A Systematic Study on the Bakers' Yeast Reduction of 2-Oxoalkyl Benzoates and 1-Chloro-2-alkanones

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The bakers' yeast reduction of a series of 2-oxoalkyl arenecarboxylates [$R(C{=}O)CH_2O(C{=}O)C_6H_4$-*p*-X] (**1a**—**f**) (R=CH_3 to *n*-C_6H_{13}; X=H) and the phenyl-modified derivatives (**1g**—**l**) (R=*n*-C_5H_{11}, X=OH, CH_3, F, Cl, Br, or I) as well as 1-chloro-2-alkanones $R(C{=}O)CH_2Cl$ (**6a**—**f**) (R=CH_3 to *n*-C_6H_{13}) were systematically investigated. The substrate specificities, configuration and %ee of the reduction products were found to be highly dependent on the length of the alkyl group (R) and the α substituent. Thus, the benzoates **1a**—**f** gave optically active 2-hydroxyalkyl benzoates (**2a**—**f**) (R, configuration, %ee) (**a**: CH_3, *S*, 99; **b**: C_2H_5, *S*, 98; **c**: C_3H_7, *S*, 26; **d**: *n*-C_4H_9, *R*, 55; **e**: *n*-C_5H_{11}, *S*, 15; **f**: *n*-C_6H_{13}, *S*, 63) in 11—91% yields. Among the modification experiments of the phenyl group, **1g**—**l**, the *p*-iodo substituent markedly increased the ee from 15 to 71%, although the yield was rather lowered (22% yield). The reduction of α-chloro ketones **6a**—**f** also gave optically active 1-chloro-2-alkanols (**7a**—**f**) [(R, configuration, %ee) (**a**: CH_3, *S*, 83; **b**: C_2H_5, *S*, 54; **c**: C_3H_7, *R*, 49; **d**: *n*-C_4H_9, *R*, 80; **e**, *n*-C_5H_{11}, *R*, 65; **f**, *n*-C_6H_{13}, *R*, 41)] in 16—69% yields.

For the stereochemical control in a bakers' yeast reduction, a modification of the substrates[1] has been employed as one of the reliable methods.[2] For example, the bakers' yeast reduction of 1-hydroxy-2-alkanones (C_1—C_6) affords (*R*)-1,2-alkanediols,[3] while 2-oxopropyl benzoate gives antipodal (*S*)-2-hydroxypropyl benzoate in high optical purity.[4] The configurational selectivity on the higher homologs of the benzoates has not been reported. If the configurational inversion by benzoylation is ascertained to occur for the higher homologs, the procedure would be simple and useful to control the stereochemistry. Therefore, we report here on a systematical study of the bakers' yeast reduction of a series of 2-oxoalkyl (C_3—C_8) benzoates; we first focussed on the configurational selectivity. Then, improving the optical yield in the reduction of 2-oxoheptyl benzoate was investigated by modifying the phenyl group with a variety of functional groups. In these connections, the yeast reduction of 1-chloro-2-alkanones (C_3—C_8) was also carried out; the results are discussed in comparison with those of the benzoates. We found that the configuration, enantiomeric excess (ee), and chemical yields varied drastically regarding both the length of the alkyl chain and the nature of the functional groups. Such a systematic study would be significant for designing the substrates which are suitable for the bakers' yeast reduction. The resulting chiral 1,2-alkanediol equivalents[5-8] and chlorohydrins[9] have been widely used as versatile synthons in organic synthesis.

Results and Discussion

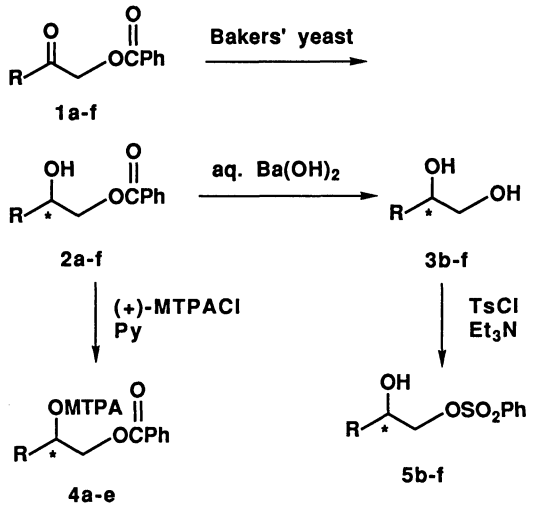
Bakers' Yeast Reduction of 2-Oxoalkyl Benzoates (1a—l). The reduction of **1a**—**l**[10] was carried out using immobilized bakers' yeast,[11] since it simplifies the work-up procedure, and sometimes improves both the

Table 1. Baker's Yeast Reduction of 2-Oxoalkyl Benzoates $R(C{=}O)CH_2O(C{=}O)Ph$ (**1a**—**f**) and Hydrolysis to 1,2-Alkanediols (**3b**—**f**)

1		BY[a]	RCH(OH)CH_2OC(=O)Ph (2)			RCH(OH)CH_2OH (3)
	R		Yield/%	ee/%[b]	Confign	$[\alpha]_D$ (*c*, EtOH)
a	CH_3	A	90	99	*S*[c]	—
a[d]	CH_3	A	65[d]	e)	*S*[f]	—
b	C_2H_5	A	91	98	*S*	−13.7 (2.90)[g]
c	C_3H_7	A	70	26	*S*	−4.73 (2.75)[h]
c	C_3H_7	B	76	57	*S*	—
d	*n*-C_4H_9	A	61	55	*R*	+9.86 (3.09)[i]
d	*n*-C_4H_9	B	62	39	*R*	—
e	*n*-C_5H_{11}	A	34	15	*S*	−3.17 (3.09)[j]
f	*n*-C_6H_{13}	A	11	63[k]	*S*	−9.62 (1.04)[l]

a) A: Oriental Yeast Co.; B: Type 1, Sigma Chemical Co. b) Determined by 500 MHz ^1H NMR measurement after conversion to MTPA ester. c) $[\alpha]_D$ +21.6° (2.96, $CHCl_3$) for **2a**. d) Reported reduction by use of free bakers' yeast (yeast:**1a**=9:1 w/w). The data are cited from the literature (Ref. 4). e) The ee value is not given in Ref. 4. f) $[\alpha]_D$ +21.8° (2.00, $CHCl_3$) for (*S*)-**2a** reported in Ref. 4. g) $[\alpha]_D$ +16.2° (8.0, EtOH) for (*R*)-**3b** reported in Ref. 3a. h) $[\alpha]_D$ +16.2° (8.0, EtOH) for (*R*)-**3c** reported in Ref. 3b. i) $[\alpha]_D$ +15.2° (13.1 EtOH) for (*R*)-**3d** reported in Ref. 3c. j) $[\alpha]_D$ +16.8° (11.7, EtOH) for (*R*)-**3e** reported in Ref. 3d. k) Determined after conversion to the tosylate **5f** (see Table 2). l) $[\alpha]_D$ −18.8° (EtOH) for (*S*)-**3f** reported in Ref. 5b.

chemical and optical yields. The yeast (A) from Oriental Yeast was generally used and comparative experiments were carried out using yeast (B) from Sigma Chemical for **1c** and **1d**, as shown in Table 1. The %ee(s) of 2-hydroxyalkyl benzoates (**2a**—**e**) were determined by 500 MHz ^{1}H NMR measurements after conversion to methoxy(trifluoromethyl)phenylacetic acid (abrev. to MTPA) esters (**4a**—**e**) (Scheme 1). That of **2f** was estimated by conversion to the tosylate **5f**, as described in the following section. The configuration of **2a** was determined by comparing the rotation with that of the reported one;[4] those of **2b**—**f** were assigned by transformations [aq $Ba(OH)_2$] to the authentic 1,2-alkanediols (**3b**—**f**),[3] as shown in Table 1. The ^{1}H NMR (500 MHz) spectra of the MTPA esters **4a**—**e** also sustained the configurational change, showing that the methoxyl groups for (*R*)-enantiomers of **4d** appear at a lower field (δ=3.55) and that for (*S*)-enantiomers at high fields [(**4b**, **4c**, and **4e** (δ = 3.52—3.53)].[12] The benzoates **1a**[4] (R=CH_3) and **1b**



a: R = CH_3, **b**: R = C_2H_5, **c**: R = C_3H_7, **d**: R = n-C_4H_9, **e**: R = n-C_5H_{11}, **f**: R = n-C_6H_{13}

Scheme 1.

(R=C_2H_5) were favorably reduced to (*S*)-**2a** and (*S*)-**2b** with 99%ee (90% yield) and 98%ee (91% yield), respectively. However, an extension of the alkyl chain drastically changed both the ee and the configuration. Thus, the configuration is (*S*) for **2a**—**c** (R=CH_3—C_3H_7), while it is changed to (*R*) at **2d** (R=*n*-C_4H_9), and then returns again to (*S*) at **2e** (R=*n*-C_5H_{11}) with the lowest 15%ee. A further extension to R=*n*-C_6H_{13} (**2f**) raised the ee to 63%, although it lowered the yield to 11%. Yeast B showed a similar configurational change, while increasing the ee of (*S*)-**2c** and slightly decreasing that of (*R*)-**2d**. The advantages of the immobilization technique were exemplified in the case of **1a**, the yield of **2a** being increased from 65[4] to 90%.

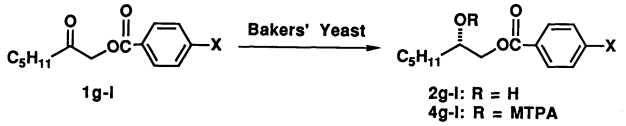
2-Hydroxyalkyl Tosylates (5b—f). In connection to our synthetic project, diols **3b**—**f** were converted to the corresponding 2-hydroxyalkyl tosylates (**5b**—**f**), which had been known to be useful starting materials in organic synthesis.[3g,h,j,7b,13] Therein, we found that the tosylates were quite useful for determining the ee and the configuration by measuring $Eu(hfc)_3$ [hfc=3-(heptafluoropropylhydroxymethylene)-*d*-camphorato)]-induced shifts in ^{1}H NMR (100 MHz) spectra. For example, the ^{1}H NMR spectrum of **5d** (R=*n*-C_4H_9) with 110% mol of $Eu(hfc)_3$ showed that a doublet due to *o*-protons at δ = 7.68 shifted to a lower field, resolving to a couple of doublets at δ=10.10 (*S*) and δ = 10.26 (*R*),[14] both of which were simplified to a couple of singlets [23 (*S*): 77 (*R*), 54%ee] by irradiation of *m*-protons at δ=7.82. The NMR method also supported the configurational changes of **2a**—**f** shown in Table 1. The ee values, thus determined, are listed in Table 2, being consistent with those estimated by the MTPA method (Table 1).

Table 2. Optically Active 2-Hydroxyalkyl Tosylates RCH(OH)CH_2OTs (**5b**—**f**)

5	R	Yield/%[a]	$[\alpha]_D$ (*c*, EtOH)/°	ee/%[b]	Config[c]
b	C_2H_5	43	−2.96 (3.18)	98	*S*
c	C_3H_7	61	−2.36 (2.71)	27	*S*
d	*n*-C_4H_9	42	+2.74 (2.74)	54	*R*
e	*n*-C_5H_{11}	45	−0.80 (2.73)	16	*S*
f	*n*-C_6H_{13}	46	−1.25 (1.55)	63	*S*

a) Yields in tosylation of **3**. b) Determined by ^{1}H NMR (100 MHz) analysis of the phenyl protones in the presence of 100—120 %mol of $Eu(hfc)_3$. c) The configurations determined at the stage of diols **3b**—**f** (Table 1) are shown and the configurational changes are consistent with the sign of the rotations of **5b**—**f** and the ^{1}H NMR analysis.[b]

Optimization of the ee by Functionalization of the Phenyl Group. We then turned our attention to improving the ee of **2e** (R=*n*-C_5H_{11}, 15%ee) by introducing a variety of substituents to the *p*-position of the phenyl group, expecting to modify both the bulkiness and electronic effects (Scheme 2).[1] The results of the yeast reduction of **1g**—**l** are summarized in Table 3.



g: X = OH, **h**: X = CH_3, **i**: X = F, **j**: X = Cl, **k**: X = Br, **l**: X = I

Scheme 2.

The choice of the hydroxyl group markedly increased the yield of **2g** from 34 to 76% without effecting the ee. Interestingly, the halogens, especially the bulkiest iodine, greatly improved the ee from 15 to 71%, although the chemical yield was rather lowered. The increasing order of the ee values was in parallel with that of the bulkiness of halogens.

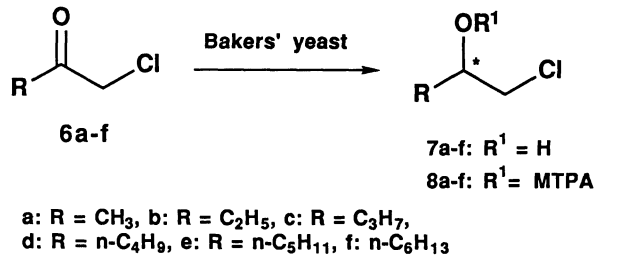
Bakers' Yeast Reduction of 1-Chloro-2-alkanones (6a—f). The reduction of 1-chloro-2-alkanones (**6a**—

Table 3. Bakers' Yeast Reduction of *p*-Substituted 2-Oxoheptyl Benzoates n-$C_5H_{11}(C{=}O)CH_2O(C{=}O)C_6H_4$-*p*-X (**1g—l**)

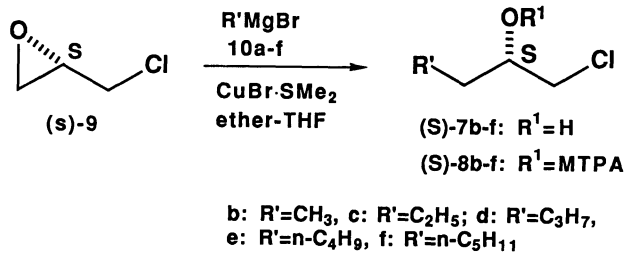
1		2		
	X	Yield/%	ee/%[a)]	Config[a)]
e	H	34	15	*S*
g	OH	76	19	*S*
h	CH_3	20	39	*S*
i	F	36	40	*S*
j	Cl	23	64	*S*
k	Br	17	67	*S*
l	I	22	71	*S*

a) Determined by ^{1}H NMR (500 MHz) spectra, where methoxyl group of the MTPA esters for (*S*) enantiomers always appeared at higher field (3.512—3.517 ppm) than that of (*R*) enantiomers (3.540—3.545 ppm).

f) is shown in Scheme 3 and the results are summarized in Table 6. The %ee(s) of the resulting chlorohydrins (**7a—f**) were determined by ^{1}H NMR (500 MHz) spectra of the MTPA esters (**8a—f**). The configurations of **7a—f** were assigned by comparison of the optical rotations with those of (*R*)-**7a**[9b)] and (*S*)-**7b—f**, the latter of which were prepared independently by the reaction of (*S*)-epichlorohydrin (*S*)-(**9**) with alkylmagnesium bromides (**10b—f**) in the presence of CuBr·SMe_2.[15)] Compounds (*S*)-**7b—f** were further transformed to the MTPA esters (*S*)-**8b—f** (Scheme 4). The variation of



Scheme 3.



Scheme 4.

the configuration and the ee of **2a—f** and **7a—f** is shown graphically in Fig. 1. Interestingly, both chlorohydrins and benzoates have a common inflection point in the variation of ee(s) at R=n-C_4H_9. These irregular changes in the configuration and the ee can not be explained simply by use of the Prelog rule[16)] and may imply that the plural enzymes are concerned in the reduction. For 1-

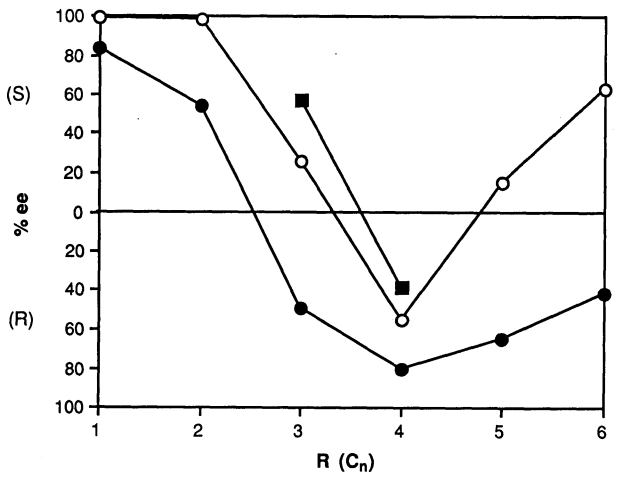


Fig. 1. Variation of the absolute configurations and the %ee values with the length of alkyl chain (R): 2-hydroxyalkyl benzoates (**2a—f**) (yeast A) (—○—); **2c, d** (yeast B) (—■—); 1-chloro-2-alkanols (**7a—f**) (—●—).

chloro-2-heptanone **6e** (R=n-C_5H_{11}), three types of bakers' yeasts (A: immobilized dry bakers' yeast, B: free dry bakers' yeast; C: free pressed bakers' yeast) were examined. The best yield (56%) and the ee (65%) were obtained by use of the immobilization method.

Experimental

Boiling points are not corrected. IR spectra were recorded with a JASCO A-102 spectrometer. ^{1}H NMR spectra were recorded at 60 (JEOL PMX-60SI), 100 (JEOL FX-100), and/or 500 MHz (Varian VXR 500). Purification with a preparative HPLC was performed by using a Hitachi 655 chromatograph. Column chromatography and preparative TLC were carried out by using silica gel (Merck Silica Gel 60 and Silica Gel 60 PF_{254}, respectively). Bakers' yeast (A) was purchased from Oriental Yeast Co., Ltd. (Tokyo). The yeast (B) was obtained from Sigma Chemical Co. (St. Louis). Elemental analysis was performed by E. Amano of this laboratory. Potassium salts of all *p*-substituted benzoic acids are commercially available. In a usual workup, the extract was washed with brine, dried over $MgSO_4$, and then concentrated with a rotary evaporator.

***t*-Butyl 2-Chloro-3-oxoalkanoates**[10)] were prepared by chlorination (SO_2Cl_2 in dichloromethane)[17)] of the corresponding t-butyl 3-oxoalkanoates, which were obtained by γ-alkylation of dianion of *t*-butyl 3-oxobutanoate.[18)]

***t*-Butyl 2-Chloro-3-oxopentanoate:** 76% yield; bp 80—85 °C [21 mm Hg (1 mmHg≈133.322 Pa)]; IR (neat) 1760, 1740, 1660, 1635 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.10 (3H, t, J=7 Hz), 1.48 (9H, s), 2.67 (2H, q, J=7 Hz), 4.48 (1H, s). Anal Calcd for $C_9H_{15}ClO_3$: C, 52.31; H, 7.31%. Found: C, 52.34; H, 7.42%.

***t*-Butyl 2-Chloro-3-oxohexanoate:** 73% yield; bp 74—78 °C (3 mmHg); IR (neat) 1760, 1735, 1640, 1620 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.93 (3H, t, J=7 Hz), 1.47 (9H, s), 1.45—1.90 (2H, m), 2.61 (2H, t, J=7 Hz), 4.46 (1H, s). Anal. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.76%. Found: C, 54.46; H, 7.54%.

***t*-Butyl 2-Chloro-3-oxoheptanoate:** 75% yield; bp 74—78 °C (3 mmHg); IR (neat) 1760, 1735, 1635, 1610 cm^{-1}; ^1H NMR (CCl_4) δ=0.93 (3H, t, J=7 H), 1.48 (9H, s), 1.05—1.90 (3H, m), 2.63 (2H, t, J=7 Hz), 4.46 (1H, s). Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.16%. Found: C, 56.32; H, 8.12%.

***t*-Butyl 2-Chloro-3-oxooctanoate:** 87% yield; bp 98—107 °C (3 mmHg); IR (neat) 1760, 1730, 1640, 1610 cm^{-1}; ^1H NMR (CCl_4) δ=0.91 (3H, t, J=7 Hz), 1.45 (9H, s), 1.10—1.90 (6H, m), 2.60 (2H, t, J=7 Hz), 4.43 (1H, s). Anal. Calcd for $C_{12}H_{21}ClO_3$: C, 57.94; H, 8.51%. Found: C, 58.16; H, 8.56%.

***t*-Butyl 2-Chloro-3-oxononanoate:** 69% yield; bp 110—116 °C (3 mmHg); IR (neat) 1760, 1735, 1640, 1612 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (3H, t, J=7 Hz), 1.45 (9H, s), 1.05—1.90 (8H, m), 2.60 (2H, t, J=7 Hz), 4.43 (1H, s). Anal. Calcd for $C_{13}H_{23}ClO_3$: C, 59.42; H, 8.82%. Found: C, 59.44; H, 8.63%.

General Procedure for the Preparation of 1-Chloro-2-alkanones (6b—f).[10] A mixture of chloro ester (20 mmol), *p*-toluenesulfonic acid (4 mmol), and benzene (20 ml) was heated under reflux for 3 h. After being neutralized with aqueous $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The usual treatment followed by distillation gave α-chloro ketone. The spectral data, which are not given in the literatures, are shown below.

1-Chloro-2-butanone (6b):[19a] 61% yield; IR (neat) 1735 cm^{-1}; ^1H NMR (CCl_4) δ=1.06 (3H, t, J=7.5 Hz), 2.61 (2H, q, J=7.5 Hz), 3.91 (2H, s).

1-Chloro-2-pentanone (6c):[10] 83% yield; bp 78—81 °C (45 mmHg); IR (neat) 1736 cm^{-1}; ^1H NMR (CCl_4) δ=0.93 (3H, t, J=7 Hz), 1.2—1.8 (2H, m), 2.55 (2H, t, J=7 Hz), 3.90 (2H, s).

1-Chloro-2-hexanone (6d):[19b] 73% yield; bp 65—67 °C (18 mmHg); IR (neat) 1738 cm^{-1}; ^1H NMR (CCl_4) δ=0.92 (3 H, t, J=7 Hz), 1.1—1.9 (4H, m), 2.57 (2H, t, J=7 Hz), 3.90 (2H, s).

1-Chloro-2-heptanone (6e):[19c] 73% yield; bp 82—88 °C (18 mmHg); IR (neat) 1738 cm^{-1}; ^1H NMR (CCl_4) δ=0.93 (3H, t, J=7 Hz), 1.1—1.9 (6H, m), 2.60 (2H, t, J=7 Hz), 3.90 (2H, s).

1-Chloro-2-octanone (6f):[19d] 71% yield; bp 95—102 °C (20 mmHg); IR (neat) 1738 cm^{-1}; ^1H NMR (CCl_4) δ=0.93 (3H, t, J=7 Hz), 1.1—1.9 (8H, m), 2.56 (2H, t, J=7 Hz), 3.90 (2H, s).

General Procedure for the Preparation of 2-Oxoalkyl Arenecarboxylates (1a—l). A mixture of chloro ketone (15 mmol), sodium benzoate or potassium salt of *p*-substituted benzoic acid (15 mmol), tetrabutylammonium bromide (241 mg, 0.75 mmol), and benzene (20 ml) was heated under reflux for 3 h. After filtration of the mixture, the benzene layer was washed with aqueous $NaHCO_3$. The aqueous layer was extracted with dichloromethane which was treated in a usual manner. The residual oil was subjected to bulb-to-bulb distillation. The yields and spectral data are shown in Table 4.

Preparation of Immobilized Bakers' Yeast. The procedure followed that reported previously.[11b,c] A suspension of sodium alginate (20 g), bakers' yeast (80 g) in water (1 L) was dropped through a dropping funnel into 2.3 L of 10% aqueous $CaCl_2 \cdot H_2O$ to form ca. 1040 ml of immobilized yeast beads with 3—4 mm in diameter.

General Procedure for the Bakers' Yeast Reduction of 1a—l. A) Immobilization Method: To a mixture of the immobilized bakers' yeast (78 ml of beads including 6 g of bakers' yeast), glucose (20 g) and boiled water (150 ml) was stirred at 35 °C for 30 min, until brisk fermentation of the yeast was confirmed by observation of rising up of the beads to the surface. 2-Oxoalkyl arenecarboxylate (2 mmol) was added and the mixture was stirred at the temperature. Glucose (20 g after 15 h and 10 g after 30 h) was added and the stirring was

Table 4. 2-Oxoalkyl Arenecarboxylates (**1b—l**)

1	Yield[a]	IR (neat)	^1H NMR (CCl_4)/δ	Anal. Found (Calcd)
	%	cm^{-1}		%
b[b]	82	1740, 1725, 1600, 1585	1.10 (s, 3H), 4.70 (s, 2H), 7.1—8.2 (m, 5H)	b)
c	72	1740, 1725, 1600, 1583	1.08 (t, 3H, J=7 Hz), 2.45 (q, 2H, J=7 Hz), 4.71 (s, 2H), 7.2—8.3 (m, 5H)	C, 69.75; H, 6.92 (C, 69.89; H, 6.84)
d[b]	78	1740, 1725, 1600, 1585	0.91 (t, 3H, J=7.5 Hz), 1.2—2.0 (m, 2H), 2.0—2.8 (m, 2H), 4.71 (s, 2H), 7.1—8.3 (m, 5H)	b)
e[c]	77	1740, 1720, 1600, 1580	0.91 (t, 3H, J=7.5 Hz), 1.1—2.0 (m, 6H), 2.43 (t, 2H, J=7 Hz), 4.71 (s, 2H), 7.2—7.7 (m, 3H), 7.7—8.3 (m, 2H)	c)
f	72	1735, 1720, 1600, 1580	0.90 (t, 3H, J=7.5 Hz), 1.1—1.9 (m, 8H), 2.40 (t, 2H, J=7 Hz), 4.71 (s, 2H), 7.1—7.6 (m, 3H), 7.7—8.1 (m, 2H)	b)
g	60	1730, 1680, 1610, 1590	0.88 (t, 3H, J=7 Hz), 1.0—1.9 (m, 6H), 1.87 (brs, 1H), 2.47 (t, 2H, J=7 Hz), 4.82 (s, 2H), 6.74, 7.84 (d each, 2H, J=7 Hz)	C, 65.66; H, 7.57 (C, 65.53; H, 7.61)
h	86	1740, 1725, 1615, 1580	0.89 (t, 3H, J=7 Hz), 1.0—1.9 (m, 6H), 2.39 (s, 3H), 2.39 (t, 2H, J=7 Hz), 4.67 (s, 2H), 7.10, 7.82 (d each, 2H, J=7 Hz)	C, 72.58; H, 8.06 (C, 72.55; H, 8.12)
i	78	1730, 1605	0.90 (t, 3H, J=7 Hz), 1.0—2.0 (m, 6H), 2.40 (t, 2H, J=7 Hz), 4.70 (s, 2H), 6.8—7.3, 7.8-8.3 (m, 4H)	C, 66.28; H, 7.61 (C, 66.12; H, 7.53)
j	83	1725, 1600	0.89 (t, 3H, J=7 Hz), 1.0—2.0 (m, 6H), 2.39 (t, 2H, J=7 Hz), 4.69 (s, 2H), 7.29, 7.88 (d each, 2H, J=7 Hz)	C, 62.37; H, 6.23 (C, 62.57; H, 6.38)
k	76	1740, 1720, 1595	0.89 (t, 3H, J=7 Hz), 1.0—1.9 (m, 6H), 2.39 (t, 2H, J=7 Hz), 4.69 (s, 2H), 7.50, 7.86 (d, each, 2H, J=7 Hz)	C, 53.81; H, 5.46 (C, 53.69; H, 5.47)
l	69	1750, 1740, 1595	0.89 (t, 3H, J=7 Hz), 1.0—1.9 (m, 6H), 2.40 (t, 2H, J=7 Hz), 4.70 (s, 2H), 7.50, 7.72 (s, 4H)	C, 46.77; H, 4.66 (C, 46.68; H, 4.76)

a) Yield after distillation. **2b**: bp 138°C (8 mmHg), **2c**: bp 115—117°C (2.5 mmHg); **2d**: bp 131—134°C (2 mmHg); **2e**: bp 140—145°C (0.2 mmHg); **2f**: bp 128—130°C (0.2 mmHg). Others were purified by column chromatography on silica gel (hexane–ethyl acetate). b) T. Sakai, K. Seko, A. Tsuji, M. Utaka, and A. Takeda, *J. Org. Chem.*, **47**, 1101 (1982). c) J. F. Peyrond, J. C. Fiaud, and H. B. Kagan, *J. Chem. Res. Synop.*, **1980**, 320.

Table 5. 2-Hydroxyalkyl Arenecarboxylates (**2b**—**l**)

2	IR	^{1}H NMR ($CDCl_3$)/δ	Anal. Found (Calcd)
	cm^{-1}		%
b[a]	3480, 1720, 1600, 1580	0.98 (t, 3H, J=7 Hz), 1.78 (q, 2H, J=7 Hz), 2.98 (br, s, 1H, OH), 3.50—4.00 (m, 1H), 4.00—4.38 (m, 2H), 7.1—8.2 (m, 5H)	a)
c	3440, 1720, 1600, 1583	0.6—1.1 (m, 3H), 1.1—2.0 (m, 4H), 2.52 (br s, 1H, OH), 3.6—4.0 (m, 1H), 4.0—4.5 (m, 2H), 7.0—8.2 (m, 2H)	C, 69.48; H, 7.86 (C, 69.21; H, 7.74)
d[b]	3460, 1725, 1601, 1583	0.7—1.1 (m, 3H), 1.1—1.9 (m, 6H), 2.49 (s, 1H, OH), 3.6—4.0 (m, 1H), 4.0—4.5 (m, 2H), 7.1—8.2 (m, 2H)	b)
e[c]	3450, 1720, 1600, 1580	0.7—1.1 (m, 3H), 1.1—1.8 (m, 8H), 2.35 (s, 1H, OH), 3.6—4.0 (m, 1H), 4.0—4.5 (m, 2H), 7.1—8.2 (m, 5H)	c)
f	3450, 1720, 1600, 1580	0.7—1.1 (m, 3H), 1.1—1.7 (m, 10H), 2.83 (s, 1H, OH), 3.5—4.0 (m, 1H), 4.0—4.3 (m, 2H), 7.1—8.2 (m, 5H)	C, 71.89; H, 7.88 (C, 71.97; H, 8.86)
g	3450, 1700, 1680, 1600	0.90 (t, 3H, J=7 Hz), 1.0—1.8 (m, 6H), 3.6—4.1 (m, 1H), 4.1—4.4 (m, 2H), 4.58 (2H, OH), 6.83, 7.92 (d each, 2H, J=7 Hz)	C, 66.88; H, 9.92 (C, 66.65; H, 7.79)
h	3450, 1715, 1605	0.90 (t, 3H, J=7 Hz), 1.0—1.8 (m, 6H), 2.38 (s, 1H), 2.55 (brs, 1H), 3.6—4.0 (m, 1H), 4.0—4.4 (m, 2H), 7.08, 7.81 (d each, 2H, J=2 Hz)	C, 71.89; H, 8.91 (C, 71.97; H, 8.86)
i	3370, 1735, 1720, 1612	0.90 (t, 3H, J=7 Hz), 1.0—1.8 (m, 6H), 2.09 (brs, 1H), 3.5—4.0 (m, 1H), 4.0—4.4 (m, 2H), 6.8—7.3, 7.8—8.2 (m, 4H)	C, 71.98; H, 9.04 (C, 71.83; H, 9.04)
j	3450, 1720, 1705, 1590	0.90 (t, 3H, J=7 Hz), 1.0—1.8 (m, 6H), 1.98 (brs, 1H), 3.5—4.0 (m, 1H), 4.0—4.4 (m, 2H), 7.31, 7.88 (d each, 2H, J=7 Hz)	C, 62.16; H, 7.01 (C, 62.11; H, 7.07)
k	3410, 1720, 1695, 1597	0.90 (t, 3H, J=7 Hz), 1.0—1.8 (m, 6H), 2.29 (brs, 1H), 3.5—4.0 (m, 1H), 4.0—4.4 (m, 2H), 7.43, 7.78 (d each, 2H, J=7 Hz)	C, 53.12; H, 6.04 (C, 53.35; H, 6.08)
l	3530, 1720, 1690, 1580	0.91 (t, 3H, J=7 Hz), 1.0—1.8 (m, 6H), 1.77 (brs, 1H), 3.6—4.0 (m, 1H), 4.0—4.4 (m, 2H), 7.70 (s, 4H)	C, 46.49; H, 5.32 (C, 46.43; H, 5.29)

a) H. Hintzer, B. Koppenhoeter, and V. Scharig, *J. Org. Chem.*, **47**, 3850 (1982). b) A. Katzakian, Jr. and R. E. Steele, Fr. Patent 1517867 (1968); *Chem. Abstr.*, **70**, P97590y (1969). c) See Ref. c in Table 4.

continued for 72 h in all. The combined ethyl acetate extracts both from the aqueous layer and from the beads were treated in a usual manner[11b,c] and the crude product was purified by column chromatography (hexane:ethyl acetate, 20—30 : 1) and/or preparative TLC (hexane-ether, 3 : 1) to give the corresponding 2-hydroxyalkyl arenecarboxylates **2a**—**l**. The IR and ^{1}H NMR spectral data are listed in Table 5.

Free Bakers' Yeast Method: Fermentation was carried out with the same quantity of free bakers' yeast and the work-up procvedure was essentially the same as that described in the foregoing experiment.

General Procedure for the Preparation of 1,2-Alkanediols (3b—f). A mixture of 2-hydroxyalkyl arenecarboxylate (3 mmol), $Ba(OH)_2$ (529 mg, 3 mmol), and 6 ml of water-ethanol (1 : 1) was stirred at 85 °C for 3 h. Use of $Ba(OH)_2$ instead of NaOH simplified the work-up procedure due to the low solubility of the resulting barium benzoate in the reaction media. Thus, the reaction progress can be observed by formation of barium benzoate as precipitates, which were removed by filtration after being cooled in an ice-bath. The filtrate was saturated with NaCl and extracted with several portions of 10 ml of ether. Usual workup followed by purification with preparative TLC (hexane–EtOAc–ether–ethanol, 6 : 2 : 2 : 1) and further vacuum distillation gave 1,2-alkanediol. The values of optical rotation are listed in Table 1 and the spectral data, which were not reported in the literatures, are shown below.

(*S*)-(—)-1,2-Butanediol (3b):[3a] 68% yield; bp 125—135 °C (27 mmHg); IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.95 (3H, t, J=7 Hz), 1.2—1.8 (2H, m), 3.1—3.85 (3H, m), 4.06 (2H, br s, 2OH).

(*S*)-(—)-1,2-Pentanediol (3c):[3b] 76% yield; bp 130—140 °C (11 mmHg); IR (neat) 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.7—1.2 (3H, m), 1.2—1.8 (4H, m), 3.1—3.9 (3H, m), 4.02 (2H, br s, 2OH).

(*R*)-(+)-1,2-Hexanediol (3d):[3c] 56% yield; bp 150—160 °C (20 mmHg); IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.7—1.1 (3H, m), 1.1—1.8 (6H, m), 3.0—3.8 (3H, m), 4.42 (2H, s, 2OH).

(*S*)-(—)-1,2-Heptanediol (3e):[3d] 58% yield; bp 140—145 °C (13 mmHg); IR (neat) 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.6—1.1 (3H, m), 1.1—1.8 (8H, m), 3.0—3.8 (3H, m), 4.42 (2H, s, 2OH).

(*S*)-(—)-1,2-Octanediol (3f):[5b] 56% yield; bp 145—155 °C (5 mmHg); IR (neat) 3380 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.6—1.1 (3H, m), 1.1—1.8 (10H, m), 3.0—3.8 (3H, m), 4.42 (2H, s, 2OH).

General Procedure for the Preparation of MTPA Esters (4a—l).[20] A solution of pyridine (0.15 ml) in dichloromethane (0.1 ml) was added to a solution of **2a**—**l** (0.02 mmol) (exception of **2f**) and (*R*)-(+)-methoxy(trifluoromethyl)phenylacetyl chloride (10.8 mg, 0.04 mmol) in dichloromethane (3 ml) at ice bath temperature. After being stirred for 24 h at room temperature, the mixture was treated in a usual manner.[20] The crude product was purified by column chromatography on silica gel (hexane : acetone 20—10:1) to give esters **4a**—**l** in 80—93% yields. ^{1}H NMR data of **4a** and **4b** as well as the partial data of OCH_3 for **4c**—**e** are shown below. Those of **4g**—**l** are consistent with these data as indicated at the footnote in Table 3.

4a: δ=1.45 (3H, d, J=6.5 Hz), 3.54 (3H, s, OCH_3), 4.33 (1H, dd, J=7.5, 12.0 Hz), 4.43 (1H, dd, J=3.0, 12.0 Hz), 5.53—5.62 (1H, m), 7.2—8.0 (5H, m).

4b: δ=1.03 (3H, t, J=7.5 Hz), 3.53 [for (*S*)] and 3.55 [for (*R*)] [s, 3H (99 : 1)], 4.35 (1H, dd, J=7.5, 12.0 Hz), 4.48 (1H, dd, J=3.0, 12.0 Hz), 5.40—5.48 (1H, m), 7.2—8.0 (5H, m).

4c: δ=3.52 [for (*S*)], 3.54 [for (*R*)] (63 : 37).
4d: δ=3.52 [for (*S*)], 3.55 [for (*R*)] (22.5 : 77.5).
4e: δ=3.52 [for (*S*)], 3.55 [for (*R*)] (57.5 : 42.5).

General Procedure for the Preparation of 2-Hydroxyalkyl Tosylates (5b—f). To a solution of *p*-toluenesulfonyl chloride (0.321 g, 1.68 mmol) in dichloromethane (5 ml) was added diols **3b—f** (1.65 mmol) and pyridine (0.25 ml) subsequently at 0 °C. After being stirred for 12 h at room temperature, the mixture was acidified with 10% HCl. The organic layer was extracted with ether and treated in a usual manner. The residual oil was purified by preparative TLC (hexane–ethyl acetate, 2 : 1) to give tosylates **5b—f**. The spectral data, which are not given in the literatures, are shown below.

(*S*)-(−)-2-Hydroxybutyl Tosylate (5b):[13c] 43% yield; IR (neat) 3350, 1600 cm^{-1}; ^{1}H NMR (CCl4) δ=0.92 (3H, t, *J*=7 Hz), 1.1—1.8 (2H, m), 2.10 (1H, br s, OH), 2.45 (3H, s), 3.5—4.1 (3H, m), 7.28 (2H, d, *J*=8 Hz), 7.25 (2H, d, *J*=7 Hz).

(*S*)-(−)-2-Hydroxypentyl Tosylate (5c): 48% yield; IR (neat) 3350, 1600 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.7—1.1 (3H, m), 1.1—1.6 (4H, m), 2.41 (3H, s), 2.73 (1H, s, OH), 3.6—4.0 (3H, m), 7.25 (2H, d, *J*=8 Hz), 7.72 (2H, d, *J*=8 Hz). Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.79; H, 7.02%. Found: C, 55.84; H, 7.05%.

(*R*)-(+)-2-Hydroxyhexyl Tosylate (5d):[13d] 42% yield; IR (neat) 3350, 1600 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.6—1.1 (3H, m), 1.1—1.6 (6H, m), 2.43 (3H, s), 2.62 (1H, s, OH), 3.6—4.0 (3H, m), 7.23 (2H, d, *J*=8 Hz), 7.58 (2H, d, *J*=8 Hz).

(*S*)-(−)-2-Hydroxyheptyl Tosylate (5e):[13e] 45% yield; IR (neat) 3350, 1598 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.7—1.1 (3H, m), 1.1—1.6 (8H, m), 2.20 (1H, s, OH), 2.43 (3H, s), 3.6—4.1 (3H, m), 7.25 (2H, d, *J*=8 Hz), 7.72 (2H, d, *J*=8 Hz).

(*S*)-(−)-2-Hydroxyoctyl Tosylate (5f): 46% yield; IR (neat) 3350, 1600 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.7—1.1 (3H, m), 1.1—1.6 (10H, m), 2.00 (1H, s, OH), 2.43 (3H, s), 3.6—4.1 (3H, m), 7.25 (2H, d, *J*=8 Hz), 7.72 (2H, d, *J*=8 Hz). Anal. Calcd for $C_{15}H_{24}O_4S$: C, 59.97; H, 8.05%. Found: C, 59.86; H, 8.07%.

^{1}H NMR Analysis of Tosylates (5b—f) in the Presence of Eu(hfc)$_3$. ^{1}H NMR (100 MHz) spectra of the tosylates **5b—f** was recorded in the presence of Eu(hfc)$_3$ and the %ee(s) were calculated on the basis of the resolution of *m*-protons of the phenyl group under the irradiation of *o*-protons. Compound, %mol of the shift reagent, and the chemical shifts (δ) of *m*-protons (configuration, intensity) are as follows: **5b**, 100, 9.87 (*S*, 99), 10.15 (*R*, 1); **5c**, 120, 10.70 (*S*, 63.5), 10.84 (*R*, 36.5); **5d**, 110, 10.10 (*S*, 23), 10.26 (*R*, 77); **5e**, 110, 10.04 (58), 10.21 (42); **5f**, 110, 10.01 (*S*, 81.5), 10.19 (*R*, 18.5). The %ee(S) thus determined are shown in Table 2. The errors on the integration ratio due to the irradiation seem to be negligible as compared with the results obtained by the MTPA method (Table 1).

(±)-2-Hydroxyhexyl Benzoate [(±)-2d].[14] To a solution of **1d** (383 mg, 1.74 mmol) in ethanol (3 ml) was added $NaBH_4$ (25 mg, 0.656 mmol) at room temperature. After being stirred for 10 min at the temperature, the mixture was acidified with 10% HCl and extracted with ether. Usual work-up followed by purification by column chromatography (hexane : EtOAc 20 : 1) gave (±)-**2d** [192 mg, 50% yield, R_f 0.55—0.68 (hexane : EtOAc 3 : 1)] and (±)-1-(hydroxymethyl)pentyl benzoate (117 mg, 30% yield, R_f 0.41—0.55): IR (neat) 3450, 1720, 1600, 1582 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.7—1.1 (3H, m), 1.1—2.0 (6H, m), 2.98 (1H, br s, OH), 3.68 (2H, d, *J*=7 Hz), 4.7—5.3 (1H, m), 7.1—7.7 (3H, m), 7.7—8.2 (2H, m). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%. Found: C, 70.36; H, 8.04%. Compound (±)-**2d** was transformed to (±)-**5d** in a similar way to that for **5b—f**.

Bakers' Yeast Reduction of 1-Chloro-2-alkanones (6a—f). The experimental procedures are similar to those described for **1a—l**. The rotation values are shown in Table 6 and ^{1}H NMR data, which are not given in the literature,[9] are shown below.

1-Chloro-2-propanol (7a):[9a,b] ^{1}H NMR (CCl_4) δ=1.22 (3H, d, *J*=7 Hz), 3.37 (1H, brs, OH), 3.30—3.80 (m, 3H).

1-Chloro-2-butanol (7b): ^{1}H NMR (CCl_4) δ=0.96 (3H, t, *J*=7 Hz), 1.30—1.80 (2H, m), 3.13 (1H, brs, OH), 3.30—3.85 (m, 3H).

1-Chloro-2-pentanol (7c): ^{1}H NMR ($CDCl_3$) δ=0.70—1.90 (7H, m), 1.96 (brs, 1H, OH), 3.41—3.56 (2H, m), 3.33—4.11 (1H, m).

1-Chloro-2-hexanol (7d): ^{1}H NMR ($CDCl_3$) δ=0.70—1.88 (9H, m), 1.05 (1H, brs, OH), 3.39—3.59 (2H, m), 3.59—4.00 (1H, m).

1-Chloro-2-heptanol (7e): ^{1}H NMR (CCl_4) δ=0.70—2.85 (11H, m), 3.43 (1H, brs, OH), 3.30—3.95 (3H, m).

1-Chloro-2-octanaol (7f):[9d] ^{1}H NMR ($CDCl_3$) δ=0.79—1.90 (13H, m), 1.90 (1H, brs, OH), 3.48—3.59 (2H, m), 3.59—3.95 (1H, m).

MTPA Esters (8a—f) Prepared from 1-Chloro-2-alkanols

Table 6. Optically Active 1-Chloro-2-alkanols (**7a-f**)

6		Bakers' Yeast[a]	**7** (B. Y. Product)				(*S*)-**7** (from (*S*)-**9**)	
	R		Yield/%	e.e./%[b]	Config.[c]	$[\alpha]_D$ (*c*, $CHCl_3$)/°	Config.	$[\alpha]_D$ (*c*, $CHCl_3$)/°
a	CH_3	A	20	83	*S*	+15.5 (3.5)	*R*[d]	−19.19 (5.17)[d]
b	C_2H_5	A	67	54	*S*	+6.8 (1.4)	*S*	+9.7 (2.6)
c	*n*-C_3H_7	A	62	49	*R*	−0.6 (2.0)	*S*	+1.1 (2.9)
d	*n*-C_4H_9	A	69	80	*R*	−1.1 (2.0)	*S*	+1.3 (3.8)
e	*n*-C_5H_{11}	A	56	65	*R*	−1.3 (1.8)[e]	—	+1.8 (3.5)
e	*n*-C_5H_{11}	B	12	63	*R*	—	—	—
e	*n*-C_5H_{11}	C	38	38	*R*	—	*S*	—
f	*n*-C_6H_{11}	A	16	41	*R*	−0.6 (5.0)[f] [+5.2 (5.0, MeOH)][g]	*S*	+1.4 (3.1) [−13.4 (3.0, MeOH)][g]

a) A: Immobilized dry bakers' yeast; B: Free dry bakers' yeast; C: Free pressed bakers' yeast. b) Determined by 500 MHz ^{1}H NMR of MTPA ester. c) Assigned by comparison of the rotations with those of (*S*)-**7a—f** and of the 500 MHz ^{1}H NMR chemical sifts of the MTPA esters with those of (*S*)-**8a—f**. d) The data reported in Ref. 9b. e) $[\alpha]_D$ −12° (MeOH) for (*S*)-**7e** reported in Ref. 9c. f) $[\alpha]_D$ +9.0° (neat) for (*R*)-**7f** (99% ee) reported in Ref. 9e. g) The value of the $[\alpha]_D$ for **7f** in chloroform is so small that it was recorded additionally in methanol.

(7a—f). These compounds were prepared in a similar way described above.[20] The ee and the configuration were determined on the basis of the signal intensity of the methoxyl group in 500 MHz ^{1}H NMR spectra [chemical shift (δ) (relative intensity)]. **8a:** 3.56 (91.5%), 3.60 (8.5%); **8b:** 3.55 (77.0%), 3.61 (23.0%); **8c:** 3.55 (25.5%), 3.61 (74.5%); **8d:** 3.55 (10.0%), 3.62 (90.0%); **8e:** 3.55 (17.5%), 3.62 (82.5%); **8f:** 3.55 (29.5%), 3.62 (70.5%).

Typical Preparation of (*S*)-(+)-1-Chloro-2-alkanols (*S*)-(7b—f). Reaction of (*S*)-(+)-Epichlorohydrin (*S*)-(9) with Pentylmagnesium Bromide (10f).[15] Pentylmagnesium bromide prepared from 1-bromopentane (2.26 g, 15 mmol), magnesium turning (364 mg, 0.015 g-atom) in ether (10 ml) was added to a cooled (−30 °C) suspension of copper(II) bromide–dimethyl sulfide (308 mg, 1.5 mmol) in THF (10 ml). The suspension was immediately colored grey. To this was added (*S*)-(+)-epichlorohydrin (1.20 g, 13 mmol) (>98%ee, $[\alpha]_D$+35.0 ° (*c* 3.44, MeOH), supplied by Daiso Co., Ltd., lit,[21] $[\alpha]_D$+33.0 ° (*c* 1.126, MeOH)) dropwise and the resulting black mixture was stirred for 5 h at −30 °C. It was then poured into 10 ml of water and acidified with 10% HCl. The organic phase was separated and the aqueous phase was extracted with ether. The usual treatment of the combined organic layer and the subsequent purification by column chlomatography (hexane : ethyl acetate=10 : 1) and further distillation [bp 150—160 °C (28 mmHg)] gave **7f** (1.35 g, 63% yield): ^{13}C NMR ($CDCl_3$) δ=13.96, 22.49, 25.41, 29.10, 31.63, 34.16, 50.40 (C-1), 71.40 (C-2).

Chlorohydrins **7b—e** were prepared in a similar way: **7b**, 19% yield, bp 140—170 °C (760 mmHg), ^{13}C NMR ($CDCl_3$) δ=9.74, 27.14, 49.54 (C-1), 72.72 (C-2); **7c**, 52% yield, bp 115—125 °C (100 mmHg), ^{13}C NMR ($CDCl_3$) δ=13.82, 18.65, 36.21, 50.36 (C-1), 71.11 (C-2); **7d**, 42% yield, bp 115—120 °C (40 mmHg), ^{13}C NMR ($CDCl_3$) δ=13.90, 22.56, 27.65, 33.93, 50.55 (C-1), 71.48 (C-2); **7e**, 60% yield, bp 130—140 °C (40 mmHg), ^{13}C NMR ($CDCl_3$) δ=13.89, 22.45, 25.11, 31.61, 34.12, 50.38 (C-1), 71.40 (C-2). ^{1}H NMR specra are consistent with those described above. The values of the optical rotation for these compounds are shown in Table 6.

MTPA Esters (*S*)-(8b—f) Prepared from (*S*)-7b—e. These compounds were prepared in a similar way to that described in above experiments. ^{1}H NMR (500 MHz, $CDCl_3$, δ) spectral data for methoxyl group are as follows: **8b:** 3.55; **8c**, 3.55; **8d**, 3.55, **8e**, 3.55, **8f**, 3.55.

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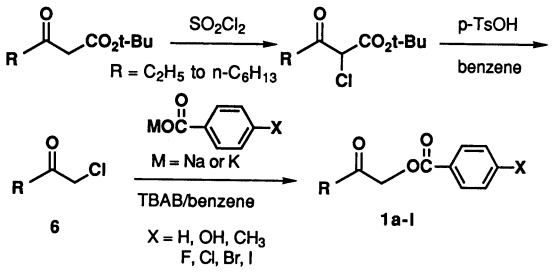

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