Enzymatic Resolution of 4-Methyl-, 4-Phenyl- and 6-Phenyltetrahydro-2H-pyran-2-one using Esterases

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Enantioselective hydrolysis of racemic tetrahydro-2H-pyran-2-ones (δ-valerolactones) using esterase resulted in the formation of optically active (R)-4-methyl-, (R)-4-phenyl- or (R)-6-phenyltetrahydro-2H-pyran-2-ones and the corresponding (S)-δ-hydroxypentanoic acid derivatives.

Chiral tetrahydro-2H-pyran-2-ones **1** (δ-valerolactones) are characteristic and crucial structural features of many biologically active and natural products and are of considerable interest as chiral building blocks in the synthesis of enantiomerically pure compounds. Recently, the use of lipases or esterases for the preparation of optically active building blocks in the synthesis of natural products has increased [1]. In connection with the enzymatic enantioselective synthesis of optically active **1**, Ohta *et al.* [2] reported the *Gluconobacter roseus* mediated oxidation of 3-substituted pentane-1,5-diols to (4R)-4-substituted tetrahydro-2H-pyran-2-one. Utaka *et al.* [3] reported that the reduction of δ-keto acids, RCO(CH$_2$)$_3$COOH, using

fermenting baker's yeast resulted in the formation of (6R)-6-substituted tetrahydro-2H-pyran-2-one with 98% *ee*. The stereoselective pig liver esterase (PLE) catalyzed hydrolyses of 3-substituted glutarate diesters and following reduction with borane-dimethyl sulfide led to the formation of (4S)- or (4R)-tetrahydro-2H-pyran-2-one derivatives [4]. On the other hand, Blanco *et al.* [5] observed that the enzymatic resolution of racemic 6-pentyl- and 6-heptyltetrahydro-2H-pyran-2-one using PLE or horse liver esterase (HLE) afforded the corresponding (6S)-tetrahydro-2H-pyran-2-ones. Fouque and Rousseau [6] also described the enzymatic resolution of racemic 6-methyltetrahydro-2H-pyran-2-one using PLE or HLE to (6S)-6-methyltetrahydro-2H-pyran-2-one. In this report, we wish to report the esterase-catalyzed hydrolyses of 4-methyl- (**1a**), 4-phenyl- (**1b**), and 6-phenyltetrahydro-2H-pyran-2-one (**1c**) derivatives.

Results and Discussion.

The results of the enzymatic resolution of (±)-**1** using esterases are summarized in Table 1. In an initial attempt, optical resolution of (±)-**1a** was performed by incubation with HLE at 25° in buffer solution (*p*H 7.2 or 7.4; entries 1~6), and the reaction proceeded rapidly to result in the formation of (3S)-5-hydroxy-3-methylpentanoic acid (S)-**2a** and (4R)-4-methyltetrahydro-2H-pyran-2-one (R)-**1a**, in spite of somewhat low selectivity. The absolute configuration of (R)-**1a** was assigned by comparison of the optical rotation with the literature data [7], and the absolute configuration of (S)-**2a** was assigned by comparison of the optical rotation with the literature data [9], after transformation by the cyclization with *p*-toluene sulfonic acid to the authentic (4S)-4-methyltetrahydro-2H-pyran-2-one (S)-**1a**. The optical purities of (S)-**1a** and (R)-**1a** were determined by chiral hplc analysis using a Daicel chiralcel column. The enzymatic hydrolysis of (+)-**1a** using PLE also afforded (S)-**1a** and (R)-**1a**, in which the optical rotations of the products were of somewhat similar degrees compared with those from the hydrolysis using HLE (entries 7 and 8). The enzymatic hydrolysis of (±)-**1a** using α-chymotrypsin, lipase from *Pseudomonas cepacia*

Scheme 1

(±)-**1**   (S)-**2**   +   (R)-**2**

p-TsOH

(S)-**1**
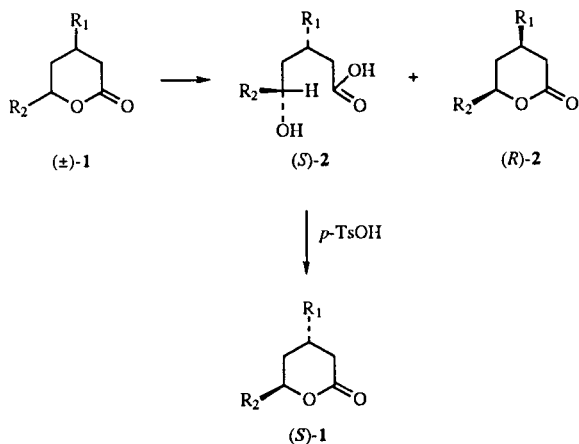
(±)-**1a**, (S)-**1a**, (R)-**1a**, (S)-**2a**: R$_1$ = CH$_3$; R$_2$ = H
(±)-**1b**, (S)-**1b**, (R)-**1b**, (S)-**2b**: R$_1$ = Ph; R$_2$ = H
(±)-**1c**, (S)-**1c**, (R)-**1c**, (S)-**2c**: R$_1$ = H; R$_2$ = Ph

(S)-**1d**   (S)-**3**
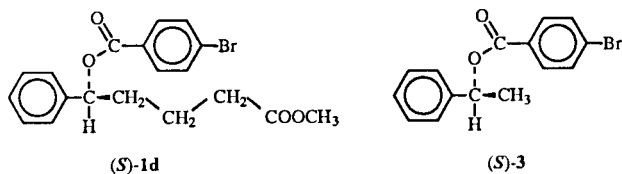
(lipase PS), and immobilized lipase of *Mucor miehei* (lipozyme) also proceeded to afford hydrolyzed products, in spite of a slower reaction rate compared with those of the reaction using HLE and PLE. But, the products showed no optical rotation (entries 9~11).

The enzymatic resolution of (±)-**1b** using HLE and PLE resulted in the formation of (3*S*)-5-hydroxy-3-phenylpentanoic acid (*S*)-**1b** as the hydrolyzed product which was isolated as (4*S*)-4-phenyltetrahydro-2*H*-pyran-2-one (*S*)-**1b** after cyclization, and (4*R*)-4-phenyltetrahydro-2*H*-

Table 1

Enzymatic Resolution of 4-Methyl-, 4-Phenyl- and 6-Phenyltetrahydro-2*H*-pyran-2-ones using Esterases

Entry	Substrate	Enzyme [a]	Buffer solution [b] (pH)	Reaction time (hours)	Conversion [c] (%)	Hydrolyzed Product				Recovered Lactone		
						Yield (%)	Config-uration	ee [d] (%)	[α] [e]	Yield (%)	Config-uration	ee [d] (%)	[α] [e]
1	1a	HLE	A (7.2)	1	42	37	(*S*)-1a	36	-10.2 (1.00)	38	(*R*)-1a	52	+14.8 (1.10)
2	1a	HLE	B (7.2)	3	27	22	(*S*)-1a	33	-9.29 (1.16)	34	(*R*)-1a	54	+15.2 (1.01)
3	1a	HLE	C (7.2)	6	30	26	(*S*)-1a	14	-3.92 (0.89)	16	(*R*)-1a	68	+19.2 (0.90)
4	1a	HLE	A (7.4)	3	24	20	(*S*)-1a	31	-8.72 (1.00)	30	(*R*)-1a	49	+13.9 (1.00)
5	1a	HLE	B (7.4)	1	27	22	(*S*)-1a	30	-8.47 (0.89)	34	(*R*)-1a	50	+14.1 (0.89)
6	1a	HLE	C (7.4)	1.5	41	36	(*S*)-1a	23	-6.49 (0.89)	30	(*R*)-1a	64	+18.1 (0.90)
7	1a	PLE	B (7.2)	3	24	19	(*S*)-1a	31	-8.84 (1.04)	35	(*R*)-1a	37	+10.3 (1.10)
8	1a	PLE	B (7.4)	4.5	44	43	(*S*)-1a	23	-6.51 (0.89)	40	(*R*)-1a	35	+9.88 (0.89)
9	1a	α-CT	B (7.8)	32	38	33	(±)-1a	0	0 (0.90)	37	(±)-1a	0	0 (0.88)
10	1a	PS	B (7.2)	48	33	30	(±)-1a	0	0 (1.00)	39	(±)-1a	0	0 (0.89)
11	1a	Lipoz	B (7.2)	24	35	29	(±)-1a	0	0 (1.02)	52	(±)-1a	0	0 (1.01)
12	1b	HLE	A (7.4)	4	39	34	(*S*)-1b	70	+3.56 (0.98)	37	(*R*)-1b	83	-4.27 (1.00)
13	1b	HLE	B (7.4)	7	46	43	(*S*)-1b	33	+1.80 (1.02)	39	(*R*)-1b	47	-2.47 (0.98)
14	1b	HLE	C (7.4)	6	43	39	(*S*)-1b	36	+1.95 (1.00)	39	(*R*)-1b	54	-2.56 (1.10)
15	1b	PLE	B (7.4)	9	42	39	(*S*)-1b	17	+1.07 (1.02)	32	(*R*)-1b	63	-3.31 (1.10)
16	1b	PLE	C (7.4)	5.5	40	35	(*S*)-1b	37	+2.08 (0.99)	30	(*R*)-1b	76	-3.95 (1.00)
17	1c	HLE	A (7.2)	48	43	39	(*S*)-1c	55	-27.3 (1.00)	39	(*R*)-1c	43	+20.8 (1.02)
18	1c	HLE	A (7.4)	48	39	35	(*S*)-1c	53	-26.3 (0.99)	41	(*R*)-1c	45	+22.2 (1.00)
19	1c	HLE	B (7.2)	48	40	35	(*S*)-1c	51	-25.4 (1.01)	39	(*R*)-1c	53	+26.2 (1.00)
20	1c	HLE	C (7.2)	48	46	42	(*S*)-1c	47	-23.4 (1.00)	37	(*R*)-1c	51	+25.3 (1.02)
21	1c	PLE	A (7.2)	336	28	23	(±)-1c	0	0 (1.00)	60	(±)-1c	0	0 (1.01)
22	1c	PLE	A (7.4)	480	20	15	(±)-1c	0	0 (1.01)	25	(±)-1c	0	0 (1.00)

[a] HLE = Horse liver esterase; PLE = Pig liver esterase; α-CT = α-Chymotrypsin; PS = Lipase PS; Lipoz = Lipozyme. [b] A = 0.2 *M* Potassium dihydrogen phosphate aqueous solution (5 ml). The *p*H was maintained using a *p*H stat with 0.2 *M* sodium hydroxide aqueous solution. B = 0.2 *M* Sodium dihydrogen phosphate aqueous solution (5 ml). The *p*H was maintained using a *p*H stat with 0.2 *M* sodium hydroxide aqueous solution. C = 0.2 *M* Potassium dihydrogen phosphate aqueous solution (5 ml). The *p*H was maintained using a *p*H stat with 0.2 *M* potassium hydroxide aqueous solution. [c] Determined by hplc (benzene : hexane = 1:3). [d] The *ee* value of the products was determined by chiral hplc analysis with a Daicel chiralcel OG (46 mm x 250 mm), with hexane-propan-2-ol (9:1) as mobile phase at a flow rate of 0.5 ml/min. [e] $[\alpha]_D^{20}$ (c in chloroform).

pyran-2-one (R)-**1b** as unreacted product (entries 12~16), and the hydrolysis of (±)-**1b** with HLE using potassium dihydrogen phosphate buffer solution (pH 7.4 was maintained using pH stat with 0.2 M sodium hydroxide aqueous solution) afforded the hydrolyzed product (S)-**1b** with high optical purities (entry 12). The absolute configurations of (S)-**1b** [7] and (R)-**1b** [8] were assigned by comparison of the optical rotations with the literature data..

The enzymatic resolution of (±)-**1c** using HLE led to the formation of (5S)-5-hydroxy-5-phenylpentanoic acid (S)-**2c** as the reacted product which was isolated as (6S)-6-phenyltetrahydro-2H-pyran-2-one (S)-**1c** after cyclization, and (6R)-6-phenyltetrahydro-2H-pyran-2-one (R)-**1c** as recovered product (entries 17~20). However, the optical resolution of (±)-**1c** using PLE afforded the hydrolyzed products with, no optical rotation (entries 21 and 22). The absolute configuration of (S)-**1c** was established to be S by a CD (circular dichroism) exciton chirality method [9]. The CD spectra of methyl (S)-(+)-5-(p-bromobenzoyloxy)-5-phenylpentanoate (S)-**1d** after transformation from (S)-**1c** by hydrolysis and following esterification was compared with those of (S)-(+)-p-bromobenzoate (S)-**3** of (S)-(-)-1-phenylethyl alcohol knowing the absolute configuration (see Figures 1 and 2). The CD spectrum of (S)-**3** showed Cotton effect (positive at 211.7 nm (Δε = +4.46), at 214.5 nm (Δε = +2.90), and at 246.5 nm (Δε = +6.34) (Figure 1). On the other hand, the CD spectra of (S)-**1d** also showed the same pattern of the

Cotton effect (positive at 212.8 nm (Δε = +2.37), at 215 nm (Δε +1.41), and at 245.5 nm (Δε = +3.45)), compared with those of (S)-**3** (Figure 2). The signs of optical rotation of methyl (S)-5-hydroxy-5-phenylpentanoate and its p-bromobenzoate (S)-**1d** are (-)- and (+)-, respectively, whereas, those of (S)-1-phenylethyl alcohol and its p-bromobenzoate (S)-**3** are also (-)- and (+)-, respectively. These phenomenon support the conclusion that the absolute configuration of (S)-**1c** is (S).
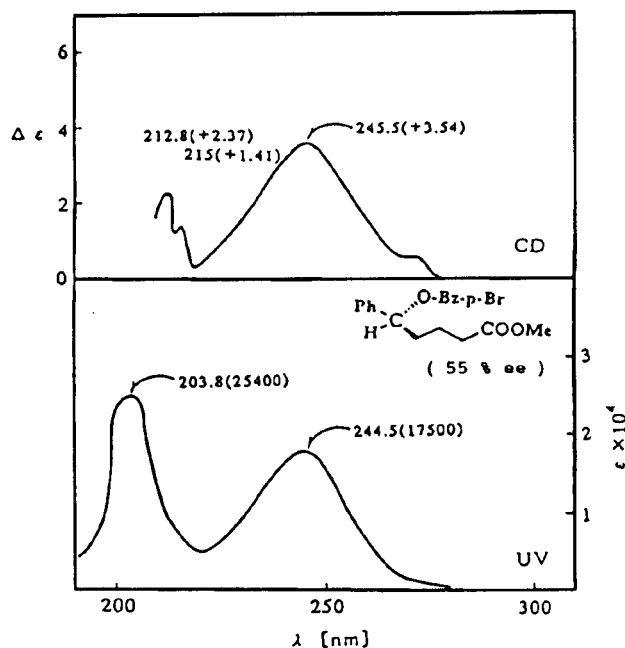

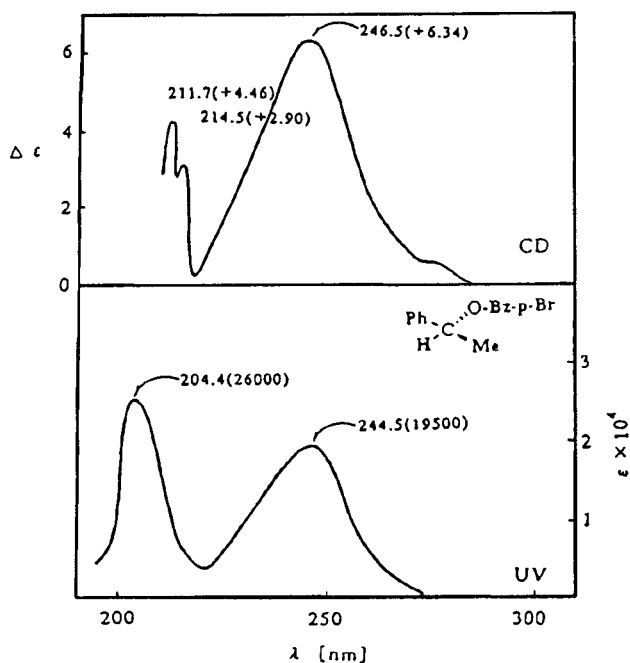Figure 2. CD and UV spectra of methyl (5S)-(+)-5-(p-bromobenzoyloxy)-5-phenylpentoate (S)-**1d** in ethanol.

EXPERIMENTAL

Infrared spectra were measured with a Hitachi 260-10 spectrometer. The ^{1}H nmr spectra were taken with a Hitachi R-90H instrument, using TMS as an internal standard. Mass spectra were obtained using a Hitachi RMU-6M mass spectrometer. Optical rotations were measured with a JASCO DIP-140 digital polarimeter. The uv spectra were recorded on a JASCO Ubest-50 spectrophotometer. The CD spectra were measured on a JASCO J-400X spectrometer.

The compounds **1a** [10], **1b** [10], and **1c** [11] were prepared as described in literature.

Pig liver esterase (PLE), horse liver esterase (HLE) and α-chymotrypsin (Type II) were obtained from Sigma Chemical Co. Lipase PS (lipase from *Pseudomonas cepacia*) and lipozyme (immobilized lipase of *Mucor miehei*) were purchased from Amano Pharmaceutical Co. and Novo Industri Co., respectively.

Enzymatic Resolution of Racemic Lactones (±)-**1a-c**. General Procedure.

Figure 1. CD and UV spectra of (S)-(+)-1-(p-bromobenzoyloxy)-1-phenylethane (S)-**3** in ethanol.

In an Erlenmeyer flask, the racemic lactone (±)-1 (500 mg) in acetone (1 ml) was stirred with a mixture of 0.2 M sodium or potassium dihydrogen phosphate aqueous solution (5 ml) and 10% calcium chloride aqueous solution (5 ml). The pH was maintained to 7.2, 7.4 or 7.8 using a pH stat with a 0.2 M sodium or potassium hydroxide aqueous solution at 25°, and then the enzyme (500 mg) was added to the mixture and stirred at the same temperature. The reaction started immediately, and after potassium hydroxide or sodium hydroxide consumption corresponding to 50–60% conversion had been noted, ice (2 g) and Celite (1 g) were added. After stirring for 5 minutes, the mixture was filtered over Celite, the cake was washed with benzene (2 x 20 ml), and aqueous phases were extracted with benzene (2 x 25 ml). The organic phases were washed with a saturated sodium hydrogen carbonate aqueous solution (10 ml), dried over anhydrous magnesium sulfate, and concentrated to give the optically active lactone (R)-1. The aqueous layers combined with washing solution are heated 5 minutes at 70°. After cooling, the solution was acidified to $pH \leq 2$ with 2 M solution of phosphoric acid and extracted with ether (3 x 7 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, and concentrated to give the optical hydroxy acids (S)-2. After refluxing the unpurified (S)-2 with p-toluenesulfonic acid (0.5 g) in benzene (20 ml) for 1 hour, the solution was successively washed with water, a saturated sodium hydrogen carbonate aqueous solution and water, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, chloroform) to afford the reacted lactone (S)-1.

The absolute configurations of (R)-1a, (R)-1b, (S)-1a, and (S)-1b were assigned by comparison of the optical rotation with the literature data. The absolute configuration of (S)-1c was determined to be (S)-(−) by comparison of the circular dichroism spectra with those of (S)-(+)-p-bromobenzoate (S)-3 of (S)-(−)-1-phenylethyl alcohol, after transformation by hydrolysis and following esterification to methyl (S)-(+)-5-(p-bromobenzoyloxy)-5-phenylpentanoate (S)-1d (see Figures 1 and 2). The optical purities of (R)-1 and (S)-1 were determined by chiral hplc analysis using a Daicel chiralcel OG column (4.6 mm x 250 mm; hexane:2-propanol = 9:1; 0.5 ml/min). The results are summarized in Table 1.

Spectroscopic and analytical data of the products are as follows:

(4S)-(−)-4-Methyltetrahydro-2H-pyran-2-one (S)-1a.

This compound was obtained as a colorless oil, bp 107-109° (15 mm/Hg) [lit [7] bp 80-85° (3 mm/Hg), $[\alpha]_D^{20}$ = -28.2° (c 1.04, chloroform), ee = 93%]; ir (neat): 1730 cm^{-1} (-COO-); ^{1}H nmr (deuteriochloroform): δ 1.06 (d, 3H, -CH_3), 1.23-1.77 (m, 1H, -CH-), 1.77-2.32 (m, 2H, -CH_2- of -C$_5$), 3.01 (q, 2H, -CH_2CO-), 4.08-4.56 ppm (m, 2H, -CH_2-O-); ms: m/z 114 [M$^+$].
Anal. Calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.03; H, 8.76.

(4R)-(+)-4-Methyltetrahydro-2H-pyran-2-one (R)-1a.

This compound was obtained as a colorless oil, bp 101-104° (12 mm/Hg) [lit [7] bp 85-90° (4 mm/Hg), $[\alpha]_D^{20}$ = +28.4° (c 0.89, chloroform), ee = 94%]; the spectroscopic data correspond with those of (S)-1a.
Anal. Calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.18; H, 8.78.

(4S)-(+)-4-Phenyltetrahydro-2H-pyran-2-one (S)-1b.

This compound was obtained as a colorless oil, bp 180-185° (5 mm/Hg), [lit [8] $[\alpha]_D^{23}$ = +3.63 (c 7.2, chloroform), ee = 98%]; ir (neat): 1735 (-COO-), 760, 705 cm^{-1} (phenyl ring); ^{1}H nmr (deuteriochloroform): δ 2.10 (q, 2H, -CH_2- of -C$_5$), 2.71 (t, 2H, -CH_2CO-), 2.90-3.51 (m, 1H, -CH-), 4.30-4.48 (m, 2H, -CH_2-O-), 7.11-7.50 ppm (m, 5H, phenyl ring protons); ms: m/z 176 [M$^+$].
Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.83; H, 6.77.

(4R)-(−)-4-Phenyltetrahydro-2H-pyran-2-one (R)-1b.

This compound was obtained as a colorless oil, bp 161-165° (2 mm/Hg), [lit [7] bp 130-140° (0.02 mm/Hg), $[\alpha]_D^{20}$ = -4.79° (c 1.17, chloroform)]; the spectroscopic data correspond with those of (S)-1b.
Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.83; H, 6.81.

(6S)-(−)-6-Phenyltetrahydro-2H-pyran-2-one (S)-1c.

This compound was obtained as colorless crystals, mp 66-68°; ir (potassium bromide): 1740 (-COO-), 750, 690 cm^{-1} (phenyl ring); ^{1}H nmr (deuteriochloroform): δ 1.76-2.06 (m, 4H, -CH_2- of -C$_4$ + -C$_5$), 2.46-2.78 (m, 2H, -CH_2- of -C$_2$), 5.20-5.51 (m, 1H, -CH-), 7.23-7.40 ppm (m, 5H, phenyl ring protons); ms: m/z 176 [M$^+$].
Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.08; H, 6.95.

(6R)-(+)-6-Phenyltetrahydro-2H-pyran-2-one (R)-1c.

This compound was obtained as colorless crystals, mp 65-68°; the spectroscopic data correspond with those of (S)- 1c.
Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.81; H, 6.77.

Methyl (5S)-(+)-5-(p-Bromobenzoyloxy)-5-phenylpentanoate (S)-1d.

The solution of 5-hydroxy-5-phenylpentanoic acid (S)-2c {entry 17; ee 55%, 0.35 g (1.80 mmoles)} in methanol (10 ml) was added at 0° to an ether solution (50 ml) of diazomethane prepared from nitrosomethylurea (3.0 g) and 50% potassium hydroxide aqueous solution (10 ml). After stirring for 4 hours at 0–5°, the resulting ether solution was successively washed with water, a saturated sodium hydrogen carbonate aqueous solution and water, dried over anhydrous magnesium sulfate and evaporated to dryness at reduced pressure. The residue was chromatographed on silica gel (chloroform) to afford methyl (5S)-(−)-5-hydroxy-5-phenylpentanoate (colorless oil, yield 95%); ^{1}H nmr (deuteriochloroform): δ 1.50-1.82 (m, 4H, -CH_2-), 2.23 (t, 2H, -CH_2CO-), 2.82-2.95 (m, 1H, -CH-OH), 3.56 (s, 3H, -CH_3), 4.51 (br-s, 1H, -OH), 7.12-7.33 ppm (m, 5H, Ar-H).

To a mixture of methyl (5S)-(−) 5-hydroxy-5-phenylpentanoate (0.153 g, 0.74 mmole), dry pyridine (4 ml) and 4-dimethylaminopyridine (0.02 g, 0.16 mmole) was added p-bromobenzoyl chloride (0.486 g, 2.22 mmoles) at 0°. After stirring for 20 hours at room temperature and for an additional 4 hours at 60°, benzene was added to the mixture (100 ml). After the resulting pale yellow crystals (pyridine hydrobromide) were removed by filtration, the benzene layer was washed with 10%

copper(II) sulphate aqueous solution (100 ml), dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (benzene) to afford (S)-1d, colorless oil, yield 53%; ir (neat): 1720 (ester), 760, 690 cm^{-1} (phenyl ring); ^{1}H nmr (deuteriochloroform): δ 1.46-2.21 (m, 4H, -CH_2-), 2.34 (t, 2H, -CH_2CO-), 3.62 (s, 3H, -CH_3), 5.97 (t, 1H, -CH-), 7.15-7.43 (m, 5H, phenyl ring protons), 7.52 (d, 2H, protons on 3 and 5 positions of benzoyl ring), 7.89 ppm (d, 2H, protons on 2 and 6 positions of benzoyl ring); ms: m/z 391[M$^+$].

Anal. Calcd. for C$_{19}$H$_{19}$BrO$_4$: C, 58.33; H, 4.89. Found: C, 58.41; H, 4.97.

Acknowledgment.

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