Lipase-Catalyzed Resolution of Racemic 1-Acyloxy-2-(*p*-tolyl)propanes

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The acetate (11), propanoate (12), butanoate (13), 2-methylpropanoate (14), hexanoate (15), decanoate (16), and hexadecanoate (17) of (±)-2-(*p*-tolyl)-1-propanol (2) were predominantly hydrolyzed with lipase to give (*S*)-(−)-2-(*p*-tolyl)-1-propanol (2). However, the 2,2-dimethylpropanoate (18), benzoate (19), and phenylacetate (20) of (±)-2 were recovered intact even when the reaction was carried out for 100 h. From the viewpoints of enantioselectivity and reaction rate, the racemic ester 11 was found to be the most suitable substrate for the optical resolution of (±)-2.

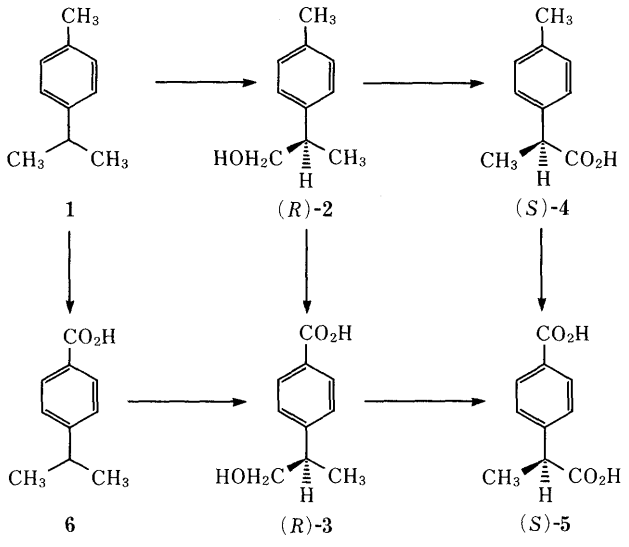
Keywords lipase; resolution; enantioselectivity; 2-(*p*-tolyl)-1-propanol; hydrolysis

In a previous paper,[1] we have reported the biotransformation of *p*-cymene (**1**) in rabbits leading to four optically active metabolites, (*R*)-2-(*p*-tolyl)-1-propanol (**2**), (*R*)-*p*-(2-hydroxy-1-methylethyl)benzoic acid (**3**), (*S*)-2-(*p*-tolyl)propanoic acid (**4**), and (*S*)-*p*-(1-carboxyethyl)benzoic acid (**5**), and three optically inactive metabolites, *p*-isopropylbenzoic acid (**6**), 2-(*p*-tolyl)-2-propanol, and *p*-(1-hydroxy-1-methylethyl)benzoic acid. This metabolic study suggested that the biogenetic oxidation of *p*-cymene (**1**) and *p*-isopropylbenzoic acid (**6**) in rabbits first occurred enantioselectively in the *pro-S* methyl group of the isopropyl moiety, and the resulting (*R*)-2-aryl-1-propanol derivatives, (*R*)-**2** and (*R*)-**3**, were further oxidized to the corresponding (*S*)-2-arylpropanoic acid derivatives, (*S*)-**4** and (*S*)-**5**, accompanied with a metabolic chiral inversion.

There are a number of nonsteroidal anti-inflammatory agents[2,3] such as ibuprofen (**7**), fenoprofen (**8**), ketoprofen (**9**), naproxen (**10**), and so on. It is of interest that these drugs possess an (*S*)-2-arylpropanoic acid moiety similar to that of the metabolites (*S*)-**4** and (*S*)-**5**. In connection with the previous work,[1] we require the optically active 2-(*p*-tolyl)-1-propanols, (*R*)-**2** and (*S*)-**2**, and we considered our previous method for the synthesis of the (*S*)-(−)-enantiomer[1] (**2**) from (*S*)-(+)-2-phenylpropanoic acid to be inadequate because of the large number of reaction steps and low overall yield. Therefore, a simpler and more effective method for the preparation of these enantiomers, (*R*)-**2** and (*S*)-**2**, was required.

Recently, enzymatic hydrolyses have been successfully employed[4-12] for the resolution of chiral alcohols. So we examined the resolution of racemic 2-(*p*-tolyl)-1-propanol[1] (**2**) by the use of lipase. For this purpose, the racemic alcohol **2**, prepared from 4-methylpropiophenone *via* methyl 2-(*p*-tolyl)propanoate, was converted to esters (±)-**11**-(±)-**20** (**11**: R = CH_3, **12**: R = CH_2CH_3, **13**: R = $(CH_2)_2CH_3$, **14**: R = $CH(CH_3)_2$, **15**: R = $(CH_2)_4CH_3$, **16**: R = $(CH_2)_8CH_3$, **17**: R = $(CH_2)_{14}CH_3$, **18**: R = $C(CH_3)_3$, **19**: R = C_6H_5, **20**: R = $CH_2C_6H_5$). This paper describes the lipase-catalyzed hydrolysis of the racemic esters (**11**—**20**), thus obtained.

Each of the esters ((±)-**11**—(±)-**20**) in methanol was shaken with lipase (PPL-Sigma L-3126) in the presence of 0.1 M phosphate buffer (pH 7.0) at 35—36 °C for 2—100 h. The reaction was monitored by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy and was stopped when about half of the substrate was hydrolyzed. The enantiomeric ratio of the hydrolyzed alcohol was determined by high-performance liquid chromatographic (HPLC) analysis of the corresponding (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA ester). The enantiomeric



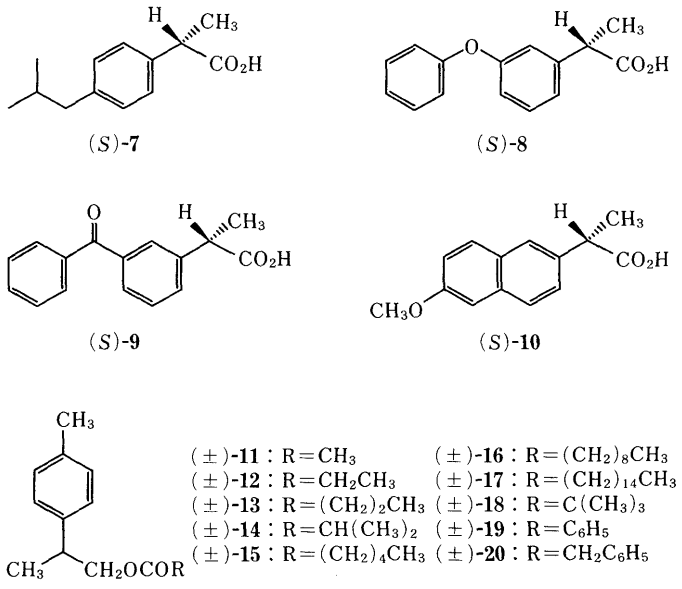
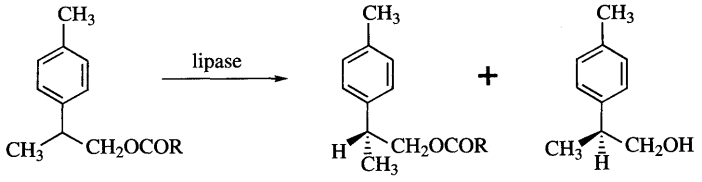


TABLE I. Lipase-Catalyzed Hydrolysis of Racemic 2-(*p*-Tolyl)-1-propanol Derivatives



(±)-**11**-(±)-**20** (*R*)-**11**-(*R*)-**17** (*S*)-**2**

Racemic substrate	Reaction time (h)	Recovered ester			Hydrolyzed alcohol		
		Yield (%)	$[\alpha]_D$ (°)	*R*/*S*	Yield (%)	$[\alpha]_D$ (°)	(*R*)-**2**/(*S*)−**2**
11	2.5	54	+5.5	86:14	43	−14.7	5:95
12	2.5	55	+3.4	80:20	43	−12.2	13:87
13	2	56	+3.9	71:29	42	−9.2	22:78
14	75	69	+2.7	69:31	28	−15.4	3:97
15	9	55	+5.0	74:26	44	−9.9	20:80
16	30	56	+3.6	73:27	40	−10.5	18:82
17	32	75	+1.1	60:40	22	−11.5	15:85
18	100	87	0		0		
19	100	93	0		0		
20	100	93	0		0		

TABLE II. Lipase-Catalyzed Hydrolysis of a Mixture of (*R*)- and (*S*)-2-(*p*-Tolyl)-1-propanol Acetate (**11**)

Substrate (*R*)-**11**/(*S*)-**11**	Reaction time (h)	Product	
		Yield (%)	(*R*)-**2**/(*S*)-**2**
14:86	1	53	0:100
	2	58	3:97
	4	83	4:96
75:25	1	16	9:91
	2	22	11:89
	3	26	14:86

ratio of the recovered ester was also determined by HPLC analysis of the corresponding MTPA ester derived from the unchanged ester. The results are summarized in Table I.

The racemic esters **11**—**17** were predominantly hydrolyzed with lipase to give (*S*)-(−)-2-(*p*-tolyl)-1-propanol (**2**) in 22—44% yields, while the racemic esters **18**—**20** were recovered intact even when the hydrolysis was carried out for 100 h. The reaction rates decreased with increasing steric hindrance of the groups near the reactive site in the substrates (**14**, **18**, **19**, and **20**) and also decreased with increase in the chain length of the acyl group (**15**, **16**, and **17**). The enantioselectivities of the esters **11** and **14** were much higher than those of the other esters (**12**, **13**, **15**, **16**, and **17**). However, since the ester **14** showed low reactivity, it seems that the ester **11** possessing an acetoxyl group is the most suitable substrate for the preparation of the optically active 2-(*p*-tolyl)-1-propanol (**2**).

Subsequently, enantiomeric mixtures (*R*/*S*=14:86 and 75:25) of 2-(*p*-tolyl)-1-propanol acetate (**11**) were also submitted to hydrolysis using lipase for 1—4 h and the results are summarized in Table II. It appears that repeated hydrolysis would raise the optical purity of the alcohol (*S*)-**2**.

Experimental

Infrared (IR) spectra and optical rotations were measured in chloroform. ^{1}H-NMR spectra were recorded with a Hitachi R-1500 spectrometer (60 MHz) in deuteriochloroform using tetramethylsilane as an internal standard, and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. The column chromatography was performed using Merck silica gel (0.063—0.200 mm). HPLC separation was carried out on a Shimadzu LC-6A liquid chromatograph using a Chiralcel OJ column (4.6×250 mm) (Daicel Chemical Industries, Ltd.) [solvent: 2-propanol–hexane (1:9); flow rate, 0.8 ml/min].

Preparation of the Racemic Esters 11—20 Racemic 2-(*p*-tolyl)-1-propanol[1] (**2**) was treated with the corresponding acid chloride (or acetic anhydride) in pyridine (or potassium *tert*-butoxide in *tert*-butyl alcohol). After the usual work-up, the crude product was purified by column chromatography on silica gel, using chloroform–hexane (3:7 amd 3:2) and chloroform as eluents to give the following pure esters (**11**—**20**).

a) (±)-1-Acetoxy-2-(*p*-tolyl)propane (**11**) (1.049 g: 90.9% yield) was prepared from a mixture of (±)-**2** (900 mg) and acetic anhydride (1.5 ml) in pyridine (2.0 ml) by heating at 80 °C for 1 h. The IR and ^{1}H-NMR spectra of (±)-**11** were identical with those of an authentic sample.[1]

b) (±)-1-Propanoyloxy-2-(*p*-tolyl)propane (**12**) (789 mg: 85.1% yield) was prepared from a mixture of (±)-**2** (675 mg) and propanoyl chloride (625 mg) in pyridine (4.0 ml) by heating at 70 °C for 3 h. IR: 1710 cm^{-1}. ^{1}H-NMR δ: 1.09 (3H, t, J=7.3 Hz, –$CH_2C\underline{H}_3$), 1.28 (3H, d, J=7.0 Hz, –$CH(C\underline{H}_3)$–), 2.29 (2H, q, J=7.3 Hz, –$C\underline{H}_2CH_3$), 2.32 (3H, s, –CH_3), 3.06 (1H, m, J=7.0 Hz, –$C\underline{H}(CH_3)$–), 4.15 (2H, d, J=6.7 Hz, –CH_2O–), 7.12 (4H, s, aromatic protons). *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.54; H, 8.88.

c) (±)-1-Butanoyloxy-2-(*p*-tolyl)propane (**13**) (1.239 g: 93.9% yield) was prepared from a mixture of (±)-**2** (900 mg) and butanoyl chloride (960 mg) in pyridine (5.0 ml) by heating at 70 °C for 3 h. IR: 1715 cm^{-1}. ^{1}H-NMR δ: 0.89 (3H, t, J=7.0 Hz, –$CH_2C\underline{H}_3$), 1.28 (3H, d, J=7.0 Hz, –$CH(C\underline{H}_3)$–), 1.61 (2H, m, J=7.0 Hz, overlap, –$C\underline{H}_2CH_3$), 2.26 (2H, t, J=7.3 Hz, overlap, –$COCH_2$–), 2.32 (3H, s, –CH_3), 3.05 (1H, m, J=7.0 Hz, –$C\underline{H}(CH_3)$–), 4.15 (2H, d, J=6.7 Hz, –CH_2O–), 7.11 (4H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.50; H, 9.24.

d) (±)-1-(2-Methylpropanoyloxy)-2-(*p*-tolyl)propane (**14**) (3.673 g: 83.4% yield) was prepared from a mixture of (±)-**2** (3.005 g) and 2-methylpropanoyl chloride (3.197 g) in pyridine (20 ml) by refluxing for 24 h. IR: 1715 cm^{-1}. ^{1}H-NMR δ: 1.11 (6H, d, J=7.0 Hz, –$CH(C\underline{H}_3)_2$), 1.28 (3H, d, J=7.0 Hz, –$CH(C\underline{H}_3)$–), 2.32 (3H, s, –CH_3), 3.06 (1H, m, J=7.0 Hz, –$C\underline{H}(CH_3)$–), 4.14 (2H, d, J=7.0 Hz, –CH_2O–), 7.11 (4H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.23; H, 9.31.

e) (±)-1-Hexanoyloxy-2-(*p*-tolyl)propane (**15**) (1.251 g: 84.1% yield) was prepared from a mixture of (±)-**2** (900 mg) and hexanoyl chloride (969 mg) in pyridine (10 ml) by heating at 75 °C for 2 h. IR: 1720 cm^{-1}. ^{1}H-NMR δ: 0.87 (3H, br t, J=6.2 Hz, –$CH_2C\underline{H}_3$), 1.28 (3H, d, J=7.0 Hz, –$CH(C\underline{H}_3)$–), 2.26 (2H, t, J=7.0 Hz, –$COCH_2$–), 2.32 (3H, s, –CH_3), 3.05

(1H, m, J=7.0 Hz, –C<u>H</u>(CH$_3$)–), 4.09 (1H, s) and 4.20 (1H, d, J=1.2 Hz) (–CH$_2$O–), 7.11 (4H, s, aromatic protons). *Anal.* Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.28; H, 9.87.

f) (±)-1-Decanoyloxy-2-(*p*-tolyl)propane (**16**) (1.765 g: 96.8% yield) was prepared from a mixture of (±)-**2** (900 mg) and decanoyl chloride (1.373 g) in pyridine (10 ml) by heating at 75 °C for 2 h. IR: 1720 cm^{-1}. ^{1}H-NMR δ: 0.88 (3H, t, J=5.6 Hz, –CH$_2$C<u>H</u>$_3$), 1.25 (14H, br s, –(CH$_2$)$_7$–), 1.27 (3H, d, J=7.0 Hz, overlap, –CH(C<u>H</u>$_3$)–), 2.26 (2H, t, J=6.7 Hz, overlap, –COCH$_2$–), 2.32 (3H, s, –CH$_3$), 3.05 (1H, m, J=7.0 Hz, –C<u>H</u>(CH$_3$)–), 4.15 (2H, br d, J=7.3 Hz, –CH$_2$O–), 7.11 (4H, s, aromatic protons). *Anal.* Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.81; H, 10.80.

g) (±)-1-Hexadecanoyloxy-2-(*p*-tolyl)propane (**17**) (903 mg: 77.6% yield) was prepared from a mixture of (±)-**2** (450 mg) and hexadecanoyl chloride (990 mg) in pyridine (6.0 ml) by heating at 75 °C for 2 h. IR: 1720 cm^{-1}. ^{1}H-NMR δ: 0.88 (3H, br t, J=5.0 Hz, –CH$_2$C<u>H</u>$_3$), 1.26 (26H, s, –(CH$_2$)$_{13}$–), 1.27 (3H, d, J=7.0 Hz, overlap, –CH(C<u>H</u>$_3$)–), 2.26 (2H, t, J=7.0 Hz, overlap, –COCH$_2$–), 2.32 (3H, s, –CH$_3$), 3.05 (1H, m, J=7.0 Hz, –C<u>H</u>(CH$_3$)–), 4.09 (1H, s) and 4.20 (1H, d, J=1.2 Hz) (–CH$_2$O–), 7.11 (4H, s, aromatic protons). *Anal.* Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 80.50; H, 11.36.

h) (±)-1-(2,2-Dimethylpropanoyloxy)-2-(*p*-tolyl)propane (**18**) (149 mg: 63.8% yield) was prepared from a mixture of (±)-**2** (150 mg), 2,2-dimethylpropanoyl chloride (225 mg), and potassium *tert*-butoxide (125 mg) in *tert*-butyl alcohol (2.0 ml) by refluxing for 6 h, with partial recovery of **2** (38 mg: 25.3%). IR: 1700 cm^{-1}. ^{1}H-NMR δ: 1.14 (9H, s, –C(CH$_3$)$_3$), 1.29 (3H, d, J=7.0 Hz, –CH(C<u>H</u>$_3$)–), 2.32 (3H, s, –CH$_3$), 3.07 (1H, m, J=7.0 Hz, –C<u>H</u>(CH$_3$)–), 4.07 (1H, d, J=1.2 Hz) and 4.19 (1H, d, J=1.8 Hz) (–CH$_2$O–), 7.11 (4H, s, aromatic protons). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.76; H, 9.54.

i) (±)-1-Benzoyloxy-2-(*p*-tolyl)propane (**19**) (183 mg: 72.0% yield) was prepared from a mixture of (±)-**2** (150 mg), benzoyl chloride (310 mg), and potassium *tert*-butoxide (125 mg) in *tert*-butyl alcohol (2.0 ml) by refluxing for 3 h, with partial recovery of **2** (37 mg: 24.7%). IR: 1700 cm^{-1}. ^{1}H-NMR δ: 1.38 (3H, d, J=7.0 Hz, –CH(C<u>H</u>$_3$)–), 2.33 (3H, s, –CH$_3$), 3.22 (1H, m, J=7.0 Hz, –C<u>H</u>(CH$_3$)–), 4.39 (2H, br d, J=7.0 Hz, –CH$_2$O–), 7.16—8.08 (9H, m, aromatic protons). *Anal.* Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.39; H, 7.27.

j) (±)-1-(Phenylacetoxy)-2-(*p*-tolyl)propane (**20**) (2.667 g: 99.4% yield) was prepared from a mixture of (±)-**2** (1.504 g) and phenylacetyl chloride (2.340 g) in pyridine (8.0 ml) by heating at 70 °C for 4 h. IR: 1720 cm^{-1}. ^{1}H-NMR δ: 1.23 (3H, d, J=7.0 Hz, –CH(C<u>H</u>$_3$)–), 2.32 (3H, s, –CH$_3$), 3.03 (1H, m, J=7.0 Hz, –C<u>H</u>(CH$_3$)–), 3.57 (2H, s, –COCH$_2$–), 4.11 (1H, s) and 4.22 (1H, d, J=1.2 Hz) (–CH$_2$O–), 7.07 (5H, s) and 7.26 (4H, br s) (aromatic protons). *Anal.* Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.47; H, 7.58.

Lipase-Catalyzed Hydrolyses of the Racemic Esters 11—20 Each of the racemic esters **11—20** was hydrolyzed with lipase (PPL-Sigma L-3126) and phosphate buffer (pH 7.0) in methanol at 35—36 °C for 2—100 h. The reaction mixture was extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel, using chloroform as an eluent, to give the recovered ester and the hydrolyzed alcohol (*S*)-**2**. The recovered ester was further hydrolyzed with aqueous sodium hydroxide in refluxing methanol for 2 h to give an alcohol (*R*)-**2**. The alcohols, (*R*)-**2** and (*S*)-**2**, were respectively converted to the corresponding MTPA esters, whose enantiomeric ratios were analyzed by HPLC: t_R (*S*)=11.6 min, t_R (*R*)=14.1 min.

a) (±)-1-Acetoxy-2-(*p*-tolyl)propane (**11**) (252 mg) was hydrolyzed with lipase (250 mg) and 0.1 M phosphate buffer (21.0 ml) in methanol (7.0 ml) for 2.5 h to give the recovered ester (*R*)-**11** (136 mg: 54.0% yield), $[\alpha]_D$ +5.5° (c=2.25), and an alcohol (*S*)-**2** (85 mg: 43.4% yield), $[\alpha]_D$ −14.7° (c=2.28), R/S=5:95. The recovered ester (*R*)-**11** was hydrolyzed with aqueous sodium hydroxide to give an alcohol (*R*)-**2**, $[\alpha]_D$ +11.9° (c=2.31), R/S=86:14.

b) (±)-1-Propanoyloxy-2-(*p*-tolyl)propane (**12**) (310 mg) was hydrolyzed with lipase (310 mg) and 0.1 M phosphate buffer (21.0 ml) in methanol (7.0 ml) for 2.5 h to give the recovered ester (*R*)-**12** (171 mg: 55.0% yield), $[\alpha]_D$ +3.4° (c=3.76), and an alcohol (*S*)-**2** (97 mg: 43.0% yield), $[\alpha]_D$ −12.2° (c=1.39), R/S=13:87. The recovered ester (*R*)-**12** was hydrolyzed with aqueous sodium hydroxide to give an alcohol (*R*)-**2**, $[\alpha]_D$ +9.9° (c=2.78), R/S=80:20.

c) (±)-1-Butanoyloxy-2-(*p*-tolyl)propane (**13**) (320 mg) was hydrolyzed with lipase (320 mg) and 0.1 M phosphate buffer (21.0 ml) in methanol (7.0 ml) for 2 h to give the recovered ester (*R*)-**13** (179 mg: 55.9% yield), $[\alpha]_D$ +3.9° (c=0.84), and an alcohol (*S*)-**2** (91 mg: 41.7% yield), $[\alpha]_D$ −9.2° (c=1.43), R/S=22:78. The recovered ester (*R*)-**13** was hydrolyzed with aqueous sodium hydroxide to give an alcohol (*R*)-**2**, $[\alpha]_D$ +6.9° (c=2.05), R/S=71:29.

d) (±)-1-(2-Methylpropanoyloxy)-2-(*p*-tolyl)propane (**14**) (330 mg) was hydrolyzed with lipase (330 mg) and 0.1 M phosphate buffer (21.0 ml) in methanol (7.0 ml) for 75 h to give the recovered ester (*R*)-**14** (228 mg: 69.1% yield), $[\alpha]_D$ +2.7° (c=3.30), and an alcohol (*S*)-**2** (63 mg: 28.1% yield), $[\alpha]_D$ −15.4° (c=1.54), R/S=3:97. The recovered ester (*R*)-**14** was hydrolyzed with aqueous sodium hydroxide to given an alcohol (*R*)-**2**, $[\alpha]_D$ +6.2° (c=1.44), R/S=69:31.

e) (±)-1-Hexanoyloxy-2-(*p*-tolyl)propane (**15**) (372 mg) was hydrolyzed with lipase (370 mg) and 0.1 M phosphate buffer (24.0 ml) in methanol (8.0 ml) for 9 h to give the recovered ester (*R*)-**15** (205 mg: 55.1% yield), $[\alpha]_D$ +5.0° (c=2.81), and an alcohol (*S*)-**2** (98 mg: 43.6% yield), $[\alpha]_D$ −9.9° (c=1.35), R/S=20:80. The recovered ester (*R*)-**15** was hydrolyzed with aqueous sodium hydroxide to give an alcohol (*R*)-**2**, $[\alpha]_D$ +7.9° (c=2.59), R/S=74:26.

f) (±)-1-Decanoyloxy-2-(*p*-tolyl)propane (**16**) (456 mg) was hydrolyzed with lipase (450 mg) and 0.1 M phosphate buffer (27.0 ml) in methanol (9.0 ml) for 30 h to give the recovered ester (*R*)-**16** (255 mg: 55.9% yield), $[\alpha]_D$ +3.6° (c=3.50), and an alcohol (*S*)-**2** (90 mg: 40.0% yield), $[\alpha]_D$ −10.5° (c=1.74), R/S=18:82. The recovered ester (*R*)-**16** was hydrolyzed with aqueous sodium hydroxide to give an alcohol (*R*)-**2**, $[\alpha]_D$ +7.6° (c=1.78), R/S=73:27.

g) (±)-1-Hexadecanoyloxy-2-(*p*-tolyl)propane (**17**) (388 mg) was hydrolyzed with lipase (380 mg) and 0.1 M phosphate buffer (24.0 ml) in methanol (12.0 ml) for 32 h to give the recovered ester (*R*)-**17** (291 mg: 75.0% yield), $[\alpha]_D$ +1.1° (c=2.46), and an alcohol (*S*)-**2** (33 mg: 22.0% yield), $[\alpha]_D$ −11.5° (c=0.74), R/S=15:85. The recovered ester (*R*)-**17** was hydrolyzed with aqueous sodium hydroxide to give an alcohol (*R*)-**2**, $[\alpha]_D$ +3.3° (c=1.43), R/S=60:40.

h) (±)-1-(2,2-Dimethylpropanoyloxy)-2-(*p*-tolyl)propane (**18**), (±)-1-benzoyloxy-2-(*p*-tolyl)propane (**19**), and (±)-1-(phenylacetoxy)-2-(*p*-tolyl)propane (**20**) were submitted to lipase-catalyzed hydrolysis for 100 h to give unchanged **18**, **19**, and **20** in 87, 93, and 93% yields, respectively.

i) A mixture of the enantiomeric 1-acetoxy-2-(*p*-tolyl)propanes (R/S=14:86) (15 mg) was hydrolyzed with lipase (15 mg) and 0.1 M phosphate buffer (1.5 ml) in methanol (0.5 ml) for 1, 2, and 4 h to give the alcohols, (*R*)-**2**/(*S*)-**2**=0:100, 3:97, and 4:96, in 53, 58, and 83% yields, respectively.

j) A mixture of the enantiomeric 1-acetoxy-2-(*p*-tolyl)propanes (R/S=75:25) (15 mg) was hydrolyzed with lipase (15 mg) and 0.1 M phosphate buffer (1.5 ml) in methanol (0.5 ml) for 1, 2, and 3 h to give the alcohols, (*R*)-**2**/(*S*)-**2**=9:91, 11:89, and 14:86, in 16, 22, and 26% yields, respectively.

Preparation of the MTPA Ester A mixture of 2-(*p*-tolyl)-1-propanol (3 mg), (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (25 mg), pyridine (0.1 ml), and carbon tetrachloride (0.2 ml) was allowed to stand at room temperature for 24 h. The mixture was diluted with ether, washed successively with dilute hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried over sodium sulfate, and evaporated *in vacuo* to give the MTPA ester.

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