrin 2 Obtained in the Transesterification. We have reported the determination of the absolute configuration of (*S*)-**2** by X-ray structural analysis after conversion to its naproxen ester **9** (Figure 3).[19c] The optically active (*S*)-**2** has been prepared by the hydrolytic resolution of acetate (±)-**7**. In the present transesterification of (±)-**2**, the remaining enantiomer of **2** was assigned to be (*R*) by

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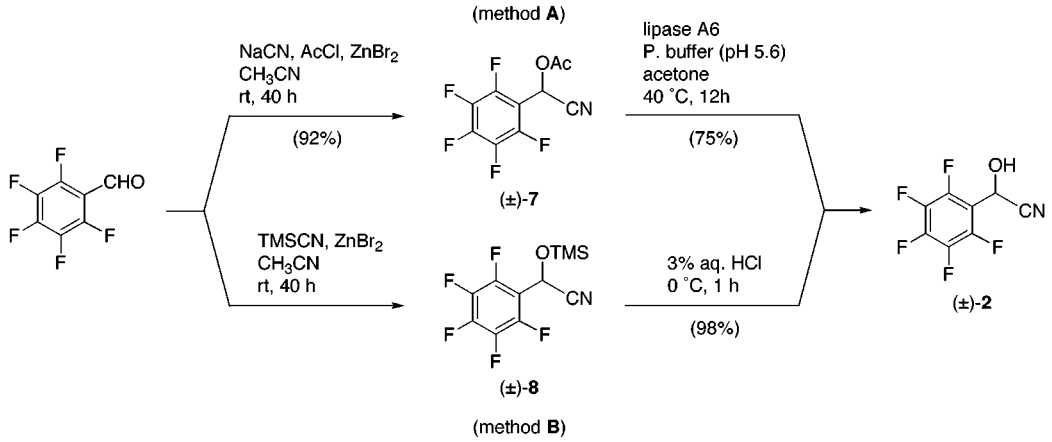
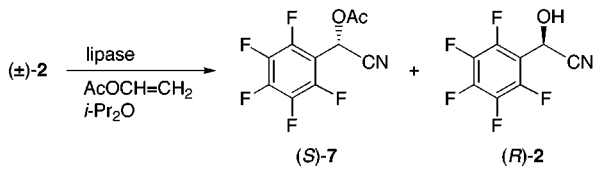
(25) We have reported the low-temperature effect for enhancement of enantioselectivity in lipase-catalyzed transesterifications of both primary and secondary alcohols: (a) Sakai, T.; Kawabata, I.; Kishimoto, T.; Ema, T.; Utaka, M. *J. Org. Chem.* **1997**, *62*, 4906−4907. (b) Sakai, T.; Kishimoto, T.; Tanaka, Y.; Ema, T.; Utaka, M. *Tetrahedron Lett.* **1998**, *39*, 7881−7884.

Scheme 3



Scheme 4



comparison of the optical rotation with that of (*S*)-(−)-**2** (Scheme 4). Therefore, produced acetate **7** was assigned to be (*S*), which was confirmed by the acidic hydrolysis to (*S*)-**2** as shown below. These facts indicate that the enantiopreference is in agreement with the empirical rule proposed by Kazlauskas et al.[26]

Packing Pattern of (*S*,*S*)-9. X-ray crystal analysis of (*S*,*S*)-**9** communicated previously[19c] is discussed here in detail. As shown in Figure 4, the crystal structure of (*S*,*S*)-**9** has an interesting well-ordered packing pattern.

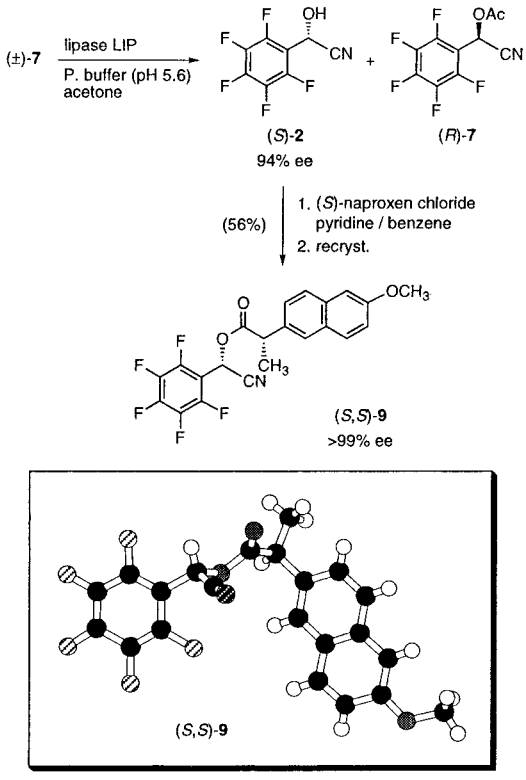


Figure 3. Synthesis and crystal structure of (*S*,*S*)-**9** for determining the absolute configuration of (*S*)-**2**.

The pentafluorophenyl and 6-methoxynaphthyl groups of the adjacent molecule are stacked alternately in a face-to-face fashion (Figure 4a). The interplate distance is approximately 3.5 Å, which is often observed between phenyl and perfluorophenyl groups. On the other hand, a view along the axis perpendicular to the π-plane of the pentafluorophenyl and the 6-methoxynaphthyl rings (Figure 4b) shows intermolecular end-to-end parallel contacts between each aromatic rings. The distances between the fluorine and the hydrogen atoms (F···H) are 3.07 and 3.70 Å, which are somewhat longer than the sum of VDW radius ($r_F + r_H = 2.55$ Å) of fluorine and hydrogen atoms. These results suggest that there are only weak interactions between the aromatic fluorine and hydrogen.[27]

Synthesis of Optically Active 1,2-Diols (1*R*,2*R*)- and (1*S*,2*S*)-1. Because cyanohydrin **2** was found to be relatively optically and structurally unstable as compared with the nonfluorinated one, we transformed it into TBS ether immediately after the lipase-catalyzed resolution. Protection of optically active (*R*)-**2** (96% ee) with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 4-(dimethylamino)pyridine (DMAP) at 0 °C gave (*R*)-**3** without racemization [94% yield (Scheme 5)]. The conventional procedure[28] for nonfluorinated analogue by using TBSCl and imidazole in DMF gave only 17% yield of (*R*)-**3** together with considerable amounts of (*R*)-**2** recovered, which is provably due to the decreased nucleophilicity of the oxygen in the hydroxyl group. Transformation of (*R*)-**3** (96% ee) into diol (1*R*,2*R*)-**1** was carried out in a similar procedure to that of racemic diol (±)-*threo*-**1** (Scheme 1). In the transformation (Scheme 5), the obtained diol (1*R*,2*R*)-**1** retained the optical purity (94% ee), although there is a possibility of partial racemization arising from imine−enamine tautomerism. One recrystallization from petroleum ether−CH_2Cl_2 increased the ee up to 99%.

The antipodal (1*S*,2*S*)-**1** was also obtained from (*S*)-**2**, which was prepared by deacetylation of (*S*)-**7** (Scheme 6). Thus, (*S*)-**7** (98% ee) was treated with 1 equiv of

(26) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656−2665.

(27) Recently, intermolecular F···H interaction between perfluoroarene- and arene-containing molecules has been reported: (a) Thalladi, V. R.; Weiss, H.-C.; Bläser, D.; Boese, R.; Nangia, A.; Desiraju, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 8702−8710. (b) Renak, M. L.; Bartholomew, G. P.; Wang, S.; Ricatto, P. J.; Lachicotte, R. J.; Bazan, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 7787−7799.

(28) Brussee, J.; Roos, E. C.; van der Gen, A. *Tetrahedron Lett.* **1988**, *29*, 4485−4488.

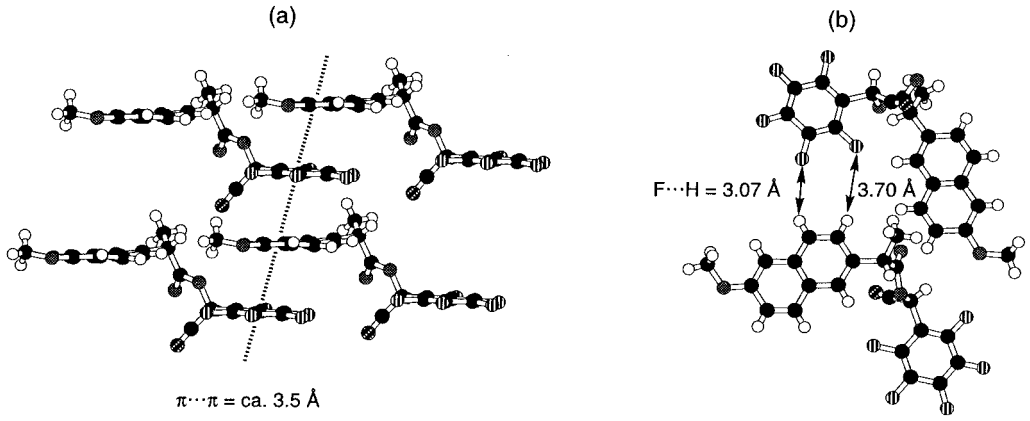
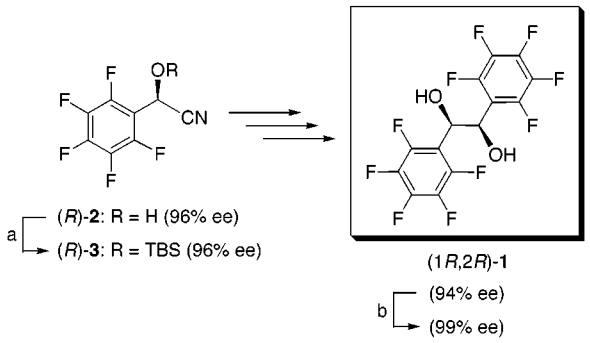


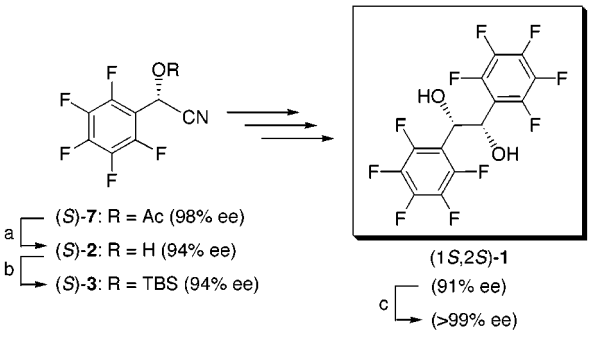
Figure 4. Packing pattern of naproxen ester (*S*,*S*)-**9**. (a) View along the horizontal axis. (b) View along the perpendicular axis for the π-plane of the pentafluorophenyl and 6-methoxynaphthayl groups.

Scheme 5[a]



[a] Reagents and condition: (a) TBSOTf, DMAP in CH_2Cl_2, 0 °C, 2.5 h, 94%; (b) recrystallization from petroleum ether−CH_2Cl_2.

Scheme 6[a]



[a] Reagents and condition: (a) TsOH in EtOH, rt, 2 days, 92%; (b) TBSOTf, DMAP in CH_2Cl_2, 0 °C, 2.0 h, 92%; (c) recrystallization from petroleum ether−CH_2Cl_2.

p-toluenesulfonic acid (TsOH) to give (*S*)-**2** with a slightly decreased optical purity (94% ee, 92% yield). Other methods for deacetylation of (*S*)-**7**, such as basic saponification, lipase-catalyzed hydrolysis, and reductive degradation by $NaBH_4$, failed to give (*S*)-**2**. Desired (1*S*,2*S*)-**1** with 91% ee was obtained by the method similar to that described for (1*R*,2*R*)-**1**. Two recrystallization from petroleum ether−CH_2Cl_2 increased the ee up to >99%.

Conclusion

We have synthesized optically pure 1,2-bis(pentafluorophenyl)ethane-1,2-diols (1*R*,2*R*)- and (1*S*,2*S*)-**1** *via* cyanohydrin intermediates (*R*)- and (*S*)-**2**, both of which were prepared by the lipase-catalyzed transesterifications. The conditions of the transformations were optimized by searching the lipases and by the low-temperature method. The X-ray crystal structure of compound (*S*,*S*)-**9** has an interesting well-ordered packing pattern which shows face-to-face stacking interaction and end-to-end parallel contacts between the pentafluorophenyl and the 6-methoxynaphthyl groups of the adjacent molecules.

Experimental Section

General Methods. All reactions were carried out under a nitrogen atmosphere with dry and freshly distilled solvents under anhydrous conditions, unless otherwise noted. Benzene, diethyl ether (ether), diisopropyl ether, and tetrahydrofuran (THF) were distilled from sodium, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Anhydrous acetonitrile was purchased from Wako Pure Chemical Industries Co., Ltd. and used without any purification. Lipase LIP was provided by TOYOBO Co., Ltd., and lipase AK, AH, and PS were provided by Amano Pharmaceutical Co., Ltd. and used without any purification. Lipase PS immobilized on Toyonite-DM was provided by Toyo Denka Kogyo Co., Ltd. Reactions were monitored by thin-layer chromatography with precoated silica gel plates (Merck 60 F_{254}, plate length 40 mm). As a usual workup procedure, the reaction mixture was extracted with ethyl acetate (EtOAc). The organic layer was dried over $MgSO_4$, filtrated with suction, and concentrated in vacuo. Preparative column chromatography were carried out by using silica gel (Fuji Silysia BW-127 ZH, 100−270 mesh). Boiling points were oven temperatures at the bulb-to-bulb distillation and are incorrected. ^{1}H NMR spectra were measured at 200 or 500 MHz and ^{13}C NMR spectra at 50 MHz, respectively, and chemical shifts are given relative to tetramethylsilane (TMS). ^{19}F NMR spectra were measured at 188 MHz and chemical shifts are given relative to C_6F_6.

(±)-2-(*tert*-Butyldimethylsiloxy)-2-(pentafluorophenyl)-acetonitrile ((±)-3). A mixture of sodium cyanide (980 mg, 20.0 mmol), zinc bromide (113 mg, 0.5 mmol), molecular sieves 4A (250 mg), and acetonitrile (20 mL) was placed in a 100 mL round-bottomed flask. To this were added pentafluorobenzaldehyde (1.96 g, 10.0 mmol, distilled before use) and *tert*-butyldimethylchlorosilane (TBSCl, 1.81 g, 12.0 mmol) dissolved in acetonitrile (8 mL) successively at room temperature through syringe. After the mixture was stirred for 12 h at room temperature, saturated aqueous $NaHCO_3$ was added to make the mixture basic (pH 9). The resulting mixture was treated in the usual manner to give a viscous brown oil, which was distilled (bp 150 °C, 15 Torr) to remove high-boiling compounds. Further purification by column chromatography (SiO_2, hexane−EtOAc, 50:1) gave (±)-**3** (2.95 g, 87% yield) as a colorless oil: R_f = 0.58 (SiO_2, hexane−EtOAc, 4:1); ^{1}H NMR

(200 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.26 (s, 3H), 0.90 (s, 9H), 5.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.3, 18.1, 25.4, 54.1, 111.2 (m), 116.6, 135.2 (m), 140.4 (m), 142.4 (m), 147.5 (m); ^{19}F NMR ($CDCl_3$) δ 1.7−2.1 (m, 2F), 11.6 (t, J = 20.3 Hz, 1F), 20.0−20.2 (m, 2F); IR (neat) 2958, 2934, 2862, 1513, 1003 cm^{-1}. Anal. Calcd for $C_{14}H_{16}F_5NOSi$: C, 49.84; H, 4.78; N, 4.15. Found: C, 49.47; H, 4.47; N, 4.49.

TBS Ether (*R*)-3: TBS Protection of Optically Active Cyanohydrin (*R*)-2. *tert*-Buthyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1.3 mL, 5.7 mmol) was slowly added to a solution of cyanohydrin (*R*)-**2** (848 mg, 3.80 mmol, 96% ee) obtained by the lipase LIP-catalyzed transesterification of cyanohydrin (±)-**2** (as shown below) and 4-(dimethylamino)-pyridine (DMAP, 928 mg, 7.60 mmol) in CH_2Cl_2 (9.5 mL) in an ice bath. After being stirred for 2.5 h in an ice bath, the mixture was acidified (pH 4) by addition of 3% aqueous HCl. The resulting mixture was treated in the usual manner. The residual mixture was purified by column chromatography (SiO_2, hexane−EtOAc, 50:1) to give (*R*)-**3** (1.21 g, 94% yield, 96% ee) as a colorless oil; >99% ee on the basis of HPLC analysis: retention time = 10.7 and 11.5 min for (*S*)- and (*R*)-**3**, respectively. The condition of HPLC is as follows: Daicel CHIRALCEL OD-H, 4.6 mm × 25 cm, hexane−*i*-PrOH (300:1), 0.5 mL min^{-1}, UV 254 nm; $[\alpha]^{28}_D$ = +30.1 (*c* 0.87, $CHCl_3$).

(±)-2-(*tert*-Butyldimethylsiloxy)-1,2-bis(pentafluorophenyl)ethan-1-one (5). To a solution of bromopentafluorobenzene (1.58 g, 6.40 mmol) in ether (10.7 mL) was added dropwise *n*-BuLi (1.54 M in hexane, 4.2 mL, 6.4 mmol) over 10 min at −78 °C. The solution was stirred for 1 h at the temperature. The resultant pale white mixture was further cooled to −85 °C, and a solution of TBS ether (±)-**3** (1.35 g, 4.00 mmol) in ether (6.7 mL) was added dropwise over 5 min. After being stirred for additional 1 h at the temperature, the mixture was quickly acidified by addition of 5% aqueous HCl-EtOH (4 + 8 mL) solution, and the combined mixture was stirred for 1.5 h in an ice bath. The resulting mixture was treated in the usual manner. The residual oil was purified by column chromatography (SiO_2, hexane−EtOAc, 100:1) to give (±)-**5** (1.06 g, 53% yield) as a light yellow oil: bp 160 °C (14 Torr); R_f = 0.65 (SiO_2, hexane−EtOAc, 4:1); ^1H NMR (200 MHz, $CDCl_3$) δ −0.16 (s, 3H), 0.10 (s, 3H), 0.71 (s, 9H), 5.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.8, −5.3, 17.9, 25.3, 71.7, 113.2 (m), 135.2 (m), 139.6 (m), 140.4 (m), 141.5 (m), 142.8 (m), 144.7 (m), 145.6 (m), 146.6 (m), 147.8 (m), 193.0; ^{19}F NMR ($CDCl_3$) δ 1.0−1.3 (m, 2F), 1.6−1.9 (m, 2F), 10.5 (t, J = 20.7 Hz, 1F), 13.0 (t, J = 19.8 Hz, 1F), 20.9 (d, J = 18.2 Hz), 21.9 (d, J = 18.2 Hz, 2F); IR (neat) 2958, 2934, 2862, 1734 (C=O), 1523, 1498, 984 cm^{-1}. Anal. Calcd for $C_{20}H_{16}F_{10}O_2Si$: C, 47.44; H, 3.18. Found: C, 47.21; H, 3.02.

(±)-*threo*-1,2-Bis(pentafluorophenyl)ethane-1,2-diol ((±)-1). To a solution of ketone (±)-**5** (1.05 g, 2.08 mmol) in EtOH (5.2 mL) was added sodium borohydride (79.0 mg, 2.08 mmol) suspended in EtOH (7.0 mL) in an ice bath under atmospheric conditions. After being stirred for 1.5 h in an ice bath, the mixture was acidified (pH 4) by addition of 3% aqueous HCl. The resulting mixture was treated in the usual manner. The obtained alcohol of (±)-**5** (1.05 g, pale yellow solid) had a satisfactory purity according to the ^1H NMR spectrum [(200 MHz, $CDCl_3$) δ −0.09 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 5.37 (s, 2H)] and was used in the following reaction without any purification. The alcohol of (±)-**5** (1.01 g, 1.99 mmol) was dissolved in THF (10.0 mL) and was allowed to react with tetra-*n*-butylammonium fluoride (TBAF, 1 M in THF, 2.0 mL, 2.0 mmol) for 30 min in an ice bath under atmospheric conditions. The resulting solution was concentrated in vacuo, and the residual viscous oil was purified by column chromatography (SiO_2, hexane−EtOAc, 4:1 then 1:1) to give (±)-*threo*-**1** (560 mg, 72% yield) and *erythro*-**1** (31.3 mg, 4.0% yield).

For (±)-*threo*-**1**: white crystals; mp 155−156 °C (petroleum ether−THF); R_f = 0.16 (SiO_2, hexane−EtOAc, 4:1); ^1H NMR (200 MHz, $CDCl_3$) δ 3.05−3.15 (m, 2H), 5.45−5.50 (m, 2H); ^{13}C NMR (acetone-d_6) δ 68.7, 115.0 (m), 135.8 (m), 139.3 (m), 140.8 (m), 143.4 (m), 144.2 (m), 148.4 (m); ^{19}F NMR ($CDCl_3$) δ 1.2−1.6 (m, 4F), 10.1 (t, J = 21.1 Hz, 2F), 20.1−20.4 (m, 4F); IR (KBr) 3476 (OH), 2955, 1529, 1504, 982 cm^{-1}. Anal. Calcd for $C_{14}H_4F_{10}O_2$: C, 42.66; H, 1.02. Found: C, 42.69; H, 1.07.

For *erythro*-**1**: white crystals; mp 185−187 °C (petroleum ether−THF); R_f = 0.35 (SiO_2, hexane−EtOAc, 4:1); ^1H NMR (200 MHz, $CDCl_3$) δ 2.45−2.60 (m, 2H), 5.32−5.45 (m, 2H); ^{13}C NMR (acetone-d_6) δ 68.2, 117.5 (m), 135.9 (m), 139.1 (m), 140.9 (m), 144.1 (m), 149.1 (m); ^{19}F NMR ($CDCl_3$) δ 0.6−1.0 (m, 4F), 9.1 (t, J = 21.1 Hz, 2F), 18.8−19.2 (m, 4F); IR (KBr) 3462 (OH), 2955, 1532, 1504, 989 cm^{-1}. Anal. Calcd for $C_{14}H_4F_{10}O_2$: C, 42.66; H, 1.02. Found: C, 42.72; H, 0.91.

1,2-Diol (1*R*,2*R*)-1. This compound was synthesized from optically active TBS ether (*R*)-**3** (1.02 g, 3.0 mmol, 96% ee) obtained by the lipase LIP-catalyzed resolution (as shown below) in a similar procedure to that for (±)-*threo*-**1**: 35% yield (420 mg) from (*R*)-**3** after column chromatography; white crystals; mp 150−152 °C (petroleum ether−CH_2Cl_2); 99% ee on the basis of HPLC analysis: retention times = 11.5 and 14.2 min for (1*R*,2*R*)- and (1*S*,2*S*)-**1**, respectively. The conditions of HPLC are as follows: column; Daicel CHIRALCEL OD-H, 4.6 mm × 25 cm, hexane−*i*-PrOH (9:1), 0.5 mL min^{-1}, UV 254 nm; $[\alpha]^{27}_D$ = +40.0 (*c* 0.54, EtOH).

1,2-Diol (1*S*,2*S*)-1. This compound was synthesized from optically active TBS ether (*S*)-**3** (266 mg, 0.8 mmol, 94% ee) obtained by the lipase LIP-catalyzed resolution and acidic alcoholysis of acetate (*S*)-**7** (as shown below) in a similar procedure to that for (±)-*threo*-**1**: 34% yield (104 mg) from (*S*)-**3** after column chromatography: white crystals; mp 151−153 °C (petroleum ether−CH_2Cl_2); >99% ee; $[\alpha]^{29}_D$ = −40.8 (*c* 0.52, EtOH).

(±)-*trans*-2-Oxo-4,5-bis(pentafluorophenyl)-1,3-dioxa-2-thiacyclopentane ((±)-*trans*-6). Thionyl chloride (15 μL, 0.20 mmol, distilled before use) was slowly added to a solution of (±)-*threo*-**1** (39.4 mg, 0.10 mmol) and triethylamine (56 μL, 0.40 mmol) in CH_2Cl_2 (1.0 mL) in an ice bath. After being stirred for 2 h in an ice bath, the mixture was acidified (pH 4) by addition of 3% aqueous HCl. The resulting mixture was treated in the usual manner. The residual oil was purified by column chromatography (SiO_2, hexane−EtOAc, 40:1) to give (±)-*trans*-**6** (41.0 mg, 87% yield) as white crystals: mp 96−97 °C (petroleum ether); R_f = 0.65 (SiO_2, hexane−EtOAc, 4:1); ^1H NMR (200 MHz, $CDCl_3$) δ 5.96 (d, J = 10.2 Hz, 1H, CH_a), 6.49 (d, J = 10.2 Hz, 1H, CH_b); ^{13}C NMR ($CDCl_3$) δ, 72.7, 76.8, 105.3 (m), 135.7 (m), 140.7 (m), 143.5 (m), 145.8 (m), 148.6 (m); ^{19}F NMR ($CDCl_3$) δ 2.4−3.2 (m, 4F), 13.7 (t, J = 20.7 Hz, 1F), 14.1 (t, J = 20.9 Hz, 1F), 21.4−21.9 (m, 4F); IR (KBr) 2963, 2939, 1531, 1505, 1223 (S=O), 1010, 986 cm^{-1}. Anal. Calcd for $C_{14}H_2F_{10}O_3S$: C, 38.20; H, 0.46. Found: C, 37.92; H, 0.37.

Sulfite *cis*-6. This compound was synthesized from *erythro*-**1** (39.4 mg, 0.10 mmol) in a procedure similar to that for (±)-*trans*-**6**: 70% yield (33.0 mg) after column chromatography; white crystals; mp 137−138 °C (petroleum ether); R_f = 0.63 (SiO_2, hexane−EtOAc, 4:1); ^1H NMR (200 MHz, $CDCl_3$) δ 6.52 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 76.3, 106.6 (m), 135.2 (m), 140.0 (m), 142.3 (m), 144.6 (m), 147.4 (m); ^{19}F NMR ($CDCl_3$) δ 2.3−2.7 (m, 4F), 12.9 (t, J = 21.2 Hz, 2F), 21.3-21.8 (m, 4F); IR (KBr) 2982, 1530, 1500, 1223 (S=O), 975 cm^{-1}. Anal. Calcd for $C_{14}H_2F_{10}O_3S$: C, 38.20; H, 0.46. Found: C, 37.98; H, 0.48.

(±)-2-Acetoxy-2-(pentafluorophenyl)acetonitrile ((±)-7). Pentafluorobenzaldehyde (3.33 g, 17.0 mmol, distilled before use) and acetyl chloride (2.4 mL, 34.0 mmol) were added successively to a mixture of sodium cyanide (1.72 g, 34.0 mmol), zinc bromide (3.8 mg, 0.017 mmol), and acetonitrile (15 mL) at room temperature. After the mixture was stirred for 40 h at room temperature, saturated aqueous $NaHCO_3$ was added to make the mixture basic (pH 9). The resulting mixture was treated in the usual manner. The residual viscous brown oil (5.56 g) was found to contain about 25% (5.5 mmol) of cyanohydrin **2** by ^1H NMR analysis. For complete conversion to acetate **7**, the mixture was allowed to react again with acetyl chloride (1.20 mL, 16.5 mmol) and pyridine (2.90 mL, 27.5 mmol) in acetonitrile (20 mL) for 19 h at room temperature.[29]

After being acidified (pH 4) by addition of 3% aqueous HCl, the resulting mixture was treated in the usual manner to give a viscous brown oil, which was distilled (bp 170 °C, 35 Torr) to remove high-boiling compounds. Further purification by column chromatography (SiO_2, hexane−EtOAc, 10:1) gave (±)-**7** (4.18 g, 92% yield) as a colorless oil: R_f = 0.55 (SiO_2, hexane−EtOAc, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (s, 3H), 6.66 (s, 1H);^{13}C NMR ($CDCl_3$) δ 20.1, 52.2, 106.7 (m), 113.5, 135.5 (m), 140.6 (m), 142.9 (m), 145.9 (m), 148.0 (m), 168.4; ^{19}F NMR ($CDCl_3$) δ 2.4−2.8 (m, 2F), 13.9 (t, J = 21.6 Hz, 1F), 22.5−22.9 (m, 2F); IR (neat) 2962, 1771, 1760 (C=O), 1515, 1029, 1005 cm^{-1}. Anal. Calcd for $C_{10}H_4F_5NO_2$: C, 45.30; H, 1.52; N, 5.28. Found: C, 45.37; H, 1.32; N, 5.45.

Acetate (*S*)-7. This compound was obtained by the lipase LIP-catalyzed resolution of cyanohydrin (±)-**2** as shown below: colorless oil; 98% ee; $[\alpha]^{28}_D$ = +1.1 (*c* 2.20, $CHCl_3$).

(±)-2-Hydroxy-2-(pentafluorophenyl)acetonitrile ((±)-2) (Method A). A mixture of acetate (±)-**7** (200 mg, 0.754 mmol), lipase A6 (600 mg), acetone (0.5 mL), and 67 mM phosphate buffer (pH 5.6, 5.0 mL) was placed in a test tube and stirred for 12 h at 40 °C under atmospheric conditions. The resulting mixture was treated in the usual manner. The residual viscous oil was purified by column chromatography (SiO_2, hexane−EtOAc, 10:1 then 4:1) to give (±)-**2** (126 mg, 75% yield) as a white solid: mp 54−56 °C (petroleum ether−CH_2Cl_2).

Cyanohydrin (±)-2: Acidic Hydrolysis of TMS Ether 8 (Method B). Pentafluorobenzaldehyde (5.93 g, 30.2 mmol) and trimethylsilyl cyanide (5.20 mL, 39.0 mmol) were added to a mixture of zinc bromide (203 mg, 0.900 mmol) and CH_3-CN (30 mL) at room temperature, and the mixture was stirred for 40 h at room temperature. After being cooled in an ice bath, the mixture was acidified by addition of 3% aqueous HCl (5 mL) and was stirred for additional 1 h in an ice bath, and then the organic layer was extracted with EtOAc. The extract was washed with 67 mM phosphate buffer (pH 8.0, 20 mL) and treated in a usual manner. The residual oil was purified by column chromatography (SiO_2, hexane−EtOAc, 4:1) to give (±)-**2** (6.60 g, 98% yield) as white crystals: mp 54−56 °C (petroleum ether−CH_2Cl_2); R_f = 0.37 (SiO_2, hexane−EtOAc, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.49 (d, J = 7.6 Hz, 1H), 5.84 (d, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.9, 109.7 (m), 116.4, 135.5 (m), 140.4 (m), 142.6 (m), 145.5 (m), 147.7 (m); ^{19}F NMR ($CDCl_3$) δ 2.2−2.7 (m, 2F), 12.7 (t, J = 20.0 Hz, 1F), 19.9−20.2 (m, 2F); IR (KBr) 3490 (OH), 2952, 1513, 1002, 982 cm^{-1}. Anal. Calcd for $C_8H_2F_5NO$: C, 43.07; H, 0.90; N, 6.28. Found: C, 42.89; H, 0.76; N, 6.33.

Cyanohydrin (*R*)-2. This compound was prepared by the lipase LIP-catalyzed resolution (as shown below) and subsequent recrystallization from petroleum ether−CH_2Cl_2: white crystals; mp 71−73 °C; >99% ee determined by HPLC after transformation into TBS ether (*R*)-**3**; $[\alpha]^{28}_D$ = +33.7 (*c* 1.14, $CHCl_3$).

Cyanohydrin (*S*)-2: Acidic Alcoholysis of Acetate (*S*)-7. *p*-Toluenesulfonic acid (TsOH) monohydride (380 mg, 2.00 mmol) was added to a solution of acetate (*S*)-**7** (530 mg, 2.00 mmol, 98% ee) obtained by lipase LIP-catalyzed transesterification of (±)-**2** (as shown below) in EtOH (10 mL) at room temperature under an atmosphere. After being stirred for 2 days at room temperature, the solution was concentrated in vacuo. The residual viscous oil was purified by column chromatography (SiO_2, hexane−EtOAc, 4:1) to give (*S*)-**2** (413 mg, 92% yield) as white crystals: mp 71−73 °C (petroleum ether−CH_2Cl_2); 94% ee determined by HPLC after transformation into TBS ether (*S*)-**3**; $[\alpha]^{27}_D$ = −30.4 (*c* 1.17, $CHCl_3$) [lit.[19c] >99% ee; $[\alpha]^{26}_D$ = −30.5 (*c* 1.10, $CHCl_3$)].

General Procedure for the Lipase-Catalyzed Transesterification. A mixture of cyanohydrin (±)-**2** (50.0 mg, 0.224 mmol), lipase (100 mg), and dry diisopropyl ether (2.5 mL) was placed in a test tube and stirred at the temperature indicated (45, 30, 15, and 0 °C) under atmospheric conditions. After the mixture was stirred for 10 min at the indicated temperature, fleshly distilled vinyl acetate (38.8 mg, 0.448 mmol) was added. The reaction progress was monitored by gas chromatography: retention times = 4.5 and 11.9 min for cyanohydrin (*R*)-**2** and antipodal acetate (*S*)-**7**, respectively. The conditions of gas chromatography are as follows: 5% PEG-20M (60−80 mesh), 2.9 mm × 3.0 m, 80−190 °C (7.5 °C min^{-1}), nitrogen (12 mL min^{-1}). When the conversion was reached at 40−50%, the mixture was filtered through Celite pad with suction, and the filtrate was concentrated in vacuo.

Determination of Optical Purity of Cyanohydrin (*R*)-2 and Acetate (*S*)-7. Cyanohydrin (*R*)-**2** as a mixture with (*S*)-**7** was allowed to react with (*R*)-2-methoxy-2-(trifluoromethyl)-phenylacetyl (MTPA) chloride (2 equiv) in the usual manner,[30] giving a mixture of the corresponding MTPA ester and remaining (*S*)-**7**. ^{1}H NMR spectrum (200 MHz) of the mixture showed two signals due to the methoxy protones at δ 3.48 and 3.60 for the MTPA esters of (*S*)- and (*R*)-**2**, respectively. On the other hand, Eu(hfc)$_3$ (1 equiv)-induced ^{1}H NMR spectrum (200 MHz) of the mixture showed two signals at δ 2.2−2.4 and 2.3−2.5 due to acetates (*S*)- and (*R*)-**7**, respectively.

Preparative-Scale Lipase LIP-Catalyzed Transesterification of (±)-2. This reaction was carried out by using (±)-**2** (2.00 g, 8.96 mmol), lipase LIP (2.00 g), dry diisopropyl ether (50 mL), and vinyl acetate (3.4 mL, 35.6 mmol) for 21 h at 0 °C in a manner similar to that described above. The residual oil was purified by column chromatography (SiO_2, hexane−EtOAc, 10:1 then 1:1) to give acetate (*S*)-**7** (1.20 g, 50% yield, 98% ee) and remaining alcohol (*R*)-**2** (0.91 g, 46% yield, 96% ee). Optically active (*R*)-**2** could be stored in a refrigerator for a few weeks without decomposition and racemization.

(*S*)-α-Cyano-2,3,4,5,6-pentafluorobenzyl (*S*)-6-Methoxy-α-methyl-2-naphthaleneacetate (Naproxen Ester, (*S*,*S*)-9). Pyridine (0.30 mL, 3.6 mmol) was added to a solution of (*S*)-**2** (80.3 mg, 0.360 mmol, 94% ee) obtained by the lipase LIP-catalyzed hydrolysis of (±)-**7**[19c] and (*S*)-6-methoxy-α-methyl-2-naphthaleneacetyl chloride (naproxen chloride, 180 mg, 0.720 mmol)[31] in benzene (5 mL) in an ice bath. The mixture was stirred for 2 h in an ice bath and then stirred for additional 18 h at room temperature. After being acidified (pH 4) by addition of 3% aqueous HCl, the resulting mixture was treated in the usual manner. The residual oil was purified by column chromatography (SiO_2, hexane−EtOAc, 5:1) and then recrystallized from petroleum ether to give (*S*,*S*)-**9** (82 mg, 56% yield) as white crystals: mp 104−105 °C; >99% ee; $[\alpha]^{27}_D$ = −26.4 (*c* 1.91, $CHCl_3$); R_f = 0.53 (SiO_2, hexane−EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (d, J = 7.0 Hz, 3H), 3.92 (s, 3H), 3.94 (q, J = 7.0 Hz, 1H), 6.64 (s, 1H), 7.12 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 9.0, 2.5 Hz, 1H), 7.35 (dd, J = 8.5, 2.0 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 9.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 45.0, 52.7, 55.5, 105.8, 106.9 (m), 113.3, 119.5, 125.8, 126.3, 127.7, 129.0, 129.4, 133.5, 134.1, 135.5 (m), 140.5 (m), 142.8 (m), 146.0 (m), 147.9 (m), 158.1, 172.2; ^{19}F NMR ($CDCl_3$) δ 2.3−2.8 (m, 2F), 13.9 (t, J = 17.3 Hz, 1F), 22.7 (d, J = 17.3 Hz, 2F); IR (KBr) 2946, 1756 (C=O), 1604, 1392, 1123, 997, 863, 823 cm^{-1}. Anal. Calcd for $C_{22}H_{14}F_5NO_3$: C, 60.70; H, 3.24; N, 3.22. Found: C, 60.45; H, 3.12; N, 3.18.

X-ray crystal data for (*S*,*S*)-9: $C_{22}H_{14}F_5NO_3$, M = 435.35, monoclinic, space group $P2_1$, a = 9.602(6) Å, b = 15.545(8) Å, c = 9.449(1) Å, β = 135.030(6)°, V = 996.89(0) Å^3, Z = 2, D_{calc} = 1.45(0) g cm^{-3}, R = 0.080 for 1273 observed reflections [$I > 3.00\sigma(I)$] and 280 variable parameters. All measurements were made on a Rigaku RAXIS-IV imaging plate area detector with Mo Kα radiation.

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(29) Addition of excess acetyl chloride directly to residual cyanohydrin **2** was unsuccessful, and thus one repetition procedure was usually required.

(30) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(31) Büyüktimkin, N.; Buschauer, A. *J. Chromatogr.* **1988**, *450*, 281−283.

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds (±)-*trans*-/*cis*-**6** and ^{13}C NMR spectra for compounds (±)-*threo*-/*erythro*-**1**, (±)-**2**, (±)-**3**, (±)-**5**, (±)-*trans*-/*cis*-**6**, (±)-**7**, and (*S*,*S*)-**9**; X-ray crystallographic data for (*S*,*S*)-**9**. This material is available free of charge via the Internet at http.//pubs.acs.org.

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