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A General Synthetic Method of Chiral 2-Arylalkanoic Esters via Thermal 1,2-Rearrangement[1)]

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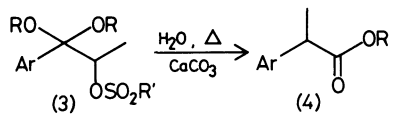
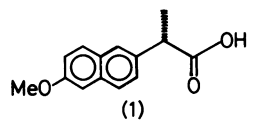
(*S*)-1-Aryl-2-sulfonyloxy-1-alkanone acetals, prepared from natural ethyl (*S*)-lactate or (*S*)-valine (chiral sources) by the use of a Grignard reaction, were rearranged under hydrolytic conditions in the presence of a base to give (*S*)-2-arylalkanoic esters which, in general, showed much higher pharmacological activities than their antipodes.

2-Arylalkanoic acids constitute a group which involves many biologically active compounds. Especially, 2-arylpropanoic acids, such as 2-(6-methoxy-2-naphthyl)propanoic acid (Naproxen, **1**), show potent antiinflammatory activity,[2)] and 2-aryl-3-methylbutanoic acid is known as the acid-moiety of pyrethroid-type insecticides (**2**) (Fig. 1).[3)] These acids have an asymmetric center at C-2, and each (*S*)-enantiomer shows much higher pharmacological activity than its antipode.[4,5)] A typical conventional process for preparing the chiral acid includes an optical resolution of the corresponding racemic derivative using a resolving reagent such as cinchonidine.[6)] However, the optical resolution is disadvantageous from an economical standpoint, since one half of the racemic acid is an unnecessary isomer and complicated racemization steps are required to reuse the antipode.[7)] On the other hand, the process starting from a chiral compound does not require optical resolution as the final step, and is economical compared with the conventional processes.

In these seven years, many investigators have reported syntheses of the racemic 2-arylalkanoic esters by a 1,2-aryl shift. Recently, a general commentary was written by C. Giordano et al.[8)] Previously, we reported that hydrolysis of 1-aryl-2-sulfonyloxy-1-propanone acetals (**3**) afforded 2-arylpropanoic esters (**4**) via 1,2-rearrengement of the aryl group (Eq. 1).[9,10)]



(1)



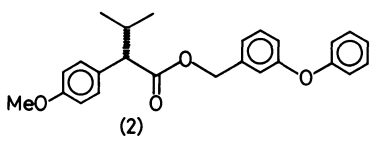
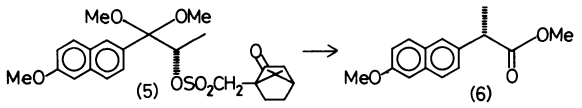


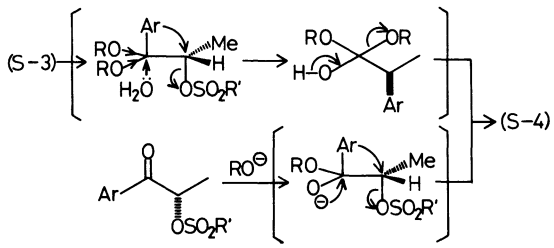
Fig. 1.

Next, optically active (*S*)-sulfonate (**5**), prepared using the optical resolution of (−)-10-camphorsulfonate, afforded (*S*)-2-arylpropanoic esters (**6**) with 100% inversion on the C-2 chiral center (Eq. 2).[11,12)]



(2)

We assume that this rearrangement proceeds through a concerted process which involves a concominant attack of H_2O, a 1,2-aryl shift, and an elimination of the sulfonyloxy group. Thus, it is regarded as a substitution-type rearrangement (Eq. 3),[13-15)] in contrast to the elimination-type (Eq. 4),[16)]



(3)
(4)

such as pinacol, Favorskii, and quasi-Favorskii rearrangements. In the former, one of the driving forces is a push effect by the electron pairs of the oxygen of an acetal oriented antiperiplanar to the migrating group and the attacking nucleophile;[17)] in the latter, an electron pair of oxygen anions plays the role.

Next, we developed a route involving a Friedel-Crafts reaction[1b,13g)] using chiral acyl chlorides (**7**)[18)] and (**8**) derived from (*S*)-lactic acid and ethyl (*S*)-lactate respectively (Fig. 2). In the case of the derivatives which have the aryl group substituted by the alkyl group, (*R*)-α-halogeno ketone (**9**) and (*S*)-α-sulfonyloxy ketone (**10**) were obtained in high yields. However, the regioselectivity of *o*- and *p*-orientation was reduced by electron-donating substituents on the aryl group.[19)] Resulting ketone (**9**) was rearranged by a treatment with silver carbonate and boron trifluoride diethyl etherate in methanol to afford (*R*)-**4**.[13a,k)] On the other hand, ketone (**9**) was treated with sodium

methoxide,[9,20] followed by sulfonylation to afford the partially racemic sulfonate (**3**). Ketone (**10**) was acetalized by a treatment with trimethoxymethane and sulfonic acid, followed by hydrolysis to afford (*S*)-**4**. However, in the case when the β-carbon atom to acetal was secondary, the reaction rate of acetalization was small.[17] Acetalization using trimethylsilyl trifluoromethanesulfonate and 2,2-dimethyl-1,3-bis(trimethylsilyloxy)propane in dichloromethane[21] was accompanied by a little racemization (98% ee).[14b]

Now, we report a general procedure for the synthesis of chiral 2-arylalkanoic esters which overcomes these faults.

Results and Discussion

At first, the synthesis of chiral α-hydroxy ketone was examined by reactions between chiral α-hydroxyalkanoic acid derivatives and organometallic reagents.[22–24] α-Amino acid can be transformed quantitatively into α-hydroxy acid by the Van-Slyke procedure.[25] *O*-Protected alkanamides,[26] for example (*S*)-2-*O*-methoxymethyl- or 2-*O*-(1-ethoxyethyl)-*N*,*N*-dimethyllactamide (**11** or **12**) and (*S*)-2-(1-ethoxyethoxy)-*N*,*N*,3-trimethylbutanamide (**13**), were readily prepared; these were suitable for reactions with organometallic reagents to give the protected α-hydroxy ketones (**14**) in high yields (Fig. 3, Table 1).

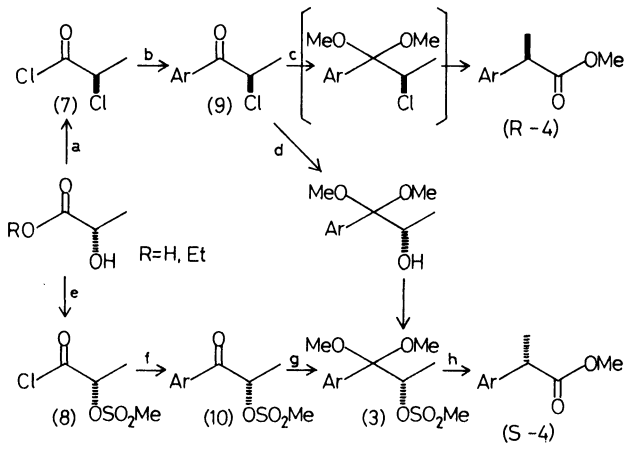


Fig. 2. Friedel–Crafts procedure.
a: 1; $SOCl_2$, pyridine, 2; PhCOCl. b: ArH, $AlCl_3$ in CS_2. c: Ag_2CO_3, BF_3–OEt_2 in MeOH. d: MeONa in MeOH. e: 1; MsCl in pyridine, 2; aq KOH, 3; SO_2Cl_2, pyridine. f: $FeCl_3$ or $FeSO_4$ in $MeNO_2$. h: $CaCO_3$ in MeOH–H_2O.

The ketone (**14**, R=1-ethoxyethyl=EE) was easily deprotected by the treatment with pyridinium *p*-toluenesulfonate (PPTS)[27] in ethanol to give the chiral α-hydroxy ketone (**15**) in a high yield. In the case of the hydrolysis of **14** (R=methoxymethyl=MOM) it was necessary to heat at 60 °C in dilute hydrochloric acid (Fig. 3, Table 1).

The sulfonylation of α-hydroxy ketone (**15**) was easily achieved by the use of methanesulfonyl chloride (MsCl) and triethylamine (Et_3N) at −42 °C[28] to give α-sulfonyloxy ketone (**16**) quantitatively, but the acetalization of **16** was accompanied with the various difficulties described above. Among the number of methods, four procedures were successfully applied

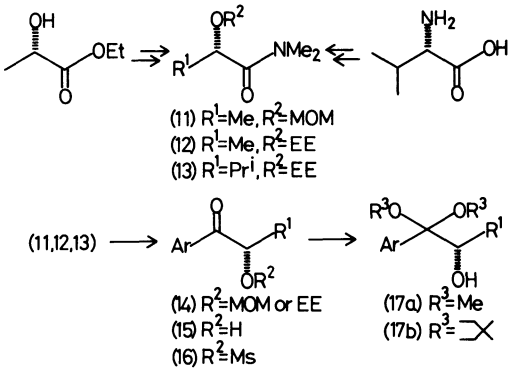
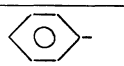
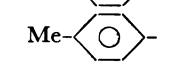
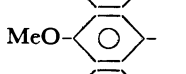
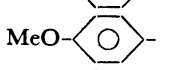
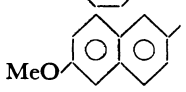


Fig. 3. Synthesis of α-hydroxy acetal (**17**).

Table 1. Synthesis of α-Hydroxy Acetal (**17**)

Run	Ar	R^1	Yield/%							
			14		**15**		**17a**		**17b**	
			R^2=MOM	R^2=EE	from 8 (R^2=MOM)	from 8 (R^2=EE)	Procedure A	Procedure B	Procedure C	Procedure D
1		Me	94	98	96	94	95	93	89	—
2		Me	98	95	93	99	82	87	93	93
3		Me	99	98	93	99	85	57	96	93
4		Pr^i	—	85	—	97	72	—	decompd	57
5		Me	92	99	96	96	96	91	94	100

for the acetalization of **15** without racemization. The α-hydroxy ketone (**15**) was treated with trimethoxymethane (5 equiv) and methanesulfonic acid (1 equiv) in anhydrous methanol[29] at 0 °C to give dimethyl acetal (**17a**) (Procedure A). On the other hand, the ketone (**14**, R=MOM) was treated with the same reagent as in procedure A at 50 °C to give dimethyl acetal (**17a**) in a moderate yield (Procedure B). The α-hydroxy ketone (**15**) was treated with 2,2-dimethyl-1,3-propanediol (10 equiv) and trimethylsilyl chloride (1.5 equiv) in anhydrous methanol[30] to give cyclic acetal (**17b**) in a good yield (Procedure C). Under acidic and dilute conditions in methanol, the reaction proceeded smoothly via internal epoxidation without racemization. Under high-concentration conditions or at high temperature, the dimer (**18** or **18'**) of the epoxide was the major product (Fig. 4). In the presence of a catalytic amount of *p*-toluenesulfonic acid, the reaction using 2,2-dimethyl-1,3-propanediol proceeded with an azeotropic removal of water with benzene under reflux at 50 °C to give cyclic acetal (**17b**) in a high yield (Procedure D). However, in the case when the β-carbon atom to carbonyl was secondary, an elimination of water easily occurred (Table 1, Run 4).

The resulting α-hydroxy acetal (**17**) was sulfonylated by the usual method to give α-sulfonyloxy acetal (**19**) (Fig. 5, Table 2). Since this sulfonate is relatively unstable, it was purified by using short silica-gel column chromatography (dichloromethane).

Sulfonate (**19**) was hydrolyzed by heating in the presence of a base to yield the desired ester (**20**) (Fig. 5, Table 2). The aryl group migrates more preferentially than the alkoxyl group. The cyclic acetal derivative gave a half ester (**20b**) in high yield without any migration of the oxygen of the acetal as the side reaction. This was because the intermediate in migration of the alkoxyl group has a seven-membered ring. The use of sodium acetate increased the reaction rate as compared with the case using calcium carbonate,[8] and enabled the lowering the reaction temperature. As the results, the formation of the by-product, α-methoxy ketone (**21**),[8] decreased in the case of the dimethyl acetal (Table 2, **20a**). The optical purity of the obtained ester was determined to be over 98% by an ^{1}H NMR measurement of methyl ester (**20a**) in the presence of a chiral shift reagent.[31] Half ester (**20b**) was transformed to methyl ester (**20a**) by the acidic ester exchange without racemization.

Consequently, it is concluded that the optical purity of the starting, *N,N*-dimethyl amide remained throughout the rearrangement and the following derivation. If ethyl (*S*)-lactate contained a trace amount of (*R*)-isomer,[32] the optical purity can be increased to 100% by the recrystallization of α-hydroxy ketones (**15**) or sulfonates (**19**). In practice, methyl ester (**20a**) and half ester (**20b**) of Naproxen (Table 2, Run 5) were obtained as a pure form by the recrystallization of α-hydroxy ketone (**15**). In our

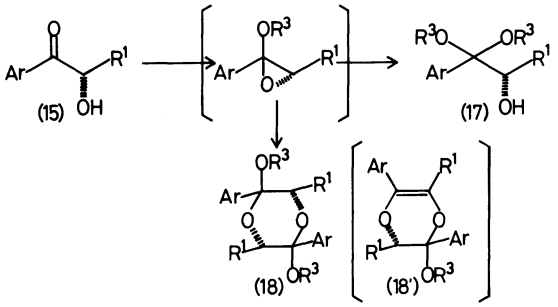


Fig. 4. Acetalization of α-hydroxy ketone (**15**).

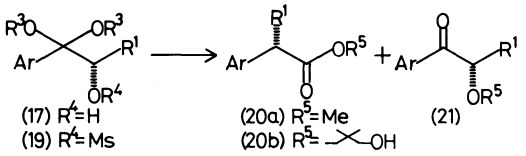
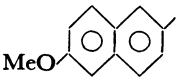


Fig. 5. Thermal 1,2-rearrangement of sulfonate (**19**).

Table 2. Synthesis of α-Aryl Esters (**20**)

Run	Ar	R¹	Yield/%			
			19a	**19b**	**20a**	**20b**
1		Me	88	98	72 (67)[a]	93
2	Me- 	Me	100	100	85	93
3	MeO- 	Me	100	100	97 (93)[a]	92
4	MeO- 	Pr^i	90	94	90	96
5		Me	96	100	97 (94,[a] 89[b])	97

a) $CaCO_3$ (2.0 equiv), 110 °C in $MeOH/H_2O=7/3$. b) $CaCO_3$ (2.0 equiv), 130 °C in $DMF/H_2O=4/1$.

laboratory, methods for obtaining the other chiral sources that are difficult to be derived from natural sources have been studied. For example, an asymmetric hydrolysis by using microorganisms to afford the chiral α-hydroxy ketones has been demonstrated.[33]

Experimental

General. Optical rotation was measured with a Japan Spectroscopic DIS-SL Polarimeter. The ^{1}H NMR spectra were recorded with a Varian EM 390 spectrometer at 90 MHz, the peak position being given in δ values. The IR spectra were recorded with a Japan Spectroscopic A-202 spectrophotometer. Kieselgel F_{254} (Merck), Wakogel C-300 (Wako), and Wacogel B-5F (Wako) were used for TLC, column chromatography, and preparative TLC, respectively.

(*S*)-*N,N*-Dimethyllactamide. According to the literature,[26] a 150-ml Pyrex heavy-walled pressure bottle was charged with ethyl (*S*)-lactate (Aldrich, 20.0 g, 0.169 mmol) and anhydrous dimethylamine (Kodack, 23.0 g, 0.510 mmol) under ice-salt cooling. The bottle was tightly sealed with a steel cap and heated at 70 °C for 60 h with stirring. After cooling, the reaction mixture was concentrated, followed by distillation under reduced pressure to yield 18.5 g (93%) of (*S*)-*N,N*-dimethyllactamide, bp 71—74 °C/0.7 mmHg (1 mmHg=133.322 Pa), $[\alpha]_D^{24}$ +0.85° (*c* 1.01, MeOH), IR (film) 3400, 1660, 1640 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ=1.33 (3H, d, *J*=6.6 Hz, H-3), 3.01 (6H, s, -NMe), 3.8 (1H, broad s, -OH), 4.47 (1H, q, *J*=6.6 Hz, H-2) ppm.

(*S*)-2-*O*-Methoxymethyl-*N,N*-dimethyllactamide (11). Into a suspension of sodium hydride (60% oily, 1.02 g, 25.5 mmol) in THF (30 ml) was added a solution of (*S*)-*N,N*-dimethyllactamide (2.00 g, 17.1 mmol) in THF (7 ml) at 0 °C. The mixture was stirred for 30 min, and then chloromethyl methyl ether (1.67 ml, 22.2 mmol) was added. After 2 h stirring, water (2 ml) was added to form the precipitate. The pH of the decanted supernatant was adjusted 6.5—7.0 by using Na_2CO_3-aqueous $NaHCO_3$. The mixture was dried over Na_2SO_4, concentrated and distilled to give 3.07 g of **11** (82%), bp 102—103 °C/15 mmHg, $[\alpha]_D^{21}$ −95.3° (*c* 1.03, MeOH), IR (film) 1650 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ=1.39 (3H, d, *J*=6.6 Hz, H-3), 2.97 (3H, s, -NMe), 3.07 (3H, s, -NMe), 3.38 (3H, s, -OMe), 4.55 (1H, q, *J*=6.6 Hz, H-2), 4.63 (2H, s, $-OCH_2O-$) ppm.

HRMS; Found: *m/z* 161.1022. Calcd for $C_7H_{15}O_3N$: M$^+$, *m/z* 161.1050.

(*S*)-2-*O*-(1-Ethoxyethyl)-*N,N*-dimethyllactamide (12). Into the mixture of (*S*)-*N,N*-dimethyllactamide (10.0 g, 85.4 mmol) and ethyl vinyl ether (8.2 ml, 128 mmol) in anhydrous dichloromethane (50 ml) was added PPTS (2.15 g, 8.6 mmol) at 0 °C. The mixture was allowed to warm to room temperature. After stirring overnight, solid $NaHCO_3$ (1.1 g) was added, and the mixture was vigorously stirred for 1 h. The reaction mixture was evaporated and the obtained residual syrup that contained salts was purified by flash column chromatography (Wacogel C-300, 50 g, hexane/ethyl acetate=3/1) to give crude **12** (15.8 g). It was distilled to yield pure **12** (15.3 g, 95%); bp 78—80 °C/0.7 mmHg; IR (film) 1660 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ=1.1—1.5 (9H, m, -CMe), 2.96 (s), 3.09 (s), 3.12 (s) (total 6H, -NMe), 3.3—3.9 (2H, m, $-OCH_2C-$), 4.4—4.9 (2H, m, -OCHO- and -CHCO-) ppm.

HRMS; Found: *m/z* 189.1351. Calcd for $C_9H_{19}O_3N$: M$^+$, *m/z* 189.1363.

Methyl (*S*)-2-Hydroxyisovalerate. According to the literature,[25] a solution of sodium nitrite (30 g, 435 mmol) in H_2O (40 ml) was added into a solution of L-valine (25.8 g, 220 mmol) in 2 M† H_2SO_4 (250 ml) over 6 h under ice-cooling. The mixture was stirred for 6 h at 0 °C, and then for 12 h at rt. Furthermore, it was treated with H_2SO_4 (10.6 g, 108 mmol) and sodium nitrite (15 g, 217 mmol) by the above procedure. The reaction mixture was saturated by NaCl, followed by extraction with diethyl ether (100 ml×12). The organic layer was dried over $MgSO_4$ and then concentrated to yield crude (*S*)-2-hydroxyisovaleric acid (25.7 g, 99%) as an oily residue: IR (film) 1730 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ=0.92 (3H, d, *J*=6.9 Hz, H-4), 1.05 (3H, d, *J*=6.9 Hz, H-4′), 1.9—2.3 (1H, m, H-3), 4.11 (1H, d, *J*=3.6 Hz, H-2), 5.77 (2H, broad s, -COOH and -OH) ppm.

The solution of the crude acid (5.00 g, 42.3 mmol) in diethyl ether (10 ml) was treated with diazomethane under ice-cooling to yield methyl (*S*)-2-hydroxyisovalerate (4.50 g, 81%); bp 90—92 °C/70 mmHg, $[\alpha]_D^{32}$ +18.2° (*c* 1.0, $CHCl_3$), IR (film) 3500, 1735 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ=0.86 (3H, d, *J*=6.6 Hz, H-4), 1.01 (3H, d, *J*=6.6 Hz, H-4′), 1.8—2.2 (1H, m, H-3), 2.06 (1H, s, -OH), 3.76 (3H, s, -COOMe), 4.03 (1H, d, *J*=3.6 Hz, H-2) ppm.

HRMS; Found: *m/z* 132.0754. Calcd for $C_6H_{12}O_3$: M$^+$, *m/z* 132.0758.

(*S*)-2-Hydroxy-*N,N*,3-trimethylbutanamide. A 150 ml Pyrex heavy-walled pressure bottle was charged with methyl (*S*)-2-hydroxyisovalerate (4.43 g, 33.5 mmol), 4-dimethylaminopyridine (0.49 g, 3.35 mmol), and anhydrous dimethylamine (6.6 ml, ab. 100 mmol) under ice-salt cooling. The bottle was heated at 70 °C for 110 h, followed by distillation to give (*S*)-2-hydroxy-*N,N*,3-trimethlbutanamide (3.87 g, 80%): bp 59—61 °C/2 mmHg, $[\alpha]_D^{25}$ +38.4° (*c* 0.97, MeOH). ^{1}H NMR ($CDCl_3$) δ=0.73 (3H, d, *J*=6.8 Hz, H-4), 0.94 (3H, d, *J*=6.8 Hz, H-4′), 1.6—1.9 (1H, m, H-3), 2.86 (6H, s, -NMe), 3.19 (1H, d, *J*=7.5 Hz, -OH), 3.93 (1H, dd, *J*=7.5 Hz, *J*=2.9 Hz, H-2) ppm.

HRMS; Found: *m/z* 128.1098. Calcd for $C_7H_{14}ON$: M$^+$−OH, *m/z* 128.1074.

(*S*)-2-(1-Ethoxyethoxy)-*N,N*,3-trimethylbutanamide (13). According to the above procedure, (*S*)-2-hydroxy-*N,N*,3-trimethylbutanamide (3.87 g, 20.67 mmol) was treated with ethyl vinyl ether (3.85 ml) and PPTS (0.72 g) to give **13** (4.35 g, 88%); bp 82—83 °C/2.2 mmHg; IR (film) 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.8—1.4 (12H, m, CMe), 2.95 (3H, s, NMe), 3.13 (3H, s, -NMe), 3.3—3.8 (2H, m, $-OCH_2C-$), 3.85 (d, *J*=8.5 Hz), 4.20 (d, *J*=8.5 Hz) (total 1H, -OCHO-), 4.6—4.8 (1H, m, H-2) ppm.

HRMS; Found: *m/z* 172.1345. Calcd for $C_9H_{18}O_2N$: M$^+$−OEt, *m/z* 172.1337.

General Procedure for a Grignard Reaction with *N,N*-Dimethylalkanamide (11—13) [Synthesis of (*S*)-2-*O*-(Protected hydroxy)ketone (14)]. Into a solution of *N,N*-dimethylamide (**11—13**, 10 mmol) in anhydrous THF (10 ml) under an argon atmosphere, cooled in an ice bath, was added a solution of arylmagnesium halide (0.5—2.0 M,

† 1 M=1 mol dm^{-3}.

12 mmol). After 1 h, the mixture was treated with 1 M aqueous ammonium chloride (30 ml), and extracted with dichloromethane (50 ml×3). The organic layer was dried over $MgSO_4$, concentrated, and purified by silica-gel column chromatography (hexane–ethyl acetate) to give ketone (**14**) as a colorless oil.

(*S*)-2-Methoxymethoxy-1-phenyl-1-propanone (94% from **11**); $[\alpha]_D^{27}$ −91.6° (*c* 1.00, $CHCl_3$); IR (film) 1695, 1595 cm^{-1}; ^1H NMR (CCl_4) δ=1.42 (3H, d, *J*=6.9 Hz, H-3), 3.22 (3H, s, -OMe), 4.51 (1H, d, *J*=7.2 Hz, $-OCH_2O-$), 4.60 (1H, d, *J*=7.2 Hz, $-OCH_2O-$), 4.77 (1H, q, *J*=6.9 Hz, H-2), 7.2—7.6 (3H, m, -Ph), 7.8—8.1 (2H, m, -Ph) ppm.

HRMS; Found: *m/z* 194.0908. Calcd for $C_{11}H_{14}O_3$: M^+, *m/z* 194.0942.

(*S*)-2-(1-Ethoxyethoxy)-1-phenyl-1-propanone (98% from **12**); IR (film) 1697, 1684, 1598 cm^{-1}; ^1H NMR (CCl_4) δ=0.9—1.6 (9H, m, -CMe), 3.2—3.7 (2H, m, $-OCH_2C-$), 4.5—5.1 (2H, m, H-2 and -OCHO-), 7.3—7.7 (3H, m, -Ph), 7.9—8.2 (2H, m, -Ph) ppm.

HRMS; Found: *m/z* 222.1271. Calcd for $C_{13}H_{18}O_3$: M^+, *m/z* 222.1255.

(*S*)-2-Methoxymethoxy-1-(3-methylphenyl)-1-propanone (98% from **11**); $[\alpha]_D^{21}$ −67.2° (*c* 1.00, MeOH); IR (film) 1690, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47 (3H, d, *J*=6.9 Hz, H-3), 2.17 (3H, s, $-C_6H_4$-Me), 3.32 (3H, s, -OMe), 4.63 (1H, d, *J*=6.9 Hz, $-OCH_2O-$), 4.73 (1H, d, *J*=6.9 Hz, $-OCH_2O-$), 5.01 (1H, q, *J*=6.9 Hz, H-2), 7.25 (2H, d, *J*=8.4 Hz, $-C_6H_4-$), 7.91 (2H, d, *J*=8.4 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 208.1099. Calcd for $C_{12}H_{16}O_3$: M^+, *m/z* 208.1099.

(*S*)-2-(1-Ethoxyethoxy)-1-(3-methylphenyl)-1-propanone (95% from **12**); IR (film) 1695, 1680, 1610 cm^{-1}; ^1H NMR (CCl_4) δ=0.99 (t, *J*=7.2 Hz), 1.07 (t, *J*=7.2 Hz) (total 3H, $-CH_2Me$), 1.19 (d, *J*=5.4 Hz), 1.21 (d, *J*=5.4 Hz) (total 3H, -CHMe), 1.37 (d, *J*=7.1 Hz), 1.40 (d, *J*=7.1 Hz) (total 3H, H-3), 2.39 (3H, s, $-C_6H_4-$) 3.2—3.6 (2H, m, $-OCH_2O-$), 4.4—5.0 (2H, m, -OCHO- and H-2), 7.15 (2H, d, *J*=8.4 Hz, $-C_6H_4-$), 7.88 (d, *J*=8.4 Hz), 7.93 (d, *J*=8.4 Hz) (total 4H, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 191.1088. Calcd for $C_{12}H_{15}O_2$: M^+−OEt, *m/z* 191.1072.

(*S*)-2-Methoxymethoxy-1-(4-methoxyphenyl)-1-propanone (99% from **11**); $[\alpha]_D^{21}$ −61.8° (*c* 1.01, MeOH); IR (film) 1690, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.48 (3H, d, *J*=7.2 Hz, H-3), 3.32 (3H, s, -OMe), 3.85 (3H, s, $-C_6H_4$-OMe), 4.62 (1H, d, *J*=6.9 Hz, $-OCH_2O-$), 4.72 (1H, d, *J*=6.9 Hz, $-OCH_2O-$), 4.98 (1H, q, *J*=7.2 Hz, H-2), 6.92 (2H, d, *J*=8.7 Hz, $-C_6H_4-$), 7.99 (2H, d, *J*=8.7 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 224.1049. Calcd for $C_{12}H_{16}O_4$: M^+, *m/z* 224.1047.

(*S*)-2-(1-Ethoxyethoxy)-1-(4-methoxyphenyl)-1-propanone (98% from **12**); IR (film) 1685, 1595 cm^{-1}; ^1H NMR (CCl_4) δ=1.00 (t, *J*=6.9 Hz), 1.07 (t, *J*=6.9 Hz) (total 3H, $-CH_2Me$), 1.19 (d, *J*=5.4 Hz), 1.21 (d, *J*=5.4 Hz) (total 3H, -CHMe), 1.38 (d, *J*=6.6 Hz), 1.40 (d, *J*=6.6 Hz) (total 3H, H-3), 3.2—3.6 (2H, m, $-OCH_2C-$), 3.83 (3H, s, -OMe), 4.4—4.9 (2H, m, -OCHO- and H-2), 6.83 (2H, d, *J*=8.4 Hz, $-C_6H_4-$), 8.00 (d, *J*=8.4 Hz), 8.03 (d, *J*=8.4 Hz) (total 4H, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 207.1008. Calcd for $C_{12}H_{15}O_3$: M^+−OEt, *m/z* 207.1020.

(*S*)-2-(1-Ethoxyethoxy)-1-(4-methoxyphenyl)-3-methyl-1-butanone (85% from **13**); IR (film) 1675, 1600 cm^{-1}; ^1H NMR (CCl_4) δ=0.8—1.3 (12H, m, -CMe), 1.9—2.3 (1H, m, H-3), 3.1—3.6 (2H, m, $-OCH_2C-$), 3.86 (3H, s, -OMe), 3.97 (d, *J*=7.5 Hz), 4.34 (d, *J*=7.5 Hz) (total 1H, -OCHO-), 4.61 (1H, m, H-2), 6.87 (2H, d, *J*=9.0 Hz), 8.06 (2H, d, *J*=9.0 Hz) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 280.1672. Calcd for $C_{16}H_{24}O_4$: M^+, *m/z* 280.1672.

(*S*)-2-Methoxymethoxy-1-(6-methoxy-2-naphtyl)-1-propanone (92% from **11**); $[\alpha]_D^{22}$ −53.9° (*c* 1.01, MeOH); IR (film) 1680, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.55 (3H, d, *J*=6.9 Hz, H-3), 3.35 (3H, s, -OMe), 3.92 (3H, s, $-C_6H_4-$), 4.69 (1H, d, *J*=6.9 Hz, $-OCH_2O-$), 4.80 (1H, d, *J*=6.9 Hz, $-OCH_2O-$), 5.17 (1H, q, *J*=6.9 Hz, H-2), 7.14 (2H, s), 7.8—8.0 (2H, m), 8.06 (1H, dd, *J*=9.0 Hz), 8.52 (1H, s) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 274.1203. Calcd for $C_{16}H_{18}O_3$: M^+, *m/z* 274.1203.

(*S*)-2-(1-Ethoxyethoxy)-1-(6-methoxy-2-naphtyl)-1-propanone (99% from **12**); IR (film) 1680, 1625, 1590 cm^{-1}; ^1H NMR (CCl_4) δ=0.8—1.4 (6H, m, -CMe), 1.46 (d, *J*=7.2 Hz), 1.49 (d, *J*=7.2 Hz) (total 3H, H-3), 3.2—3.7 (2H, m, $-OCH_2C-$), 3.90 (3H, s, -OMe), 4.6—5.2 (2H, m, -OCHO- and H-2), 7.03 (1H, s), 7.0—7.2 (1H, m), 7.64 (1H, d, *J*=9.0 Hz), 7.78 (1H, d, *J*=9.0 Hz), 7.9—8.2 (1H, m), 8.53 (1H, d, *J*=6.0 Hz) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 302.1491. Calcd for $C_{18}H_{22}O_4$: M^+, *m/z* 302.1516.

General Synthetic Procedure of (*S*)-1-Aryl-2-hydroxyl-1-alkanone (15): 1) From **14** (R′=MOM); Into a solution of **14** (10 mmol) in methanol (80 ml) was added 1 M HCl (30 ml), and then the mixture was stirred at 60 °C for 6 h. Extraction with dichloromethane was repeated three times (50 ml each). The organic layer was washed with water (100 ml), dried over $MgSO_4$, concentrated, and purified by silica-gel column chromatography (hexane-ethyl acetate) to give α-hydroxy ketone (**15**).

2) From **14** (R′=EE); Into a solution of **14** (10 mmol) in ethanol (30 ml) was added PPTS (250 mg, 1 mmol). After 6 h, saturated aq NaCl (50 ml) was added, and then extracted with dichloromethane (50 ml×3). The organic layer was treated by the above procedure to give **15**.

(*S*)-2-Hydroxy-1-phenyl-1-propanone [96% from **14** (R′=MOM), 94% from **14** (R′=EE)]; colorless semicrystaline residue; $[\alpha]_D^{20}$ −48.4° (*c* 1.00, MeOH); IR (film) 3470, 1685, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.44 (3H, d, *J*=6.9 Hz, H-3), 3.80 (1H, d, *J*=6.9 Hz, -OH), 5.15 (1H, quintet, *J*=6.9 Hz, H-2), 7.4—7.8 (3H, m, $-C_6H_4-$), 7.9—8.1 (2H, m, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 150.0685. Calcd for $C_9H_{10}O_2$: M^+, *m/z* 150.0680.

(*S*)-2-Hydroxy-1-(4-methylphenyl)-1-propanone [93% from **14** (R′=MOM), 99% from **14** (R′=EE)]; colorless crystals from hexane–diethyl ether; mp 49.5—50.5 °C; $[\alpha]_D^{21}$ −41.1° (*c* 1.11, MeOH); IR (film) 3430, 1680, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.43 (3H, d, *J*=6.5 Hz, H-3), 2.42 (3H, s, $-C_6H_4$-Me), 3.82 (1H, d, *J*=6.5 Hz, -OH), 5.12 (1H, quintet, *J*=6.5 Hz, H-2), 7.29 (2H, d, *J*=8.4 Hz, $-C_6H_4-$), 7.84 (2H, d, *J*=8.4 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 164.0857. Calcd for $C_{10}H_{12}O_2$: M^+, *m/z* 164.0837.

(*S*)-2-Hydroxy-1-(4-methoxyphenyl)-1-propanone [93% from **14** (R′=MOM), 99% from **14** (R′=EE)]; colorless oil;

$[\alpha]_D^{21}$ −33.4° (*c* 1.05, MeOH); IR (film) 3475, 1670, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.36 (3H, d, *J*=7.0 Hz, H-3), 3.84 (3H, s, -OMe), 3.8 (1H, m, -OH), 5.05 (1H, quintet, *J*=7.0 Hz, H-2), 6.94 (2H, d, *J*=9.1 Hz, $-C_6H_4-$), 7.90 (2H, d, *J*=9.1 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 180.0798. Calcd for $C_{10}H_{12}O_3$: M^+, *m/z* 180.0686.

(*S*)-2-Hydroxy-1-(6-methoxy-2-naphtyl)-1-propanone [96% from **14** (R′=MOM), 99% from **14** (R′=EE)]; colorless crystals from diethyl ether; mp 68.6—70.0 °C; $[\alpha]_D^{23}$ −98.4° (*c* 1.01, $CHCl_3$), $[\alpha]_D^{23}$ −59.4° (*c* 1.05, MeOH); IR (film) 3440, 1685, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.51 (3H, d, *J*=6.7 Hz, H-3), 3.94 (3H, s, -OMe), 4.30 (1H, q, *J*=6.7 Hz, H-2), 7.17 (1H, s), 7.1—7.3 (1H, m), 7.6—8.0 (3H, m), 8.39 (1H, s) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 230.0943. Calcd for $C_{14}H_{14}O_3$: M^+, *m/z* 230.0943.

(*S*)-2-Hydroxy-1-(4-methoxyphenyl)-3-methyl-1-butanone [97% from **14** (R′=EE)]; colorless oil; $[\alpha]_D^{23}$ +37.5° (*c* 1.00, MeOH); IR (film) 3480, 1665, 1600 cm^{-1}; ^1H NMR (CCl_4) δ=0.61 (3H, d, *J*=6.9 Hz, H-4), 1.12 (3H, d, *J*=6.9 Hz, H-4′), 2.05 (1H, m, *J*=2.4 Hz, *J*=6.9 Hz, H-3), 3.33 (1H, d, *J*=6.3 Hz, -OH), 3.86 (3H, s, -OMe), 4.73 (1H, dd, *J*=6.3 Hz, *J*=2.4 Hz, H-2), 6.89 (2H, d, *J*=9.0 Hz, $-C_6H_4-$), 7.84 (2H, d, *J*=9.0 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 208.1127. Calcd for $C_{12}H_{16}O_3$: M^+, *m/z* 208.1099.

General Synthetic Procedure of (*S*)-1-Aryl-2-hydroxy-1-alkanone Dimethyl Acetal (17a): 1) Procedure A [from **14** (R′=MOM)]; Into a solution of **14** (10 mmol) in anhydrous methanol (150 ml) were added trimethoxymethane (5.53 ml, 50 mmol) and methanesulfonic acid (0.65 ml, 10 mmol) under an argon atmosphere. The mixture was heated at 50 °C for 1 h and allowed to cool to rt. The reaction mixture was poured into the vigorously stirred $NaHCO_3$ solution at 0 °C, and then extracted with diethyl ether (100 ml×3). The organic layer was washed with water (50 ml), dried over $MgSO_4$ in the presence of pyridine (1 ml), concentrated, and then purified by column chromatography (Florisil, Waco, hexane-diethyl ether) to give **17a** as a colorless oil.

2) Procedure B (from **15**); Into a solution of **15** (10 mmol) and trimethoxymethane (5.53 g, 50 mmol) in anhydrous methanol (150 ml), cooled in an ice bath, was added methanesulfonic acid (0.65 g, 10 mmol). The reaction mixture was treated by the above procedure to give **17a** (procedure B).

(*S*)-2-Hydroxy-1-phenyl-1-propanone Dimethyl Acetal (93% from **14**, 85% from **15**); $[\alpha]_D^{28}$ −17.7° (*c* 1.11, MeOH); IR (film) 3500 cm^{-1}; ^1H NMR (CCl_4) δ=0.88 (3H, d, *J*=6.9 Hz, H-3), 2.41 (1H, s, -OH), 3.16 (3H, s, -OMe), 3.38 (3H, s, -OMe), 3.98 (1H, q, *J*=6.9 Hz, H-2), 7.2—7.6 (5H, m, -Ph) ppm.

HRMS; Found: *m/z* 179.1035. Calcd for $C_{11}H_{15}O_2$: M^+—OH, *m/z* 179.1071.

(*S*)-2-Hydroxy-1-(4-methylphenyl)-1-propanone Dimethyl Acetal (87% from **14**, 82% from **15**); $[\alpha]_D^{20}$ −15.5° (*c* 1.29 MeOH); IR (film) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.95 (3H, d, *J*=6.6 Hz, H-3), 2.34 (3H, s, $-C_6H_4-Me$), 2.40 (1H, d, *J*=3.0 Hz, -OH), 3.21 (3H, s, -OMe), 3.37 (3H, s, -OMe), 4.09 (dq, 1H, *J*=3.0 Hz, *J*=6.6 Hz, H-2), 7.17 (2H, d, *J*=8.1 Hz, $-C_6H_4-$), 7.38 (2H, d, *J*=8.1 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 210.1248. Calcd for $C_{12}H_{18}O_3$: M^+, *m/z* 210.1254.

(*S*)-2-Hydroxy-1-(4-methoxyphenyl)-1-propanone Dimethyl Acetal (57% from **14**, 85% from **15**); $[\alpha]_D^{19}$ −13.1° (*c* 0.98, MeOH), IR (film) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.95 (3H, d, *J*=6.6 Hz, H-3), 2.34 (1H, d, *J*=3.0 Hz, -OH), 3.21 (3H, s, -OMe), 3.35 (3H, s, -OMe), 3.81 (3H, s, $-C_6H_4-OMe$), 4.09 (1H, dq, *J*=3.0 Hz, *J*=6.6 Hz, H-2), 6.90 (2H, d, *J*=12.0 Hz, $-C_6H_4-$) ppm, 7.39 (2H, d, *J*=12.0 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 209.1183. Calcd for $C_{12}H_{17}O_3$: M^+—OH, *m/z* 209.1176.

(*S*)-2-Hydroxy-1-(4-methoxyphenyl)-3-methyl-1-butanone Dimethyl Acetal (72% from **15**); $[\alpha]_D^{24}$ −9.1° (*c* 1.20 MeOH); IR (film) 3550 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.70 (3H, d, *J*=6.6 Hz, H-4), 0.87 (3H, d, *J*=6.6 Hz, H-4′), 1.2—1.7 (1H, m, H-3), 2.51 (1H, s, *J*=2.1 Hz, -OH), 3.24 (3H, s, -OMe), 3.26 (3H, s, -OMe), 3.7—3.9 (1H, m, H-2), 3.81 (3H, s, $-C_6H_4-OMe$), 6.88 (2H, d, *J*=9.0 Hz, $-C_6H_4-$), 7.78 (2H, d, *J*=9.0 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 223.1350. Calcd for $C_{13}H_{19}O_3$: M^+—OMe, *m/z* 233.1333.

(*S*)-2-Hydroxy-1-(6-methoxy-2-naphthyl)-1-propanone Dimethyl Acetal (91% from **14**, 96% from **15**); $[\alpha]_D^{21}$ −13.9° (*c* 0.92, MeOH); IR (film) 3520 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (3H, d, *J*=6.6 Hz, H-3), 2.60 (1H, broad s, -OH), 3.26 (3H, s, -OMe), 3.43 (3H, s, -OMe), 3.92 (3H, s, $-C_{10}H_6-OMe$), 4.21 (1H, q, *J*=6.6 Hz, H-2), 7.1—7.2 (2H, m), 7.56 (1H, dd, *J*=1.8 Hz, *J*=8.5 Hz), 7.7—7.9 (2H, m), 7.97 (1H, s) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 276.1363. Calcd for $C_{16}H_{20}O_4$: M^+, *m/z* 276.1360.

General Synthetic Procedure of (*S*)-1-Aryl-2-hydroxy-1-alkanone 2,2-Dimethyltrimethylene Acetal (17b): 1) Procedure C (from **15**); Into a solution of **15** (10 mmol) and 2,2-dimethyl-1,3-propanediol (10.42 g, 100 mmol) in anhydrous methanol (150 ml), cooled in an ice bath, was added trimethylchlorosilane (27.16 g, 25 mmol). The mixture was stirred in an ice bath for 2 h. The reaction mixture was poured into the vigorously stirred $NaHCO_3$ solution at 0 °C, and then extracted with ethyl acetate (100 ml×3). The organic layer was dried over magnesium sulfate, concentrated, and then purified by silica-gel column chromatography (hexane/ethyl acetate) to give **17b** as a colorless oil.

2) Procedure D (from **15**); Into a 500 ml flask equipped with a Soxlet's extractor packed by molecular sieves 4A 1/16 was charged **15** (10 mmol), 2,2-dimethyl-1,3-propanediol (1.56 g, 15 mmol), *p*-toluenesulfonic acid (0.34 g, 2 mmol), and benzene (200 ml). The resulting mixture was heated at 50 °C and a vacuum was applied in order to maintain a smooth reflux. After completion, the reaction mixture was cooled and poured into the stirred aqueous $NaHCO_3$, and then extracted with diethyl ether (50 ml×3). The organic layer was treated by the above procedure to give **17b** as a colorless oil.

(*S*)-2-Hydroxy-1-phenyl-1-propanone 2,2-Dimethyl-trimethylene Acetal [89% from **15** (Procedure C)]; $[\alpha]_D^{28}$ −0.7° (*c* 1.12 MeOH); IR (film) 3510 cm^{-1}; ^1H NMR (CCl_4) δ=0.60 (3H, s, -CMe), 0.93 (3H, d, *J*=6.6 Hz, H-3), 1.25 (3H, s, -CMe), 2.24 (1H, d, *J*=3.6 Hz, H-3), 3.39 (4H, s, $-CCH_2C-$), 3.62 (1H, dq, *J*=3.6 Hz, *J*=6.6 Hz, H-2), 7.2—7.5 (5H, m, -Ph) ppm.

HRMS; Found: *m/z* 219.1362. Calcd for $C_{14}H_{19}O_2$: M^+—OH, *m/z* 219.1383.

(*S*)-2-Hydroxy-1-(4-methylphenyl)-1-propanone 2,2-Dimeth-

yl-trimethylene Acetal [93% from **15** (Procedure C), 93% from **15** (procedure D)]; $[\alpha]_D^{19}$ −0.05° (*c* 1.10, MeOH); IR (film) 3510 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.58 (3H, s, -CMe), 1.03 (3H, d, *J*=6.6 Hz, H-3), 1.27 (3H, s, -CMe), 2.37 (3H, s, $-C_6H_4$-Me), 2.51 (1H, d, *J*=3.6 Hz, -OH), 3.39 (2H, d, *J*=9.3 Hz, $-OCH_2C$-), 3.52 (2H, d, *J*=9.3 Hz, $-OCH_2C$-), 3.73 (1H, dq, *J*=3.6 Hz, *J*=6.6 Hz, H-2), 7.2—7.5 (4H, m, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 233.1558. Calcd for $C_{15}H_{21}O_2$: M^+−OH, *m/z* 233.1541.

(*S*)-2-Hydroxy-1-(4-methoxyphenyl)-1-propanone 2,2-Dimethyl-trimethylene Acetal [96% from **15** (Procedure C), 93% from **15** (Procedure D)]; $[\alpha]_D^{28}$ −2.0° (*c* 0.99, MeOH); IR (film) 3505 cm^{-1}; ^1H NMR (CCl_4) δ=0.59 (3H, s, -CMe), 0.93 (3H, d, *J*=6.3 Hz, H-3), 1.25 (3H, s, -CMe), 2.13 (1H, broad s, -OH), 3.28 (2H, d, *J*=12.0 Hz, $-OCH_2C$-), 3.42 (2H, d, *J*=12.0 Hz, $-OCH_2C$-), 3.60 (1H, q, *J*=6.3 Hz, H-2), 3.83 (3H, s, -OMe), 6.81 (2H, d, *J*=9.0 Hz, $-C_6H_4$-), 7.21 (2H, d, *J*=9.0 Hz, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 266.1488. Calcd for $C_{15}H_{22}O_4$: M^+, *m/z* 266.1516.

(*S*)-2-Hydroxy-1-(4-methoxyphenyl)-3-methyl-1-propanone 2,2-Dimethyl-trimethylene Acetal [57% from **15** (Procedure D)]; $[\alpha]_D^{24}$ −8.9° (*c* 1.01, MeOH); IR (film) 3580 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.58 (3H, s, -CMe), 0.83 (3H, d, *J*=6.6 Hz, H-4), 0.89 (3H, d, *J*=6.6 Hz, H-4′), 1.27 (3H, s, -CMe), 1.66 (1H, double heptet, *J*=6.6 Hz, *J*=2.7 Hz, H-3), 2.38 (1H, d, *J*=5.4 Hz, -OH), 3.4—3.7 (1H, m, H-2), 3.42 (4H, s, $-CCH_2C$-), 6.92 (2H, d, *J*=9.0 Hz, $-C_6H_4$-), 7.32 (2H, d, *J*=9.0 Hz, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 294.1833. Calcd for $C_{17}H_{26}O_4$: M^+, *m/z* 294.1830.

(*S*)-2-Hydroxy-1-(6-methoxy-2-naphtyl)-1-propanone 2,2-Dimethyltrimethylene Acetal [94% from **15** (Procedure C), 100% from **15** (Procedure D)]; $[\alpha]_D^{22}$ +0.7° (*c* 1.10, MeOH); IR (film) 3520 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.55 (3H, s, -CMe), 1.07 (3H, d, *J*=6.3 Hz, H-3), 1.30 (3H, s, -CMe), 2.56 (1H, d, *J*=3.9 Hz, -OH), 3.3—3.7 (4H, m, $-OCH_2C$-), 3.83 (1H, dd, *J*=3.9 Hz, *J*=6.3 Hz, H-2), 3.94 (3H, s, -OMe), 7.1—7.3 (2H, m), 7.48 (1H, dd, *J*=1.8 Hz, *J*=9.0 Hz), 7.7—7.9 (3H, m) (total 6H, $-C_{10}H_6$-) ppm.

HRMS; Found: *m/z* 316.1643. Calcd for $C_{19}H_{24}O_4$: M^+, *m/z* 316.1673.

General Synthetic Procedure of (*S*)-1-Aryl-2-methylsulfonyloxy-1-alkanone Acetal (19): Into a solution of **17** (10 mmol) in pyridine (100 ml), cooled in an ice bath, was added methanesulfonyl chloride (1.16 g, 15 mmol). After stirring for 12 h at room temperature, water (300 ml) was added into the mixture, which was then extracted with diethyl ether (50 ml×3), and washed with water (50 ml×2). The organic layer was dried over $MgSO_4$, concentrated, and purified by the short silica-gel column chromatography (dichloromethane) to give **19**.

(*S*)-2-Methylsulfonyloxy-1-phenyl-1-propanone Dimethyl Acetal (95% from **17a**); colorless oil; $[\alpha]_D^{25}$ −14.7° (*c* 1.13, $CHCl_3$); IR (film) 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.19 (3H, d, *J*=6.6 Hz, H-3), 3.12 (3H, s, -OMs), 3.25 (3H, s, -OMe), 3.33 (3H, s, -OMe), 5.01 (1H, q, *J*=6.6 Hz, H-2), 7.3—7.7 (5H, m, -Ph) ppm.

HRMS; Found: *m/z* 274.0851. Calcd for $C_{12}H_{18}O_5S$: M^+, *m/z* 274.0873.

(*S*)-2-Methylsulfonyloxy-1-phenyl-1-propanone 2,2-Dimethyl-trimethylene Acetal (98% from **17b**); colorless oil; $[\alpha]_D^{25}$ −2.6° (*c* 0.98, $CHCl_3$); IR (film) 1350, 1170 cm^{-1}; ^1H NMR ($CHCl_3$) δ=0.59 (3H, s, -CMe), 1.28 (3H, s, -CMe), 1.39 (3H, d, *J*=6.6 Hz, H-3), 2.69 (3H, s, -OMs), 3.46 (4H, s, $-CCH_2C$-), 4.60 (1H, q, *J*=6.6 Hz, H-2), 7.45 (s, 5H) ppm.

HRMS; Found: *m/z* 219.1349. Calcd for $C_4H_{19}O_2$: M^+−OMs, *m/z* 219.1383.

(*S*)-2-Methylsulfonyloxy-1-(4-methylphenyl)-1-propanone Dimethyl Acetal (99% from **17a**); colorless oil; $[\alpha]_D^{23}$ −15.0° (*c* 1.20, $CHCl_3$); IR (film) 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.18 (3H, d, *J*=6.6 Hz, H-3), 2.35 (3H, s, $-C_6H_4$-Me), 3.11 (3H, s, -OMs), 3.23 (3H, s, -OMe), 3.32 (3H, s, -OMe), 4.99 (1H, q, *J*=6.6 Hz), 7.17 (2H, d, *J*=8.4 Hz, $-C_6H_4$-), 7.36 (2H, d, *J*=8.4 Hz, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 257.0839. Calcd for $C_{12}H_{17}O_4S$: M^+−OMe, *m/z* 257.0845.

(*S*)-2-Methylsulfonyloxy-1-(4-methylphenyl)-1-propanone 2,2-Dimethyl-trimethylene Acetal (100% from **17b**); colorless oil; $[\alpha]_D^{13}$ −2.0° (*c* 0.98, $CHCl_3$); IR (film) 1360, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.59 (3H, s, -CMe), 1.28 (3H, s, -CMe), 1.37 (3H, d, *J*=6.6 Hz, H-3), 2.38 (3H, s, $-C_6H_4$-), 2.73 (3H, s, -OMs), 3.46 (4H, s, $-CCH_2C$-), 4.60 (1H, q, *J*=6.6 Hz, H-2), 7.2—7.5 (4H, m, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 327.1275. Calcd for $C_{16}H_{23}O_5S$, M^+−1, *m/z* 327.1265.

(*S*)-2-Methylsulfonyloxy-1-(4-methoxyphenyl)-1-propanone Dimethyl Acetal (99% from **17a**); colorless oil; $[\alpha]_D^{22}$ −15.2° (*c* 1.03, $CHCl_3$); IR (film) 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.17 (3H, d, *J*=6.6 Hz, H-3), 3.11 (3H, s, -OMs), 3.24 (3H, s, -OMe), 3.31 (3H, s, -OMe), 3.82 (3H, s, $-C_6H_4$-OMe), 4.98 (1H, q, *J*=6.6 Hz, H-2), 6.89 (2H, d, *J*=8.7 Hz, $-C_6H_4$-), 7.39 (2H, d, *J*=8.7 Hz, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 273.0818. Calcd for $C_{12}H_{17}O_5S$: M^+−OMe, *m/z* 273.0796.

(*S*)-2-Methylsulfonyloxy-1-(4-methoxyphenyl)-1-propanone 2,2-Dimethyl-trimethylene Acetal (95% from **17b**); colorless crystals from diethyl ether; mp 127.0—128.0 °C; $[\alpha]_D^{29}$ −3.7° (*c* 1.00, $CHCl_3$); IR (film) 1360—1330, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.59 (3H, s, -CMe) 1.26 (3H, s, -CMe), 1.36 (3H, d, *J*=6.6 Hz, H-3), 2.76 (3H, s, -OMs), 3.85 (3H, s, -OMe), 4.57 (1H, q, *J*=6.6 Hz, H-2), 6.90 (2H, d, *J*=9.0 Hz, $-C_6H_4$-), 7.34 (2H, d, *J*=9.0 Hz, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 249.1477. Calcd for $C_{15}H_{21}O$: M^+−Ms, *m/z* 249.1489.

(*S*)-2-Methylsulfonyloxy-1-(4-methoxyphenyl)-3-methyl-1-butanone Dimethyl Acetal (90% from **17a**); colorless oil; $[\alpha]_D^{26}$ −4.6° (*c* 1.01, $CHCl_3$); IR (film) 1390, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.70 (3H, d, *J*=6.9 Hz, H-4), 0.90 (3H, d, *J*=6.9 Hz, H-4′), 1.6—1.9 (1H, m, H-3), 3.19 (3H, s, -OMs), 3.21 (3H, s, -OMe), 3.26 (3H, s, -OMe), 3.81 (3H, s, $-C_6H_4$-), 4.77 (1H, d, *J*=3.6 Hz, H-2), 6.89 (2H, d, *J*=9.0 Hz, $-C_6H_4$-), 7.43 (2H, d, *J*=9.0 Hz, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 301.1100. Calcd for $C_{14}H_{21}O_5S$: M^+−OMe, *m/z* 301.1108.

(*S*)-2-Methylsulfonyloxy-1-(4-methoxyphenyl)-3-methyl-1-butanone 2,2-Dimethyl-trimethylene Acetal (94% from **17b**); colorless oil; $[\alpha]_D^{24}$ −10.2° (*c* 0.97, $CHCl_3$); IR (film) 1360, 1170 cm^{-1}; ^1H NMR (CCl_4) δ=0.59 (3H, s, -CMe), 0.83 (3H, d, *J*=7.5 Hz, H-4), 0.91 (3H, d, *J*=7.5 Hz, H-4′), 1.27 (3H, s, -CMe), 1.91 (1H, double septet, *J*=2.1 Hz, *J*=7.5 Hz, H-3), 2.79 (3H, s, -OMs), 3.39 (4H, s, $-OCH_2C$-), 6.87 (2H, d, *J*=9.0 Hz, $-C_6H_4$-), 7.30 (2H, d, *J*=9.0 Hz, $-C_6H_4$-) ppm.

HRMS; Found: *m/z* 372.1600. Calcd for $C_{18}H_{28}O_6S$: M^+, *m/z* 372.1604.

(*S*)-2-Methylsulfonyloxy-1-(6-methoxy-2-naphthyl)-1-propanone Dimethyl Acetal (96% from **17a**); colorless oil; $[\alpha]_D^{21}$ −17.3° (*c* 1.01, $CHCl_3$); IR (film) 1385, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.21 (3H, d, *J*=6.6 Hz, H-3), 3.14 (3H, s, -OMs), 3.28 (3H, s, -OMe), 3.39 (3H, s, -OMe), 3.93 (3H, s, $-C_6H_4-$), 5.12 (1H, q, *J*=6.6 Hz, H-2), 7.1—7.2 (2H, m), 7.55 (1H, dd, *J*=1.8 Hz, *J*=8.5 Hz), 7.7—7.9 (2H, m), 7.98 (1H, s) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 354.1123. Calcd for $C_{17}H_{22}O_6S$: M^+, *m/z* 354.1135.

(*S*)-2-Methylsulfonyloxy-1-(6-methoxy-2-naphtyl)-1-propanone 2,2-Dimethyl-trimethylene Acetal (100% from **17b**); colorless oil; $[\alpha]_D^{19}$ +1.5° (*c* 0.98, $CHCl_3$); IR (film) 1390, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.56 (3H, s, -CMe), 1.30 (3H, s, -CMe), 1.41 (3H, d, *J*=6.6 Hz, H-3), 2.67 (3H, s, -OMs), 3.51 (4H, s, $-OCH_2C-$), 3.94 (3H, s, -OMe), 4.70 (1H, q, *J*=6.6 Hz, H-2), 7.17 (1H, s), 7.1—7.3 (1H, m), 7.51 (1H, dd, *J*=1.8 Hz, *J*=8.4 Hz), 7.7—7.9 (3H, m) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 394.1441. Calcd for $C_{20}H_{26}O_6S$, M^+, *m/z* 394.1292.

General Synthetic Procedure of Methyl (*S*)-Alkanoate (20a) or 3-Hydroxy-2,2-dimethylpropyl (*S*)-Alkanoate (20b): A Pyrex pressure bottle was charged with **19** (10 mmol), sodium acetate (984 mg, 12 mmol), and methanol–water (7:3 v/v, 50 ml). The bottle was tightly closed with a cap and heated at 100—110 °C for 6—18 h with stirring. After cooling, the reaction mixture was poured into a stirred ice water (100 ml), which was then extracted with diethyl ether (50 ml×3). The organic layer was dried over $MgSO_4$, concentrated, and purified by silica-gel column chromatography (hexane–ethyl acetate) to give **20**.

Methyl (*S*)-2-Phenylpropionate (72% from **19a**); colorless oil; $[\alpha]_D^{28}$ +93.3° (*c* 0.96, EtOH); IR (film) 1735 cm^{-1}; ^1H NMR (CCl_4) δ=1.10 (3H, d, *J*=7.2 Hz, H-3), 3.57 (3H, s, -COOMe), 3.58 (1H, q, *J*=7.2 Hz, H-2), 7.20 (5H, s, -Ph) ppm.

HRMS; Found: *m/z* 164.0838. Calcd for $C_{10}H_{12}O_2$: M^+, *m/z* 164.0836.

3-Hydroxy-2,2-dimethylpropyl (*S*)-2-Phenylpropionate (93% from **19b**); colorless oil; $[\alpha]_D^{25}$ +38.3° (*c* 1.00, $CHCl_3$); IR (film) 3470, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.82 (6H, s, -CMe), 1.52 (3H, d, *J*=7.2 Hz, H-3), 1.99 (1H, broad s, -OH), 3.13 (2H, s, $-OCH_2C-$), 3.74 (1H, q, *J*=7.2 Hz, H-2), 3.82 (1H, d, *J*=11.4 Hz, $-COOCH_2-$), 4.00 (1H, d, *J*=11.4 Hz, $-COOCH_2-$), 7.32 (5H, s, -Ph) ppm.

HRMS; Found: *m/z* 219.1354. Calcd for $C_{14}H_{19}O_2$: M^+-OH, *m/z* 219.1383.

Methyl (*S*)-2-(4-Methylphenyl)propionate (85% from **19a**); colorless oil; $[\alpha]_D^{20}$ +84.4° (*c* 0.98, $CHCl_3$); IR (film) 1740 cm^{-1}; ^1H NMR (CCl_4) δ=1.39 (3H, d, *J*=7.2 Hz, H-3), 2.26 (3H, s, $-C_6H_4-Me$), 3.53 (1H, q, *J*=7.2 Hz, H-2), 3.55 (3H, s, -COOMe), 6.9—7.2 (4H, m, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 177.0891. Calcd for $C_{11}H_{13}O_2$: M^+-1, *m/z* 177.0914.

3-Hydroxy-2,2-dimethylpropyl (*S*)-2-(4-Methylphenyl)propionate (93% from **19b**); colorless oil; $[\alpha]_D^{20}$ +35.8° (*c* 1.03, $CHCl_3$); IR (film) 3460, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.83 (6H, s, -CMe–), 1.49 (3H, d, *J*=7.2 Hz, H-3), 2.31 (3H, s, $-C_6H_4-Me$), 2.46 (1H, broad s, -OH), 3.13 (2H, s, $-OCH_2C-$), 3.70 (1H, q, *J*=7.2 Hz, H-2), 3.81 (1H, d, *J*=12.0 Hz, $-COOCH_2-$), 3.99 (1H, d, *J*=12.0 Hz, $-COOCH_2-$), 7.17 (4H, s, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 250.1554. Calcd for $C_{15}H_{22}O_3$: M^+, *m/z* 250.1567.

Methyl (*S*)-2-(4-Methoxyphenyl)propionate (97% from **19a**); colorless oil; $[\alpha]_D^{21}$ +75.3° (*c* 1.02, $CHCl_3$); IR (film) 1735 cm^{-1}; ^1H NMR (CCl_4) δ=1.39 (3H, d, *J*=7.2 Hz, H-3), 3.52 (1H, q, *J*=7.2 Hz, H-2), 3.56 (3H, s, -COOMe), 3.70 (3H, s, -OMe), 6.71 (2H, d, *J*=8.7 Hz, $-C_6H_4-$), 7.09 (2H, d, *J*=8.7 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 194.0954. Calcd for $C_{11}H_{14}O_3$: M^+, *m/z* 194.0942.

3-Hydroxy-2,2-dimethylpropyl (*S*)-2-(4-Methoxyphenyl)propionate (92% from **19b**); colorless oil; $[\alpha]_D^{30}$ +30.2° (*c* 1.00, $CHCl_3$); IR (film) 3500, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47 (3H, d, *J*=7.2 Hz, H-3), 3.67 (2H, s, $-OCH_2C-$), 3.68 (1H, q, *J*=7.2 Hz, H-2), 3.80 (3H, s, -OMe), 6.87 (2H, d, *J*=8.7 Hz, $-C_6H_4-$), 7.24 (2H, d, *J*=8.7 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 266.1524. Calcd for $C_{15}H_{22}O_4$: M^+, *m/z* 266.1517.

Methyl (*S*)-2-(4-Methoxyphenyl)-3-methylbutanoate (90% from **19a**); colorless oil; $[\alpha]_D^{23}$ +61.6° (*c* 1.01, MeOH); IR (film) 1735 cm^{-1}; ^1H NMR (CCl_4) δ=0.70 (3H, d, *J*=6.6 Hz, H-4), 1.00 (3H, d, *J*=6.6 Hz, H-4′), 2.28 (1H, m, *J*=10.5 Hz, *J*=6.6 Hz, H-3), 3.07 (1H, d, *J*=10.5 Hz, H-2), 3.65 (3H, s, -COOMe), 3.79 (3H, s, -OMe), 6.83 (2H, d, *J*=9.0 Hz, $-C_6H_4-$), 7.24 (2H, d, *J*=9.0 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 222.1253. Calcd for $C_{13}H_{18}O_3$: M^+, *m/z* 222.1254.

3-Hydroxy-2,2-dimethylpropyl (*S*)-2-(4-Methoxyphenyl)-3-methylbutanoate (96% from **19b**); colorless oil; $[\alpha]_D^{24}$ +24.9° (*c* 1.00, $CHCl_3$); IR (film) 3510, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.71 (3H, d, *J*=6.6 Hz, H-4), 0.85 (6H, s, $-CMe_2C-$), 1.03 (3H, d, *J*=6.6 Hz, H-4′), 2.1—2.5 (2H, m, H-2), 3.0—3.3 (3H, m, $-CCH_2OH$ and -OH), 3.77 (3H, s, -OMe), 3.90 (2H, s, $-COOCH_2C-$), 6.84 (2H, d, *J*=9.0 Hz, $-C_6H_4-$), 7.22 (2H, d, *J*=9.0 Hz, $-C_6H_4-$) ppm.

HRMS; Found: *m/z* 294.1844. Calcd for $C_{17}H_{26}O_4$: M^+, *m/z* 294.1830.

Methyl (*S*)-2-(6-Methoxy-2-naphthyl)propionate (97% from **19a**); colorless crystals from hexane–diethyl ether; mp 91.0—92.0 °C; $[\alpha]_D^{21}$ +78.4° (*c* 1.05, $CHCl_3$); IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.57 (3H, d, *J*=7.2 Hz, H-3), 3.68 (3H, s, -COOMe), 3.90 (1H, q, *J*=7.2 Hz, H-2), 3.91 (3H, s, -OMe), 7.13 (1H, s), 7.1—7.2 (1H, s), 7.43 (1H, dd, *J*=1.8 Hz, *J*=8.4 Hz), 7.70 (2H, s), 7.79 (1H, s) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 244.1109. Calcd for $C_{15}H_{16}O_3$: M^+, *m/z* 244.1099.

3-Hydroxy-2,2-dimethylpropyl (*S*)-2-(6-Methoxy-2-naphtyl)propionate (95% from **19b**); colorless crystals from hexane–diethyl ether; mp 59.0—60.0 °C; $[\alpha]_D^{21}$ +31.2°C (*c* 0.92, $CHCl_3$); IR (film) 3500, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.84 (6H, s, $-CMe_2C-$), 1.58 (3H, d, *J*=7.2 Hz), 2.17 (1H, s, -OH), 3.12 (2H, s, $-OCH_2C-$), 3.84 (1H, d, *J*=10.5 Hz, $-COOCH_2C-$), 3.87 (1H, q, *J*=7.2 Hz, H-2), 3.91 (3H, s, -OMe), 4.01 (1H, d, *J*=10.5 Hz, $-COOCH_2C-$), 7.12 (1H, s), 7.1—7.3 (1H, m), 7.42 (1H, dd, *J*=1.8 Hz, *J*=8.4 Hz), 7.6—7.8 (3H, m) (total 6H, $-C_{10}H_6-$) ppm.

HRMS; Found: *m/z* 316.1676. Calcd for $C_{19}H_{24}O_4$: M^+, *m/z* 316.1656.

Transformation of 3-Hydroxy-2,2-dimethylpropyl Ester

(20b) to Methyl Ester (20a): A Pyrex pressure bottle was charged with **19b** (1 mmol), anhydrous methanol (15 ml), and sulfuric acid (41 mg, 0.7 mmol). The bottle was tightly closed with a cap and heated at 110 °C for 1 d. After cooling in an ice bath, the reaction mixture was powered into a stirred aqueous $NaHCO_3$ solution (100 ml), and extracted with diethyl ether (30 ml×3). The organic layer was concentrated and purified by silica-gel column chromatography to give the corresponding methyl ester (**20a**) quantitatively. Enantiomeric excess was determined to be over 98% by ^1H NMR measurement using $Eu(tfc)_3$.

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14) Some synthetic approach of the chiral 2-arylalkanoic esters by the use of asymmetric syntheses of the intermediates for rearrangement has been reported. a) The acetal of

racemic 2-chloro-1-(6-methoxy-2-naphtyl)-1-propanone with (+)-dimethyl (*R,R*)-tartrate was treated with KH_2PO_4–NaOH to afford (*S*)-Naproxen ester (diastereo selective rearrangement, 62% ee): C. Giordano, G. Castaldi, F. Uggeri, and S. Cavicchioli, EP 158255 (1985); b) Asymmetric bromination of the acetal of 1-(6-methoxy-2-naphtyl)-1-alkanone with (+)-dimethyl (*R,R*)-tartrate, followed by rearrangement, afforded the ester of 5′-bromo-(*S*)-naproxen (97% ee): C. Giordano, G. Castaldi, and F. Uggeri, EP 158913 (1985); c) Asymmetric reduction of 1-aryl-1,1-dimethoxy-2-alkanone with $LiAlH_4$ and the chiral ligand, (*S*)-(+)-2-(anilinomethyl)pyrrolidine[34] or (*S*)-(−)-2,2′-dihydroxy-1,1′-binaphtyl,[35] followed by sulfonylation and rearrangement, afforded (*S*)-2-arylalkanoic ester (69—79% ee): Y. Honda and G. Tsuchihashi, Ref. 1b.

15) On this basis, substitution-type rearrangements accompanied by the introduction of some anions, for example hydride,[a] alkyl, alkynyl,[b] and cyano anion,[c] have been developed. a) Y. Honda, M. Sakai, and G. Tsuchihashi, *Chem. Lett.*, **1985**, 1153; b) Y. Honda, E. Morita, and G. Tsuchihashi, *ibid*, **1986**, 277; c) Y. Honda, M. Sakai, and G. Tsuchihashi, 50th National Meeting of the Chemical Society of Japan, April 2, 1985, Abstr. II, 1023.

16) Some elimination-type rearrangements which afforded 2-arylalkanoic esters have been reported in these seven years; a) Aryl methyl ketone was treated with lead(IV) acetate in the presence of methanol and boron trifluoride diethyl etherate: B. Myrboth, H. Ila, and H. Junjappa, *Synthesis*, **1981**, 126; b) Aryl ethyl ketone was treated with lead acetate in the presence of trialkoxymethane and perchloric acid: K. Fujii, K. Nakao, and T. Yamauchi, *Synthesis*, **1982**, 456; *ibid*, **1983**, 444; c) Chiral 1-aryl-2-sulfonyloxy-1-alkanone acetal was treated with iodotrimethylsilane and Lewis acid, for example aluminum trichloride and titanium tetrachloride: K. Kitajima, S. Mitamura, Y. Honda, and G. Tsuchihashi, unpublished data; G. C. Shloemer, Ref. 13g.

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32) Enantiomeric excess of ethyl (*S*)-lactate (Aldrich) was determined to be over 99% by HPLC measurement of the (+)-2-methoxy-2-trifluoromethyl-(*R*)-phenylacetic acid ester[36] of the corresponding alcohol, which was prepared by the treatment with $LiAlH_4$, by using Develosil 60-3 (Nomura Chemical); hexane/dichloromethane/methanol=6/1/0.007 (v/v/v), flow rate 0.5 ml min^{-1}, k'_{SR}=3.24, $\alpha=k'_{RR}/k'_{SR}$=1.21.

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