# Enzymatic Resolution of (±)-5-Acetoxy-4-aryl-(2*E*)-pentenoate Derivatives

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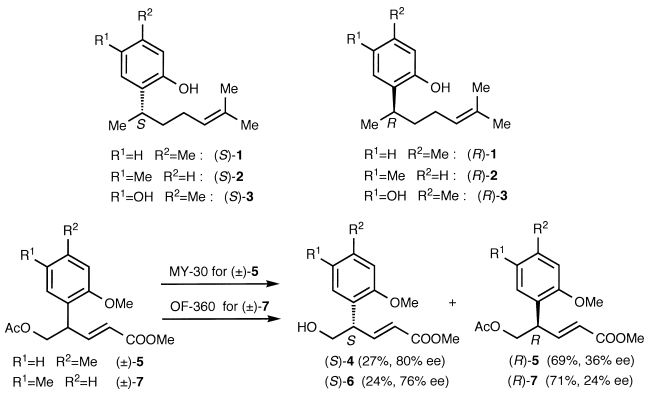
Received September 17, 2004; accepted February 13, 2005

**Enzymatic resolution of six (±)-5-acetoxy-4-aryl-(2*E*)-pentenoate derivatives, compounds 9, 11, 13, 15, 17, and 19 bearing a different aromatic substitution pattern, using lipase OF-360 from *Candida rugosa* was carried out. The absolute configurations of all hydrolyzed products and all unchanged acetates were found to be *S* and *R*, respectively. Moreover, the enantiomeric excess of the enzymatic resolution products from 9, 11, and 13 with the *ortho*-methoxyl group in the aromatic ring was higher than that of the substrates with no methoxyl group at the *ortho*-position in the aromatic ring.**

**Key words** bisabolane sesquiterpene; enzymatic resolution; lipase

Phenolic sesquiterpenes of the bisabolane family have been isolated from many different natural sources.[1] In the preceding paper, we reported the total synthesis of (*S*)- and (*R*)-curcuphenols (**1**)[2,3] and (*S*)- and (*R*)-elvirols (**2**).[4] The (*S*)-curcuphenol (**1**), isolated from the marine sponge *Epipolasis* sp., strongly inhibits the activity of gastric H, K-ATPase,[5—7] while the (*R*)-(−)-curcuphenol (**1**), isolated from the Caribbean gorgonians *Pseudopterogorgia rigida* and *Lasianthaea podocephala*, exhibits antibacterial activities against *Staphylococcus aureus* and *Vibrio anguillarum*.[8] Accordingly, the establishment of an efficient and general synthetic route to both enantiomers of these sesquiterpenoids is of significance. In the chiral synthesis of (*S*)- and (*R*)-**1**, and (*S*)- and (*R*)-**2**, enzymatic resolutions of an acetate (±)-**5** with lipase MY-30 from *Candida rugosa* and an acetate (±)-**7** with lipase OF-360 from *Candida rugosa*, respectively, are found to be the crucial step in their total synthesis. Although racemic syntheses of bisabolane sesquiterpenes have been developed,[9—11] useful asymmetric synthesis bearing a benzylic asymmetric center has not been reported except for a few examples.[12—14] We report here enzymatic resolutions of (±)-4-aryl-5-acetoxy-(2*E*)-pentenoate derivatives **9**, **11**, **13**, **15**, **17**, and **19** bearing a different aromatic substitution pattern for the sake of the other chiral synthesis of bisabolane sesquiterpens such as (*S*)- and (*R*)-curcuhydroquinones (**3**).

**Enzymatic Resolutions** Six racemic acetates **9**, **11**, **13**, **15**, **17**, and **19** were obtained in good yield by the usual acetylation from the reported racemic alcohols **8**, **10**, **12**, **14**, **16**, and **18**,[15] respectively. In the present case, lipase OF-360 from *Candida rugosa* was applied for the enzymatic resolutions and the results are shown in Table 1.




Chrat 1

Initially, **9** was subjected to enzymatic resolution in water-saturated diisopropyl ether, and the alcohol (*S*)-**8** [(16%, 81%, enantiomeric excess (ee)] and unchanged (*R*)-**9** (79%, 22% ee) were obtained (entry 1). The ee of all enzymatic resolution products mentioned below was obtained based on HPLC analysis using a chiral column, and the detailed procedure is described in the Experimental section. The ee of (*R*)-**9** was obtained by means of HPLC analysis of the deacylated compound (*R*)-**8**. Determination of the absolute structure of all enzymatic resolution products are described below. The substrates **11**, **13**, **15**, **17**, and **19** were subjected to enzymatic resolution in water-saturated isopropyl ether, and the results are shown in Table 1 (entries 2—4, 7, 8). To improve the ee of (*S*)-**14**, the 40% ee of (*S*)-**14** was subjected to enzymatic acetylation in the presence of isopropenyl acetate in diisopropyl ether to provide (*S*)-**14** (77%, 34% ee) and (*S*)-**15** (19%, 67% ee) (entry 5), and the 67% ee of (*S*)-**15** was again subjected to enzymatic resolution in water-saturated isopropyl ether to give the alcohol (*S*)-**14** (60%, 79% ee) and unchanged (*S*)-**15** (23%, 36% ee) (entry 6). From these enzymatic resolution experiments, it became apparent that the ee values of the enzymatic resolution products from **9**, **11**, and **13** with the *ortho*-methoxyl group in the aromatic ring were higher than those of the substrates with no methoxyl group (entries 1—3).

**Determination of the Absolute Structure of Enzymatic Products** To determine the absolute configuration of the product (+)-**8**, it was successfully converted to the reported $\alpha$-ketoester (*S*)-**22**.[4] Treatment of (+)-**8** (81% ee) with *p*-tosyl chloride (*p*-TsCl) followed by the consecutive catalytic hydrogenation and $NaBH_4$ reduction provided 4-aryl-substituted pentanoate **21** in 44% overall yield from (+)-**8**. Oxidative cleavage of the aromatic ring of **21** with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3 \cdot 3H_2O$ followed by esterification with $CH_2N_2$ gave (+)-**22** {16% yield, $[\alpha]_D^{26}$ +3.4° ($c$=1.57, $CHCl_3$), corresponding to 81% ee}. The physical data ($[\alpha]_D$, $^1$H-NMR) of (+)-**22** derived from (+)-**8** were consistent with those {$[\alpha]_D^{27}$ +3.2° ($c$=1.35, $CHCl_3$),

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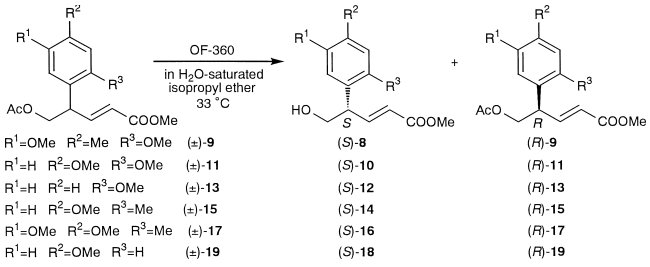
Table 1. Enzymatic Resolution of (±)-5-Acetoxy-4-aryl-(2*E*)-pentenoate Derivatives




| Entry | Substrate (g) | Time (h) | Product (%, ee) | |
|---|---|---|---|---|
| 1 | (±)-**9** (0.5 g×4) | 8 | (*S*)-**8** (16%, 81% ee) | (*R*)-**9** (79%, 22% ee) |
| 2 | (±)-**11** (0.095 g) | 24 | (*S*)-**10** (61%, 52% ee) | (*R*)-**11** (29%, 84% ee) |
| 3 | (±)-**13** (0.096 g) | 48 | (*S*)-**12** (61%, 43% ee) | (*R*)-**13** (31%, 80% ee) |
| 4 | (±)-**15** (6.75 g×2) | 24 | (*S*)-**14** (13%, 40% ee) | (*R*)-**15** (80%, 15% ee) |
| 5[a)] | (±)-**14** (1.5 g, 40% ee) | 24 | (*S*)-**14** (77%, 34% ee) | (*S*)-**15** (19%, 67% ee) |
| 6 | (±)-**15** (0.34 g, 67% ee) | 72 | (*S*)-**14** (60%, 79% ee) | (*S*)-**15** (23%, 36% ee) |
| 7 | (±)-**17** (0.1 g) | 8 | (*S*)-**16** (34%, 25% ee) | (*R*)-**17** (61%, 20% ee) |
| 8 | (±)-**19** (0.098 g) | 24 | (*S*)-**18** (77%, 7% ee) | (*R*)-**19** (18%, 29% ee) |

*a*) Enzymatic acetylation with isopropenyl acetate was carried out.

corresponding to 76% ee} of the authentic (*S*)-(+)-**22**[4)] and thence the absolute configurations of (+)-**8** was determined to be *S*. The absolute configuration of the (−)-**14** was also determined in the same way as that from (+)-**8**. Thus treatment of (−)-**14** (79% ee) with *p*-TsCl gave the tosylate (+)-**23** {$[\alpha]_D^{21}$ +4.3° (*c*=1.56, $CHCl_3$)} in 89% yield, which was subjected to consecutive catalytic hydrogenation and $NaBH_4$ reduction to provide the 4-aryl-substituted pentanoate **24** in 56% overall yield from (+)-**23**. Oxidative cleavage of the aromatic ring of **23** with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3 \cdot 3H_2O$ followed by esterification with $CH_2N_2$ gave (+)-**25** {33% yield, $[\alpha]_D^{21}$ +13.9° (*c*=0.78, $CHCl_3$), corresponding to 79% ee}. The physical data ($[\alpha]_D$, $^1$H-NMR) of (+)-**25** derived from (−)-**14** were consistent with those {$[\alpha]_D^{25}$ +15.8° (*c*=0.72, $CHCl_3$), corresponding to 90% ee} of the reported dimethyl 2-methylglutarate (*S*)-(+)-**25**[4)] and thus the absolute configurations of (−)-**14** was determined to be *S*.

By applying the reported procedure,[15)] the four (*S*)-4-aryl-5-hydroxy-(2*E*)-pentenoate derivatives **10**, **12**, **18**, and **16** were obtained by the reaction of (4*S*)-(4,5)-epoxy-(2*E*)-pentenoate **26**[16)] and substituted benzene derivatives in the presence of $BF_3 \cdot Et_2O$. The reaction of (*S*)-**26** (93% ee) and 1,3-dimethoxybenzene in the presence of $BF_3 \cdot Et_2O$ gave (*S*)-**10** {38%, $[\alpha]_D^{29}$ −15.2° (*c*=0.50, $CHCl_3$), corresponding to 93% ee}. The reaction of (*S*)-**26** (93% ee) and anisole in the presence of $BF_3 \cdot Et_2O$ afforded (*S*)-**12** {10%, $[\alpha]_D^{21}$ −17.9° (*c*=0.51, $CHCl_3$), corresponding to 93% ee} and (*S*)-**18** {42%, $[\alpha]_D^{22}$ −2.2° (*c*=0.51, $CHCl_3$), corresponding to 93% ee}. The reaction of (*S*)-**26** (93% ee) and 3,4-dimethoxytoluene in the presence of $BF_3 \cdot Et_2O$ provided (*S*)-**16** {46%, $[\alpha]_D^{29}$ +22.7° (*c*=0.33, $CHCl_3$), corresponding to 93% ee}. The absolute configurations of the hydrolyzed products (−)-**10**, (−)-**12**, (−)-**18**, and (+)-**16** were confirmed by a direct comparison of the retention time of the synthesized authentic samples (*S*)-**10**, (*S*)-**12**, (*S*)-**18**, and (*S*)-**16**, respectively. The detailed data are shown in the Experimental section.

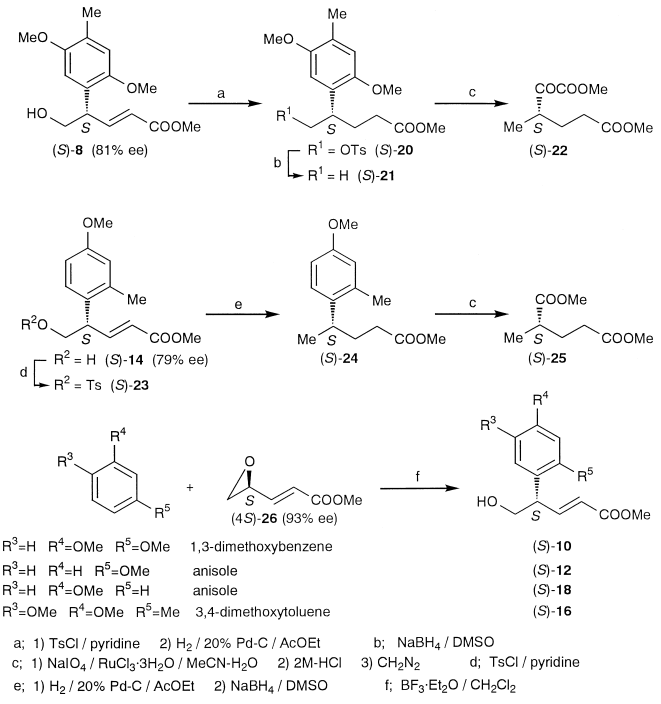



Chart 2

## Discussion

Although lipases are widely used as enantioselective hydrolysis or transesterification catalysts, the structural basis for this enantioselectivity was unknown so far. The specificity of lipase from *Candida rugosa* has established a simple empirical rule that predicts its enantiopreference for secondary alcohols. On the other hand, the explanation concerning the molecular recognition of primary alcohols has been more difficult. Most lipases show low enantioselectivity toward primary alcohols. Only lipase from *Pseudomonas cepacia* (PCL) and lipase from porcine pancreas (PPL) show moderate to high enantioselectivity toward a wide range of primary alcohols, but even for these the enantioselectivity is

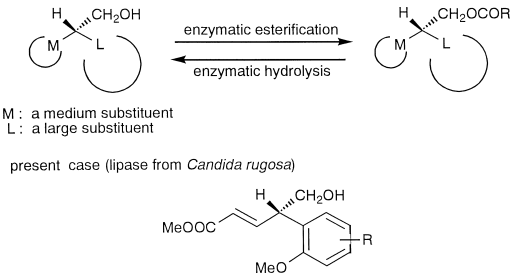



Fig. 1

usually lower than that toward secondary alcohols. The empirical rule summarizes the enantiopreference of PCL for primary alcohol or its acylated derivative, as shown in Fig. 1.[17,18] When the hydroxyl methyl (–$CH_2OH$) or acyloxy methyl (–$CH_2OCOR$) group exists in the plane of the page, the favored enantiomer bears a large substituent (L) on the right, and a medium substituent (M) on the left. The enantiopreference toward primary alcohols or their acetates using lipase OF-360 from *Candida rugosa* might be explained by the present empirical rule.

## Conclusion

Enzymatic resolution of the six (±)-5-acetoxy-4-aryl-(2*E*)-pentenoate derivatives **9**, **11**, **13**, **15**, **17**, and **19** bearing a different aromatic substitution pattern, using lipase OF-360 from *Candida rugosa* was carried out. The absolute configurations of all hydrolyzed products and all unchanged acetates were found to be *S* and *R*, respectively. Moreover, the ee of the enzymatic resolution products from (±)-**9**, (±)-**11**, and (±)-**13** with the *ortho*-methoxyl group in the aromatic ring was higher than that of the substrates with no methoxyl group at this position.

### Experimental

All melting points were measured on a Yanaco MP-3S micromelting point apparatus and are uncorrected. $^1$H-NMR (400-MHz) spectra were recorded by a JEOL EX 400 spectrometer (Tokyo, Japan). Spectra were recorded with 5—10% (w/v) solution in $CDCl_3$ with $Me_4Si$ as an internal reference. High-resolution mass spectra (HR-MS) and fast-atom bombardment mass spectra (FAB-MS) were obtained with a JEOL JMS-DX 303 (matrix; glycerol, *m*-nitrobenzyl alcohol) spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. The HPLC system was composed of a detector (UV detector SSC-5200, Senshu), pump (SSC-3210, Senshu), and integrator (chromatocorder SIC 21). HPLC analysis conditions were: column, Chiralcel OD and Chiralpac AD and AS; detection, UV at 254 nm, and flow rate, 1 ml/min. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

**Syntheses of Substrates. Methyl (±)-5-Acetoxy-4-(2,5-dimethoxy-4-methylphenyl)-(2*E*)-pentenoate (9)** A solution of (±)-**8** (4.018 g, 14.4 mmol) in pyridine (10 ml) was treated with $Ac_2O$ (2.14 g, 21.0 mmol), and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with $H_2O$ and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, and saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (60 g, *n*-hexane : AcOEt = 7 : 1) to give a colorless oil (±)-**9** (3.897 g, 84%). (±)-**9**: IR (neat): 1710 $cm^{-1}$. NMR: 2.02 (3H, s), 2.21 (3H, s), 3.72 (3H, s), 3.76 (3H, s), 3.77 (3H, s), 4.12—4.19 (1H, m), 4.31 (1H, dd, *J*=6, 11 Hz), 4.40 (1H, dd, *J*=6, 11 Hz), 5.86 (1H, dd, *J*=2, 16 Hz), 6.59 (1H, s), 6.71 (1H, s), 7.16 (1H, dd, *J*=7, 16 Hz). FAB-MS (HR-MS) *m/z*: Calcd for $C_{17}H_{22}O_6$: 322.1416 ($M^+$). Found: 322.1447.

**Methyl (±)-5-Acetoxy-4-(2,4-dimethoxyphenyl)-(2*E*)-pentenoate (11)** A solution of (±)-**10** (2.629 g, 9.9 mmol) in pyridine (5 ml) was treated with $Ac_2O$ (1.51 g, 15.4 mmol), and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was worked up in the same way as for (±)-**9** to give a crude oil, which was chromatographed on silica gel (60 g, *n*-hexane : AcOEt = 5 : 1) to give a colorless oil (±)-**11** (2.566 g, 84%). (±)-**11**: IR (neat): 1725 $cm^{-1}$. NMR: 2.02 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 4.11—4.18 (1H, m), 4.29 (1H, dd, *J*=6, 11 Hz), 4.37 (1H, dd, *J*=8, 11 Hz), 5.85 (1H, dd, *J*=2, 16 Hz), 6.43 (1H, d, *J*=8 Hz), 6.46 (1H, s), 7.01 (1H, d, *J*=8 Hz), 7.14 (1H, dd, *J*=7, 16 Hz). *Anal.* Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.40; H, 6.43. EI-MS *m/z*: 308 ($M^+$).

**Methyl (±)-5-Acetoxy-4-(2-methoxyphenyl)-(2*E*)-pentenoate (13)** A solution of (±)-**12** (0.331 g, 1.4 mmol) in pyridine (2 ml) was treated with $Ac_2O$ (0.28 g, 2.7 mmol), and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was worked up in the same way as for (±)-**9** to give a crude oil, which was chromatographed on silica gel (30 g, *n*-hexane : AcOEt = 6 : 1) to give a colorless oil (±)-**13** (0.323 g, 83%). (±)-**13**: IR (neat): 1740 $cm^{-1}$. NMR: 2.02 (3H, s), 3.72 (3H, s), 3.82 (3H, s), 4.23 (1H, br q, *J*=7 Hz), 4.33 (1H, dd, *J*=5, 11 Hz), 4.40 (1H, dd, *J*=9, 11 Hz), 5.87 (1H, dd, *J*=2, 16 Hz), 6.88 (1H, dd, *J*=2, 8 Hz), 6.92 (1H, dt, *J*=2, 8 Hz), 7.11 (1H, dd, *J*=2, 8 Hz), 7.16 (1H, dd, *J*=7, 16 Hz), 7.25 (1H, dt, *J*=2, 8 Hz). *Anal.* Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.60; H, 6.50. FAB-MS *m/z*: 279 ($M^+ + 1$).

**Methyl (±)-5-Acetoxy-4-(4-methoxy-2-methylphenyl)-(2*E*)-pentenoate (15)** A solution of (±)-**14** (11.63 g, 46.5 mmol) in pyridine (30 ml) was treated with $Ac_2O$ (5.3 g, 52.3 mmol), and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was worked up in the same way as for (±)-**9** to give a crude oil, which was chromatographed on silica gel (100 g, *n*-hexane : AcOEt = 9 : 1) to give a colorless oil (±)-**15** (13.46 g, 99%). (±)-**15**: IR (neat): 1739 $cm^{-1}$. NMR: 2.03 (3H, s), 2.32 (3H, s), 3.72 (3H, s), 3.78 (3H, s), 3.99—4.05 (1H, m), 4.29 (1H, dd, *J*=6, 11 Hz), 4.31 (1H, dd, *J*=6, 11 Hz), 5.81 (1H, dd, *J*=2, 16 Hz), 6.73 (1H, dd, *J*=2, 8 Hz), 6.74 (1H, d, *J*=2 Hz), 7.03 (1H, dd, *J*=2, 8 Hz), 7.08 (1H, dd, *J*=7, 16 Hz). *Anal.* Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.66; H, 7.03. FAB-MS *m/z*: 293 ($M^+ + 1$).

**Methyl (±)-5-Acetoxy-4-(4,5-dimethoxy-2-methylphenyl)-(2*E*)-pentenoate (17)** A solution of (±)-**16** (4.683 g, 16.7 mmol) in pyridine (10 ml) was treated with $Ac_2O$ (1.53 g, 15.0 mmol), and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was worked up in the same way as for (±)-**9** to give a crude oil, which was chromatographed on silica gel (60 g, *n*-hexane : AcOEt = 6 : 1) to give a colorless oil (±)-**17** (4.656 g, 86%). (±)-**17**: IR (neat): 1710 $cm^{-1}$. NMR: 2.04 (3H, s), 2.28 (3H, s), 3.73 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 3.97—4.03 (1H, m), 4.32 (1H, dd, *J*=5, 11 Hz), 4.34 (1H, dd, *J*=9, 11 Hz), 5.83 (1H, dd, *J*=2, 16 Hz), 6.61 (1H, s), 6.70 (1H, s), 7.08 (1H, dd, *J*=7, 16 Hz). EI-MS (HR-MS) *m/z*: Calcd for $C_{17}H_{22}O_6$: 322.1416 ($M^+$). Found: 322.1440.

**Methyl (±)-5-Acetoxy-4-(4-methoxyphenyl)-(2*E*)-pentenoate (19)** A solution of (±)-**18** (2.15 g, 9.1 mmol) in pyridine (5 ml) was treated with $Ac_2O$ (2.02 g, 19.7 mmol), and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was worked up in the same way as for (±)-**9** to give a crude oil, which was chromatographed on silica gel (60 g, *n*-hexane : AcOEt = 6 : 1) to give a colorless oil (±)-**19** (2.19 g, 86%). (±)-**19**: IR (neat): 1740 $cm^{-1}$. NMR: 2.02 (3H, s), 3.73 (3H, s), 3.78 (1H, br q, *J*=7 Hz), 3.79 (3H, s), 4.28—4.35 (2H, m), 5.86 (1H, dd, *J*=2, 16 Hz), 6.88 (2H, d, *J*=9 Hz), 7.09 (1H, dd, *J*=7, 16 Hz), 7.12 (2H, d, *J*=9 Hz). *Anal.* Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.34; H, 6.49. FAB-MS *m/z*: 279 ($M^+ + 1$).

**Enzymatic Resolution of (±)-9, (±)-11, (±)-13, (±)-15, (±)-17, and (±)-19** i) Table 1, Entry 1: A suspension of (±)-**9** (0.53 g) and lipase OF-360 (0.2 g) in $H_2O$-saturated-diisopropyl ether (60 ml) was incubated at 33 °C for 8 h. This scale experiment was simultaneously carried out four times (total amount of (±)-**9** was 2.12 g). After the reaction mixture was filtered, the precipitate was washed with diisopropyl ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (50 g) to give (*R*)-**9** [1.675 g, 79%, 22% ee of the corresponding acetate (*R*)-**9**, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH = 60 : 1 : 1, $t_R$ = 16.9 min (61%), $t_R$ = 19.0 min (39%)] from *n*-hexane : AcOEt = 7 : 1 eluate and (*S*)-**8** {0.295 g, 16%, $[\alpha]_D^{25}$ +0.32° (*c*=1.19, $CHCl_3$), corresponding to 81% ee, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH = 60 : 1 : 1, $t_R$ = 16.9 min (9.5%), $t_R$ = 19.0 min (90.5%)} as a homogeneous oil from *n*-hexane : AcOEt = 3 : 1 eluate. The NMR data of (*S*)-**8** were identical with those of the reported (±)-**8**.[15]

ii) Table 1, Entry 2: A suspension of (±)-**11** (0.095 g) and lipase OF-360 (0.1 g) in $H_2O$-saturated-diisopropyl ether (20 ml) was incubated at 33 °C for 24 h. The reaction mixture was worked up in the same way as (±)-**9** to give a crude oil, which was chromatographed on silica gel (15 g) to give (*R*)-**11** {0.027 g, 29%, $[\alpha]_D^{29}$ +13.6° (*c*=0.39, $CHCl_3$), corresponding to 84% ee, Chiralpac AD, eluent, *n*-hexane : EtOH = 10 : 1, $t_R$ = 11.7 min (92%),

$t_R$=13.3 min (8%)} from *n*-hexane : AcOEt=8 : 1 eluate and (*S*)-**10** {(0.050 g, 61%, $[\alpha]_D^{29}$ −8.5° (*c*=0.42, $CHCl_3$), corresponding to 52% ee, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH=60 : 1 : 1, $t_R$=38.0 min (24%), $t_R$=65.0 min (76%)} as a homogeneous oil from *n*-hexane : AcOEt=3 : 1 eluate. The NMR data of (*S*)-**10** were identical with those of the reported (±)-**10**.[15]

iii) Table 1, Entry 3: A suspension of (±)-**13** (0.096 g) and lipase OF-360 (0.1 g) in $H_2O$-saturated-diisopropyl ether (20 ml) was incubated at 33 °C for 48 h. The reaction mixture was worked up in the same way as (±)-**9** to give a crude oil, which was chromatographed on silica gel (15 g) to give (*R*)-**13** {0.030 g, 31%, $[\alpha]_D^{24}$ +7.1° (*c*=0.34, $CHCl_3$), corresponding to 80% ee, Chiralcel OD, eluent, *n*-hexane : EtOH=1000 : 2, $t_R$=83.6 min (10%), $t_R$=97.2 min (90%)} from *n*-hexane : AcOEt=8 : 1 eluate and (*S*)-**12** {0.050 g, 61%, $[\alpha]_D^{25}$ −7.6° (*c*=0.49, $CHCl_3$), corresponding to 43% ee, Chiralpac AD, eluent, *n*-hexane : EtOH=10 : 1, $t_R$=13.3 min (72%), $t_R$=15.1 min (29%)} as a homogeneous oil from *n*-hexane : AcOEt=3:1 eluate. The NMR data of (*S*)-**12** were identical with those of the reported (±)-**12**.[15]

iv) Table 1, Entry 4: A suspension of (±)-**15** (6.75 g) and lipase OF-360 (0.6 g) in $H_2O$-saturated-diisopropyl ether (600 ml) was incubated at 33 °C for 48 h. This scale experiment was simultaneously carried out two times (total amount of (±)-**15** was 13.5 g). The reaction mixture was worked up in the same way as (±)-**9** to give a crude oil, which was chromatographed on silica gel (200 g) to give (*R*)-**15** [(10.8 g, 80%, 15% ee, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH=60 : 1 : 1, $t_R$=8.6 min (42.5%), $t_R$=9.9 min (57.5%)] from *n*-hexane : AcOEt=10 : 1 eluate and (*S*)-**14** [(1.734 g, 13 %, 40% ee, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH=60 : 1 : 1, $t_R$=27.2 min (30%), $t_R$=34.4 min (70%)] as a homogeneous oil from *n*-hexane : AcOEt=3 : 1 eluate. The NMR data of (*S*)-**14** were identical with those of the reported (±)-**14**.[15]

v) Table 1, Entry 5: A suspension of (*S*)-**14** (1.5 g, 40% ee) and lipase OF-360 (0.6 g) and isopropenyl acetate (3.06 g, 30.5 mmol) in diisopropyl ether (200 ml) was incubated at 33 °C for 24 h. The reaction mixture was worked up in the same way as (±)-**9** to give a crude oil, which was chromatographed on silica gel (50 g) to give (*S*)-**15** (0.333 g, 19%, 67% ee) from *n*-hexane : AcOEt=10 : 1 eluate and (*S*)-**14** (1.155 g, 77%, 34% ee) as a homogeneous oil from *n*-hexane : AcOEt=3 : 1 eluate.

vi) Table 1, Entry 6: A suspension of (*S*)-**15** (0.333 g, 67% ee) and lipase OF-360 (0.1 g) in $H_2O$-saturated-diisopropyl ether (40 ml) was incubated at 33 °C for 72 h. The reaction mixture was worked up in the same way as (±)-**9** to give a crude oil, which was chromatographed on silica gel (10 g) to give (*S*)-**15** (0.077 g, 23%, 36% ee) from *n*-hexane : AcOEt=10 : 1 eluate and (*S*)-**14** {0.171 g, 60 %, $[\alpha]_D^{27}$ −4.5° (*c*=1.08, $CHCl_3$), corresponding to 79% ee)} as a homogeneous oil from *n*-hexane : AcOEt=3 : 1 eluate.

vii) Table 1, Entry 7: A suspension of (±)-**17** (0.106 g) and lipase OF-360 (0.1 g) in $H_2O$-saturated-diisopropyl ether (20 ml) was incubated at 33 °C for 8 h. The reaction mixture was worked up in the same way as (±)-**9** to give a crude oil, which was chromatographed on silica gel (15 g) to give (*R*)-**17** [(0.065 g, 61%, 20% ee, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH=60 : 1 : 1, $t_R$=14.5 min (40%), $t_R$=23.1 min (60%)] from *n*-hexane : AcOEt=8 : 1 eluate and (*S*)-**16** {0.031 g, 34%, $[\alpha]_D^{28}$ 7.10° (*c*=0.31, $CHCl_3$), corresponding to 25% ee, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH=60 : 1 : 1, $t_R$=47.7 min (62.5%), $t_R$=60.0 min (37.5%)} as a homogeneous oil from *n*-hexane : AcOEt=3 : 1 eluate. The NMR data of (*S*)-**16** were identical with those of the reported (±)-**16**.[15]

viii) Table 1, Entry 8: A suspension of (±)-**19** (0.095 g) and lipase OF-360 (0.1 g) in $H_2O$-saturated-diisopropyl ether (20 ml) was incubated at 33 °C for 24 h. The reaction mixture was worked up in the same way as (±)-**9** to give a crude oil, which was chromatographed on silica gel (15 g) to give (*R*)-**19** [(0.018 g, 18%, 29% ee, Chiralpac AD, eluent, *n*-hexane : EtOH=50 : 1, $t_R$=34.5 min (35.5%), $t_R$=39.0 min (64.5%)] from *n*-hexane : AcOEt=8 : 1 eluate and (*S*)-**18** [(0.064 g, 77%, 7% ee, Chiralpac AS, eluent, *n*-hexane : EtOH=10 : 1, $t_R$=13.2 min (53.5%), $t_R$=16.1 min (46.5%)] as a homogeneous oil from *n*-hexane : AcOEt=3 : 1 eluate. The NMR data of (*S*)-**18** were identical with those of the reported (±)-**18**.[15]

**Structure Elucidation. Synthesis of Methyl (4*S*)-(2,5-Dimethoxy-4-methylphenyl)pentanoate (21) and Degradation of the Phenyl Part** i) A solution of (*S*)-**8** (81% ee, 0.613 g, 2.2 mmol) and *p*-TsCl (0.63 g, 3.3 mmol) in pyridine (10 ml) was allowed to stand for 12 h at room temperature. The reaction mixture was diluted with ether. The organic layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, and saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue that was chromatographed on silica gel (25 g, *n*-hexane : AcOEt=8 : 1) to afford the corresponding tosylate (0.704 g, 74%). A solution of the tosylate in AcOEt (10 ml) was hydrogenated over 20% Pd-C (50 mg) at room temperature under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated quantitatively to give crude (*S*)-**20**, which was used for the next reaction without further purification. The NMR data of (*S*)-**20** were identical with those of the reported (±)-**20**.[11] A solution of the crude (*S*)-**20** and $NaBH_4$ (0.31 g, 8.2 mmol) in DMSO (10 ml) was warmed for 3 h at 80 °C, then allowed to cool. Small amounts of acetone, ether, and 7% aqueous $NaHCO_3$ were added to the reaction mixture and the organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane : AcOEt=30 : 1) to afford (*S*)-**21** [(0.260 g, 44% overall yield from (*S*)-**8**]. The NMR data of (*S*)-**21** were identical with those of the reported (±)-**21**.[11] ii) To a solution of (+)-**21** (0.260 g, 0.97 mmol) in MeCN (1 ml) was added $NaIO_4$ (4.19 g, 19.6 mmol) and $H_2O$ (1.5 ml) at 0 °C. A mixture of $RuCl_3 \cdot 3H_2O$ (20 mg) in $CCl_4$ (1 ml) was added to the above reaction mixture, and the whole mixture was vigorously stirred at room temperature for 6 h and allowed to stand for 12 h. The reaction mixture was filtered with the aid of Celite, and the precipitate was washed with MeCN. The filtrate and washing were combined and concentrated to give a residue, which was acidified with 2 M aqueous HCl. The acidic layer was extracted with ether, and the organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue, which was treated with an excess of $CH_2N_2$-ether solution to afford a crude oil. It was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=20 : 1) to afford (+)-**22** (0.031 g, 16%) as a homogeneous oil. (+)-**22**: $[\alpha]_D^{26}$ +3.4° (*c*=1.57, $CHCl_3$), corresponding to 81% ee. The NMR data of (+)-**22** were identical with those of the reported (*S*)-**22** {$[\alpha]_D^{27}$ +3.2° (*c*=1.35, $CHCl_3$) corresponding to 76% ee}.[4]

**Synthesis of Methyl (4*S*)-(4-Methoxy-2-methylphenyl)pentanoate (24) and Degradation of the Phenyl Part** i) A solution of (*S*)-**14** (79% ee, 1.247 g, 5.0 mmol) and *p*-TsCl (1.42 g, 7.4 mmol) in pyridine (20 ml) was allowed to stand for 12 h at room temperature. The reaction mixture was diluted with ether. The organic layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, and saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane : AcOEt=8 : 1) to afford (*S*)-**23** (1.801 g, 89%). (*S*)-**23**: $[\alpha]_D^{21}$ +4.3° (*c*=1.56, $CHCl_3$). NMR: 2.04 (3H, s), 2.44 (3H, s), 3.71 (3H, s), 3.76 (3H, s), 3.98—4.05 (1H, m), 4.18—4.24 (2H, m), 5.75 (1H, dd, *J*=2, 16 Hz), 6.65 (1H, dd, *J*=3, 9 Hz), 6.69 (1H, d, *J*=3 Hz), 6.86 (1H, d, *J*=9 Hz), 6.95 (1H, dd, *J*=7, 16 Hz), 7.31 (2H, d, *J*=9 Hz), 7.71 (2H, d, *J*=9 Hz). HR-MS-(EI) *m/z*: Calcd for $C_{21}H_{24}O_6S$: 404.1294 ($M^+$), Found: 404.1321. ii) A solution of (*S*)-**23** (1.801 g, 4.5 mmol) in AcOEt (20 ml) was hydrogenated over 20% Pd–C (50 mg) at room temperature under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated to give a crude tosylate, which was used for the next reaction without further purification. A solution of the tosylate and $NaBH_4$ (0.80 g, 21.1 mmol) in DMSO (20 ml) was warmed for 3 h at 80 °C and then allowed to cool. Small amounts of acetone, ether, and 7% aqueous $NaHCO_3$ were added to the reaction mixture, and the organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane : AcOEt=30 : 1) to afford (*S*)-**24** [0.589 g, 56% overall yield from (*S*)-**23**]. (*S*)-**24**: $[\alpha]_D^{25}$ +12.7° (*c*=1.97, $CHCl_3$). IR ($CHCl_3$): 1735 $cm^{-1}$. NMR: 1.19 (3H, d, *J*=7 Hz), 1.86—1.92 (1H, m), 2.19—2.23 (2H, m), 2.28 (3H, s), 2.94 (1H, sextet, *J*=7 Hz), 3.62 (3H, s), 3.76 (3H, s), 6.68 (1H, d, *J*=3 Hz), 6.73 (1H, dd, *J*=3, 9 Hz), 7.08 (1H, d, *J*=9 Hz). HR-MS-(EI) *m/z*: Calcd for $C_{14}H_{20}O_3$: 236.1412 ($M^+$), Found: 236.1401. iii) To a solution of (+)-**24** (0.317 g, 1.34 mmol) in MeCN (2 ml) was added $NaIO_4$ (5.75 g, 26.9 mmol) and $H_2O$ (3 ml) at 0 °C. A mixture of $RuCl_3 \cdot 3H_2O$ (20 mg) in $CCl_4$ (2 ml) was added to the above reaction mixture, and the whole mixture was vigorously stirred at room temperature for 6 h and allowed to stand for 12 h. The reaction mixture was filtered with the aid of Celite, and the precipitate was washed with MeCN. The filtrate and washing were combined and concentrated to give a residue, which was acidified with 2 M aqueous HCl. The acidic layer was extracted with ether, and the organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue, which was treated with an excess of $CH_2N_2$-ether solution to afford a crude oil. It was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=40 : 1) to afford (+)-**25** (0.078 g, 33%) as a homogeneous oil. (+)-**25**: $[\alpha]_D^{21}$ +13.9° (*c*=0.78, $CHCl_3$), corresponding to 79% ee. The NMR data of (+)-**25** were identical with those of the reported (*S*)-**25** {$[\alpha]_D^{25}$ +15.8° (*c*=0.72, $CHCl_3$), corresponding to 90% ee}.[4]

**Synthesis of Authentic Samples (*S*)-10, (*S*)-12, (*S*)-16, and (*S*)-18** i) To a solution of (*S*)-**26** (93% ee, 0.5 g, 3.9 mmol)[16] and 1,3-dimethoxyben-

zene (1.08 g, 7.8 mmol) in $CH_2Cl_2$ (10 ml) was added $BF_3 \cdot Et_2O$ (0.55 g, 3.9 mmol) at −78 °C, and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (28 g, *n*-hexane : AcOEt=4 : 1) to afford (*S*)-**10** (0.39 g, 38%) as a colorless oil. The NMR data of (*S*)-**10** were identical with those of the reported (±)-**10**.[15] (*S*)-**10**: $[\alpha]_D^{29}$ −15.2° (*c*=0.50, $CHCl_3$), corresponding to 93% ee, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH=60 : 1 : 1, $t_R$=38.0 min (3.5%), $t_R$=65.0 min (96.5%). ii) To a solution of (*S*)-**26** (93% ee, 0.727 g, 5.7 mmol)[16] and anisole (1.23 g, 11.4 mmol) in $CH_2Cl_2$ (10 ml) was added $BF_3 \cdot Et_2O$ (0.85 g, 6 mmol) at −78 °C, and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (30 g) to afford (*S*)-**12** (0.139 g, 10%) as a colorless oil from *n*-hexane : AcOEt=3 : 1 eluate and (*S*)-**18** (0.564 g, 42%) as a colorless oil from *n*-hexane : AcOEt=2 : 1 eluate. The NMR data of (*S*)-**12** and (*S*)-**18** were identical with those of the reported (±)-**12** and (±)-**18**, respectively.[15] (*S*)-**12**: $[\alpha]_D^{21}$ −17.9° (*c*=0.51, $CHCl_3$), corresponding to 93% ee, Chiralpac AD, eluent, *n*-hexane : EtOH=10 : 1, $t_R$=13.3 min (96.5%), $t_R$=15.1 min (3.5%). (*S*)-**18**: $[\alpha]_D^{22}$ −2.2° (*c*=0.51, $CHCl_3$), corresponding to 93% ee, Chiralpac AS, eluent, *n*-hexane : EtOH=10 : 1, $t_R$=13.2 min (96.5%), $t_R$=16.1 min (3.5%). iii) To a solution of (*S*)-**26** (93% ee, 1.23 g, 9.6 mmol)[16] and 3,4-dimethoxytoluene (2.19 g, 14.4 mmol) in $CH_2Cl_2$ (10 ml) was added $BF_3 \cdot Et_2O$ (1.36 g, 9.6 mmol) at −78 °C, and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (20 g, *n*-hexane : AcOEt=2 : 1) to afford (*S*)-**16** (1.237 g, 46%) as a colorless oil. The NMR data of (*S*)-**16** were identical with those of the reported (±)-**16**.[15] (*S*)-**16**: $[\alpha]_D^{29}$ +22.7° (*c*=0.33, $CHCl_3$), corresponding to 93% ee, Chiralcel OD, eluent, *n*-hexane : EtOH : *iso*-PrOH=60 : 1 : 1, $t_R$=47.7 min (96.5%), $t_R$=60.0 min (3.5%).

**Acknowledgment** The authors are grateful to Meito Sangyo Co., Ltd., Japan, for providing the lipase OF-360.

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