Lipase-Catalyzed Asymmetric Desymmetrization of Prochiral 2,2-Disubstituted 1,3-Propanediols Using 1-Ethoxyvinyl Benzoate

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The lipase-catalyzed asymmetric desymmetrization of the prochiral 2,2-disubstituted 1,3-propanediols was studied using various types of 1-ethoxyvinyl esters (1a—i). Although 1a—e with aliphatic acyl groups were not sufficient, use of the benzoate (1f) in combination with *Candida rugosa* lipases converted acyclic diols (2, 6) and cyclic diols (11—14) to the optically active compounds (3f, 7f, 15f—18f), bearing a quaternary carbon center, with moderate-to-high optical yields. These products were fairly stable against racemization under acidic conditions.

Key words lipase; desymmetrization; 1-ethoxyvinyl benzoate; prochiral 2,2-disubstituted 1,3-propanediol

The development of highly enantioselective, catalytic methodology for the construction of optically active quaternary carbon centers has been a challenging subject during this decade.[1)] In additon to an increasing number of novel chemical methods, methodologies using biocatalysts have also become significant. The latter include the enzyme-catalyzed asymmetric desymmetrization reactions of molecules having a prochiral quaternary carbon center such as the esterification of 2,2-disubstituted 1,3-propanediols (**I**) (Chart 1),[2)] the hydrolysis of 2,2-disubstituted malonates,[1a,3)] the hydrolysis of the esters of 2,2-disubstituted 1,3-propanediols,[4)] and the reduction of 2,2-disubstituted 1,3-diones.[1a)] Among them, the process of Chart 1 is the most attractive in terms of easy operation in organic solvents and simple work up.

However, this approach has rarely been reported due to the low reactivity of sterically congested substrates (**I**) and the easy racemization of products (**II**) through acyl group migration.[2)] Although Fadel *et al.* first reported practical enzymatic desymmetrization of **I** using vinyl and isopropenyl esters as an acyl donor, the reaction took several days or more. More seriously, a decrease in the optical purity of **II** (R=Me) was observed in some cases under acidic conditions. During the course of our research on the enzyme-catalyzed transesterification of alcohols with novel acyl donors, 1-ethoxyvinyl esters (**1**),[5)] we have briefly presented a solution of these problems using 1-ethoxyvinyl benzoate (**1f**).[6)] In this paper, we fully describe the details of our results.

Results and Discussion

In order to overcome the previously discussed problems, namely, low reactivity of the substrate (**I**) and acyl migration of the product (**II**), the following two points were thought to be of significance: 1) improvement of the reactivity of the acyl donors and 2) the choice of a suitable acyl group for both the efficient enzymatic desymmetrization[7)] and the inertness to the acyl migration of **II**. When we started this project, we envisioned that use of the 1-ethoxyvinyl esters (**1**) would provide an efficient solution for the following two reasons: First, we had already found that **1** were in some cases more reactive than the vinyl esters and isopropenyl esters.[5a,c)] Second, **1** with various acyl groups (COR^1) can be easily prepared by the addition of carboxylic acids (R^1COOH) to ethoxyacetylene.[8)] We believed that by screening various **1**, we would be able to find such an effective acyl group.

First, we examined the applicability of 1-ethoxyvinyl acetate (**1a**) for the desymmetrization of the diol (**2**) in the presence of various types of lipases in hexane or wet iso-Pr_2O (see, General in the Experimental) at 30 °C.[9)] The maximum ee of the desired monoacetate (**3a**) was 37% which was obtained using lipase AY (from *Candida rugosa*) in wet iso-Pr_2O (run 1 in Table 1). Next, several other ethoxyvinyl esters (**1b—e**) possessing different alkyl chain lengths were investigated using lipase AY. Although the reaction was completed in a short period when ethoxyvinyl butyrate (**1c**) was used, the optical purity of the product (**3c**) was not so high (63% ee) (run 3). Other aliphatic acyl donors (**1b, d, e**) were less effective (runs 2, 4, 5).

We then focused our attention on the use of an aroyl reagent, ethoxyvinyl benzoate (**1f**). Although aroyl esters, *e.g.*, vinyl benzoate (**5**), were not familiar acyl donors in enzymatic acylation reactions due to their low reactivity,[10)] we were encouraged at the preliminary results, in which **1f** showed several times higher reactivity for lipase AY-catalyzed esterification of 1-octanol than **5** (Fig. 1). In addition, judging from the general tendency for the benzoic acid derivatives to be less reactive for chemical hydrolysis (or alcoholysis) under both acidic and basic conditions than the acetic acid derivatives,[11)] the benzoate (**II**, R=Ph) was expected to be less sensitive to the acyl group migration than the acetate (**II**, R=Me).

The reaction of **2** with the benzoate (**1f**), as well as with a few related benzoyl donors (**1g—i**), was investigated in the presence of lipase AY (Table 2). Several aspects are noteworthy. 1) The benzoate (**1f**) was the most effective in terms of reactivity and selectivity among all the esters (**1a—i**) examined. Substituents on the phenyl ring improved neither reactivity nor enantiotopic selectivity (runs 3—5). 2) A prolonged reaction caused kinetic resolution of the product (**3f**)

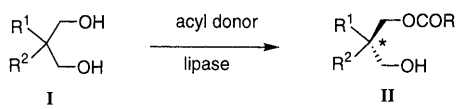

Chart 1

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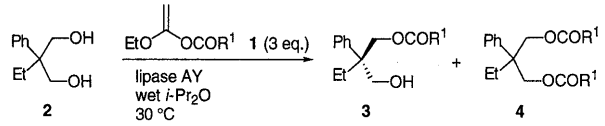
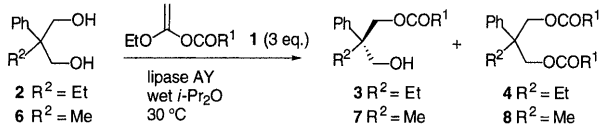
Table 1. Lipase-Catalyzed Desymmetrization of the 1,3-Diol (**2**) Using Aliphatic Esters (**1a—e**)



Run	1, R^1	Reaction time	Monoester (3)			Diester (4)	
				Isolated yield (%)[a]	Ee (%)[b]		Isolated yield (%)[a]
1	**1a** Me	4 d	**3a**	66	37	**4a**	—
2	**1b** CH_2Cl	7 d	**3b**	36	1[c]	**4b**	64
3	**1c** *n*-Pr	5 h	**3c**	86	63	**4c**	14
4	**1d** *n*-C_7H_{15}	4 d	**3d**	85	36	**4d**	12
5	**1e** *n*-$C_{11}H_{23}$	21 d	**3e**	78	0[c]	**4e**	—

a) Purified by SiO_2-column chromatography. *b*) Determined by HPLC using a Daicel CHIRALCEL OD column (hexane–iso-PrOH). *c*) Determined after transformation into **9** by a method similar to that shown in Chart 2.

Table 2. Lipase-Catalyzed Desymmetrization of the 1,3-Diols (**2**, **6**) Using Aromatic Esters (**1f—i**)



Run	Diol	1, R^1	Reaction time	Monoester (3, 7)			Diester (4, 8)	
					Isolated yield (%)[a]	Ee (%)[b]		Isolated yield (%)[a]
1	**2**	**1f** Ph	6 h	**3f**	90	81	**4f**	—
2	**2**	**1f** Ph	18 h	**3f**	39	91	**4f**	61
3	**2**	**1g** 4-MeO–C_6H_4	8.5 d	**3g**	50	69	**4g**	33
4	**2**	**1h** 4-NO_2–C_6H_4	13 d	**3h**	64	53	**4h**	[c]
5	**2**	**1i** 2,6-diMe–C_6H_3	30 d	**3i**	<5	—	**4i**	—
6	**6**	**1a** Me	8 d	**7a**	46	1	**8a**	*ca.* 10
7	**6**	**1f** Ph	3 d	**7f**	71	84	**8f**	26

a) Purified by SiO_2-column chromatography. *b*) Determined by HPLC using a Daicel CHIRALCEL OD column (hexane–iso-PrOH). *c*) Not determined.

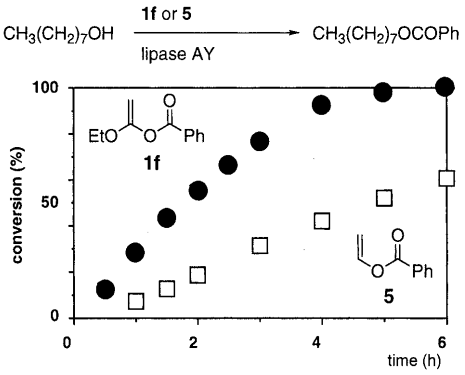


Fig. 1. Time-Course of the Transesterification of 1-Octanol (0.77 mmol) with the Acyl Donor (**1f** or **5**, 2.3 mmol) Catalyzed by Lipase AY (300 mg) in Wet Iso-Pr_2O (20 ml) at 30 °C

The conversion was determined by GLC using a G-100 column.

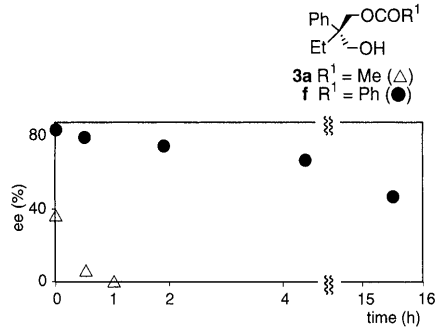


Fig. 2. Racemization of Optically Active **3a**, **f** in the Presence of CSA (0.1 eq) at Room Temperature

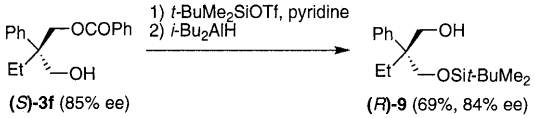


Chart 2

to give a slightly better ee of **3f**, although its yield decreased (run 2). 3) The product (**3f**) was found to be fairly stable against racemization. A comparison of the stability of **3a** and **3f** under acidic conditions [0.1 eq of camphorsulfonic acid (CSA), 4×10^{-4} M in CH_2Cl_2, room temperature] is shown in Fig. 2.[12]

Similarly, the desymmetrization of **6** using **1f** and lipase AY gave the optically active product (**7f**) in 71% yield with 84% ee, while a similar reaction using **1a** was not satisfactory (runs 6, 7).

The transformation of the functional group of **3f** into the silyl ether (**9**) was attained without loss of its optical purity (Chart 2).

The absolute stereochemistry of **3f** was determined to be *S* by its derivation to the known hydroxyacid (**10**) and by com-

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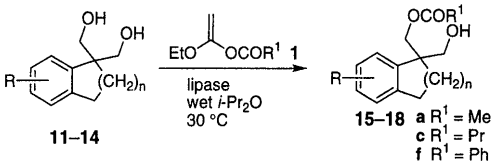
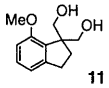
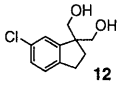
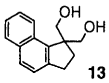
Table 3. Lipase-Catalyzed Desymmetrization of the 1,3-Diols (**11**—**14**)



Run	Diol	Lipase	**1**, R^1	Reaction time	Product	Isolated yield (%)[a]	Ee (%)[b]
1		AY	**1a** Me	25 d	**15a**	41	10
2		AY	**1c** *n*-Pr	25 d	**15c**	37	10
3	**11**	AY	**1f** Ph	4 d	**15f**	50	72
4		MY	**1f** Ph	4 d	**15f**	82	71
5		OF	**1f** Ph	4 d	**15f**	67	58
6	 **12**	MY	**1f** Ph	4 d	**16f**	74	74
7	 **13**	MY	**1f** Ph	7 d	**17f**	53	73
8	 **14**	MY	**1f** Ph	7 d	**18f**	74	46

a) Purified by SiO_2-column chromatography. *b*) Determined by HPLC using a Daicel CHIRALCEL OD column (hexane–iso-PrOH).

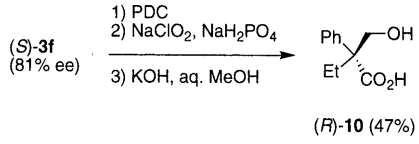


Chart 3

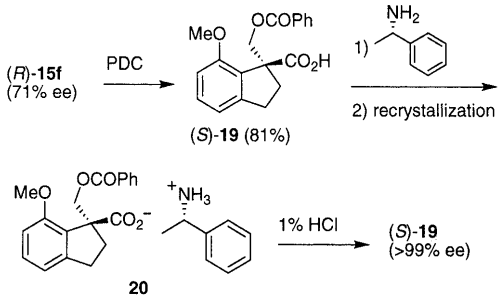


Chart 4

parison of its specific rotation with that of the reported compound (Chart 3).[3a] On the basis of the similarity of the specific rotation of **7f** to that of **3f**, the absolute stereochemistry of **7f** could be considered to be *S*.

The reagent (**1f**) was also applicable to the more hindered diol (**11**) to give 72% ee of **15f** in 50% isolated yield (Table 3, run 3), while the use of **1a** or **1c** was again insufficient (runs 1, 2). A better result (82% yield, 71% ee) was obtained using a similar lipase MY (from *Candida rugosa*) (run 4). Similarly, the desymmetrization of **12**, **13** and **14** was also attained using **1f** and lipase MY to give the products (**16f**—**18f**) with 74% ee, 73% ee and 46% ee, respectively (runs 6—8).

The product (**15f**) (71% ee) was converted to the carboxylic acid **19** (81% yield). An enantiomerically pure **19** was obtained through the formation of a crystalline salt (**20**) with (*S*)-1-phenylethylamine followed by recrystallization from ethyl acetate (Chart 4). In contrast to the cases of **3f** and **7f**, the absolute stereochemistry of the chiral center of **15f** was disclosed to be *R*, because the X-ray crystallographic analysis of **20** unambiguously showed that the chiral center of **19** was *S* (Fig. 3).

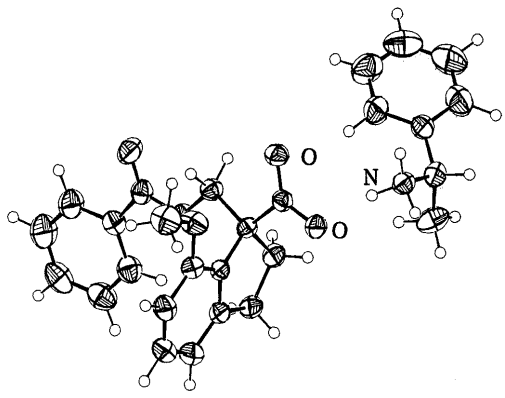


Fig. 3. The X-Ray Crystallographic Structure of the Salt (**20**)

Conclusions

In this study, the use of 1-ethoxyvinyl benzoate (**1f**) provided promising access to efficient enantiotopic differentiation of the prochiral 2,2-disubstituted 1,3-propanediols. The advantages of this method are good-to-high optical yields of the products and their reduced racemization under acidic conditions. These are outstanding results because the successful applications of vinyl benzoate for the enzymatic reactions have been reported in limited cases.[10]

Experimental

General All melting points (mp) and boiling points (bp) are uncorrected. Gas-liquid chromatography (GLC) analyses were carried out using a G-100 column (40 m×1.2 mm, Chemical Inspection and Testing Institute,

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Japan). ^{1}H-NMR spectra were measured at 200—300 MHz with tetramethylsilane as an internal standard. IR spectra were recorded by diffuse reflectance measurement of samples dispersed in KBr powder or as a $CHCl_3$ solution. Chiral HPLC analyses of the products (**3a**—**i**, **7a**, **7f**, **9**, **15a**, **15c**, **15f**—**18f**) were carried out using a Daicel CHIRALCEL OD column (250 mm×4.6 mm, eluent: hexane–iso-PrOH). Column chromatographic purification was performed using Silica gel 60 (70—230 mesh, Merck Co., Ltd.) or Silica gel BW-300 (200—400 mesh, Fuji Silysia Chemical Co., Ltd., Japan). Precoated Silica gel 60 F_{254} plates (E. Merck) were used for preparative TLC. Lipase AY (from *Candida rugosa*) was a gift from Amano Pharmaceutical Co., Ltd., Japan. Lipase MY (from *Candida rugosa*) and OF (from *Candida rugosa*) were gifts from Meito Sangyo Co., Ltd., Japan. Enzymes were dried (1 mmHg, room temperature, overnight) prior to use. Wet iso-Pr_2O was prepared by vigorously stirring a 1000 : 1 mixture of distilled iso-Pr_2O and water for 20—30 min using a magnetic stirrer and decanting the ether layer after settling down. Yields refer to isolated materials of ≥95% purity as determined by ^{1}H-NMR analysis.

Known ethoxyvinyl esters (**1a**, **1b**, **1d**, **1f**—**i**) were prepared by the reported method.[8] Unknown esters (**1c**, **e**) were similarly prepared.

1-Ethoxyvinyl Butyrate (1c) 81% yield. A colorless oil, bp 80—82 °C (25 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.0 Hz), 1.33 (3H, t, J=7.0 Hz), 1.71 (2H, sext., J=7.5 Hz), 2.41 (2H, t, J=7.5 Hz), 3.76 (1H, d, J=3.0 Hz), 3.81 (1H, d, J=3.0 Hz), 3.87 (2H, q, J=7.0 Hz). IR ($CHCl_3$) cm^{-1}: 1765, 1675. *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.96; H, 8.84.

1-Ethoxyvinyl Dodecanoate (1e) 77% yield. A pale yellow oil, bp 85—90 °C (0.2 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.20—1.45 (19H, m), 1.66 (2H, quint., J=7.0 Hz), 2.41 (2H, t, J=7.0 Hz), 3.76 (1H, d, J=3.5 Hz), 3.81 (1H, d, J=3.5 Hz), 3.87 (2H, q, J=7.0 Hz). IR ($CHCl_3$) cm^{-1}: 1765, 1675. *Anal.* Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.28; H, 11.08.

2,2-Disubstituted 1,3-propanediols (**2**, **6**, **11**—**14**) were prepared by a standard method using $LiAlH_4$ from the corresponding malonates.[13]

2-Ethyl-2-phenyl-1,3-propanediol (2) Colorless crystals, mp 79—80 °C (ethyl acetate–hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.68 (3H, t, J=7.5 Hz), 1.68 (2H, q, J=7.5 Hz), 2.17 (2H, t, J=5.5 Hz), 3.94 (2H, dd, J=10.5, 5.5 Hz), 4.13 (2H, dd, J=10.5, 5.5 Hz), 7.22—7.45 (5H, m). IR (KBr) cm^{-1}: 3460. *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.18; H, 8.85.

2-Methyl-2-phenyl-1,3-propanediol (6) Colorless crystals, mp 88—89 °C (ethyl acetate–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, s), 2.00 (2H, t, J=6.0 Hz), 3.86 (2H, dd, J=10.5, 6.0 Hz), 3.99 (2H, dd, J=10.5, 6.0 Hz), 7.24—7.46 (5H, m). IR (KBr) cm^{-1}: 3300. *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.37; H, 8.40.

1,1-Bis(hydroxymethyl)-7-methoxyindan (11) Colorless crystals, mp 129—130 °C (ethyl acetate–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.96—2.02 (2H, m), 2.86 (2H, dd, J=8.0, 2.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.69 (2H, dd, J=11.0, 9.0 Hz), 3.88 (3H, s), 3.93 (2H, dd, J=11.0, 4.5 Hz), 6.75 (1H, d, J=8.0 Hz), 6.88 (1H, dd, J=8.0, 1.0 Hz), 7.22 (1H, t, J=8.0 Hz). IR (KBr) cm^{-1}: 3300. *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.29; H, 7.64.

1,1-Bis(hydroxymethyl)-6-chloroindan (12) Colorless crystals, mp 116—117 °C (ethyl acetate–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.04 (2H, t, J=5.5 Hz), 2.09 (2H, t, J=7.5 Hz), 2.91 (2H, t, J=7.5 Hz), 3.78 (2H, dd, J=11.0, 5.5 Hz), 3.86 (2H, dd, J=11.0, 5.5 Hz), 7.16 (1H, d, J=8.0 Hz), 7.18 (1H, d, J=8.0 Hz), 7.29 (2H, d, J=2.0 Hz). IR (KBr) cm^{-1}: 3260. *Anal.* Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16. Found: C, 62.19; H, 6.03.

1,1-Bis(hydroxymethyl)benz[*e*]indan (13) Colorless crystals, mp 104—105 °C (ethyl acetate–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, t, J=6.0 Hz), 2.39 (2H, t, J=7.5 Hz), 3.09 (1H, t, J=7.5 Hz), 4.07 (2H, dd, J=11.0, 6.0 Hz), 4.28 (2H, dd J=11.0, 6.0 Hz), 7.37—7.52 (3H, m), 7.74 (1H, d, J=8.0 Hz), 7.87 (1H, d, J=8.5 Hz), 8.20 (1H, d, J=8.0 Hz). IR (KBr) cm^{-1}: 3250. *Anal.* Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.98; H, 7.10.

1,1-Bis(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (14) Colorless crystals, mp 114—115 °C (ethyl acetate–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.57—2.06 (6H, m), 2.79 (2H, t, J=6.0 Hz), 3.78 (2H, dd, J=11.0, 5.5 Hz), 3.95 (2H, dd, J=11.0, 6.0 Hz), 7.11—7.19 (3H, m), 7.34—7.37 (1H, m). IR (KBr) cm^{-1}: 3545. *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.12; H, 8.28.

Enzymatic Desymmetrization of the 1,3-Diols (2, 6, 11—14): A Typical Procedure To a suspension of **2** (0.55 mmol) and lipase (300 mg) in wet iso-Pr_2O (3.5 ml) was added a solution of **1** (1.65 mmol) in wet iso-Pr_2O (2.0 ml). The reaction mixture was stirred at 30 °C for the time shown in Table 1 and filtered through a Celite pad. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane–ethyl acetate) to give the mono ester (**3**) and the diester (**4**). The isolated yields of the products (**3**, **4**, **7**, **8**, **15**—**18**) are listed in Tables 1—3.

(*S*)-2-Hydroxymethyl-2-phenyl-1-butyl Benzoate (**3f**): A colorless oil, 91% ee, $[\alpha]_D^{22}$ −28.7° (c=1.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, t, J=8.0 Hz), 1.88 (2H, q, J=8.0 Hz), 1.96—2.15 (1H, m), 3.90 (2H, d, J=5.0 Hz), 4.73 (2H, br s), 7.25—7.70 (8H, m), 7.99 (2H, d, J=7.5 Hz). IR ($CHCl_3$) cm^{-1}: 3490, 1715. *Anal.* Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.60; H, 7.10.

2-Hydroxymethyl-2-phenyl-1-propyl Benzoate (**7f**): A colorless oil, 84% ee, $[\alpha]_D^{22}$ −9.9° (c=1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, s), 2.20 (1H, br s), 3.84 (2H, s), 4.61 (2H, s), 7.30—7.60 (8H, m), 7.99 (2H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3500, 1713. *Anal.* Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.07; H, 6.82.

(1-Hydroxymethyl-7-methoxyindan-1-yl)methyl Benzoate (**15f**): A colorless gum, 71% ee, $[\alpha]_D^{24}$ −39.9° (c=0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.07 (1H, m), 2.18—2.26 (1H, m), 2.80 (1H, dd, J=8.0, 5.0 Hz), 2.94—3.01 (2H, m), 3.83 (3H, s), 3.90 (1H, dd, J=11.0, 4.5 Hz), 4.02 (1H, dd, J=11.0, 8.0 Hz), 4.49 (1H, d, J=11.0 Hz), 4.69 (1H, d, J=11.0 Hz), 6.74 (1H, d, J=8.5 Hz), 6.90 (1H, d, J=7.0 Hz), 7.22 (1H, t, J=7.5 Hz), 7.42 (2H, t, J=7.5 Hz), 7.55 (1H, t, J=7.5 Hz), 7.97 (2H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3350, 1720. *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.79; H, 6.60.

[6-Chloro-1-(hydroxymethyl)indan-1-yl]methyl Benzoate (**16f**): A colorless gum, 74% ee, $[\alpha]_D^{21}$ +11.8° (c=1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.06—2.23 (2H, m), 2.96 (2H, t, J=7.5 Hz), 3.72 (2H, br s), 4.49 (2H, br s), 7.18 (1H, d, J=7.5 Hz), 7.22 (1H, dd, J=7.5, 1.5 Hz), 7.37 (1H, d, J=1.5 Hz), 7.47 (2H, t, J=7.5 Hz), 7.60 (1H, tt, J=7.5, 1.5 Hz), 8.05 (2H, br d, J=7.0 Hz). IR (KBr) cm^{-1}: 3540, 1720. *Anal.* Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41. Found: C, 67.95; H, 5.61.

[1-(Hydroxymethyl)benz[*e*]indan-1-yl]methyl Benzoate (**17f**): A colorless gum, 73% ee, $[\alpha]_D^{21}$ −32.5° (c=1.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.30—2.70 (2H, m), 3.13 (2H, t, J=7.5 Hz), 4.11 (1H, d, J=12.0 Hz), 4.32 (1H, d, J=12.0 Hz), 4.68 (1H, d J=11.5 Hz), 4.95 (1H, d, J=11.5 Hz), 7.30—7.70 (5H, m), 7.76 (1H, d, J=8.0 Hz), 7.87 (1H, d, J=8.0 Hz), 7.92 (2H, d, J=8.0 Hz), 8.11 (1H, d, J=8.0 Hz), 8.18 (1H, d, J=8.0 Hz). IR (KBr) cm^{-1}: 3560, 1720. *Anal.* Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.12; H, 6.30.

(1-Hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl Benzoate (**18f**): A colorless gum, 46% ee, $[\alpha]_D^{21}$ +11.2° (c=1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.78—2.08 (4H, m), 2.83 (2H, t, J=6.5 Hz), 3.81 (1H, d, J=11.5 Hz), 3.88 (1H, d, J=11.5 Hz), 4.49 (1H, d, J=11.0 Hz), 4.53 (1H, d, J=11.0 Hz), 7.13—7.30 (3H, m), 7.38—7.62 (4H, m), 8.03 (2H, d, J=8.5 Hz). IR (KBr) cm^{-1}: 3490, 1720. *Anal.* Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.64; H, 7.02.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)methyl-2-phenyl-1-butanol (9) Under a nitrogen atmosphere, *tert*-butyldimethylsilyl trifluoromethanesulfonate (*tert*-$BuMe_2SiOTf$) (0.050 ml, 0.22 mmol) was added to an ice-cooled solution of (*S*)-**3f** (85% ee) (25 mg, 0.088 mmol) and pyridine (0.10 ml) in dry *N*,*N*-dimethylformamide (DMF) (0.5 ml). The reaction mixture was stirred at room temperature for 25 min, and diethyl ether and water were added to it. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude silyl ether of **3f**. A solution of this crude product in dry CH_2Cl_2 (1 ml) was cooled to −50 °C, to which was added (iso-$Bu)_2AlH$ (0.95 M solution in hexane, 0.28 ml, 0.27 mmol) over a period of 2 min. The reaction mixture was stirred at −50 °C for 30 min, and sat. aqueous NH_4Cl was added. The whole mixture was stirred at room temperature for 10 min and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (hexane–ethyl acetate 6 : 1) to give (*R*)-**9** (19 mg, 69%, 84% ee) as a pale yellow syrup. $[\alpha]_D^{19}$ −3.7° (c=1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.08 (3H, s), 0.68 (3H, t, J=7.5 Hz), 0.85 (9H, s), 1.70—1.90 (2H, m), 2.76—2.81 (1H, m), 3.84—3.93 (2H, m), 4.02—4.07 (2H, m), 7.20—7.36 (5H, m). IR (KBr) cm^{-1}: 3480. *Anal.* Calcd for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27. Found: C, 69.88; H, 10.30. HR-FAB-MS *m/z*: 295.2094 $[M+H]^+$ (Calcd for $C_{17}H_{31}O_2Si$: 295.2093).

(*R*)-2-Hydroxymethyl-2-phenylbutanoic Acid (10) A mixture of (*S*)-**3f** (81% ee) (47 mg, 0.17 mmol) and pyridinium dichromate (PDC) (0.19 g, 0.51 mmol) in DMF (1 ml) was stirred at room temperature for 6 h, and diethyl ether and water were added to it. The organic layer was separated, washed with brine, dried with $MgSO_4$, and concentrated *in vacuo* to give the

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crude aldehyde (47 mg), which was dissolved in *tert*-BuOH (2.0 ml) and water (0.4 ml). NaH_2PO_4 (50 mg, 0.42 mmol), 2-methyl-2-butene (0.10 ml, 0.94 mmol), and $NaClO_2$ (20 mg, 0.17 mmol) were successively added in turn. The reaction mixture was stirred at room temperature for 3 h and concentrated *in vacuo* to about one-fifth of its original volume. The residue was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude carboxylic acid (46 mg). This product was dissolved in MeOH (1 ml), and a solution of KOH (48 mg) in water (1 ml) was added. The reaction mixture was stirred at room temperature for 3 d, and CH_2Cl_2 and 1% aqueous NaOH were added to it. The aqueous layer was separated, and the organic layer was extracted with 1% aqueous NaOH. After the addition of CH_2Cl_2, the combined aqueous layer was made acidic (pH 2—3) by the addition of 10% HCl with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate) to give (*R*)-**10** (16 mg, 47%) as colorless crystals, mp 75—77 °C (Et_2O–hexane), $[\alpha]_D^{24}$ +12.1° (*c*=1.1, $CHCl_3$) {lit.[3a] mp 75.3 °C, $[\alpha]_D^{20}$ −16.5° (*c*=1.0, $CHCl_3$) for 97% ee of (*S*)-form}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, *J*=7.5 Hz), 2.17 (2H, q, *J*=7.5 Hz), 4.03 (1H, d, *J*=11.5 Hz), 4.13 (1H, d, *J*=11.5 Hz), 7.20—7.45 (5H, m). IR (KBr) cm^{-1}: 3650—2250, 1705.

(*S*)-1-Benzoyloxymethyl-7-methoxyindan-1-carboxylic Acid (19) (a) By Oxidation of (*R*)-**15f**: To a solution of (*R*)-**15f** (71% ee) (0.92 g, 2.9 mmol) in dry DMF (10 ml) was added PDC (3.9 g, 10 mmol). The mixture was stirred at room temperature for 3 d. Water was added to the reaction mixture, and the product was extracted with diethyl ether. The organic layer was concentrated *in vacuo*. The residue was dissolved in 1% aqueous NaOH and washed with CH_2Cl_2. After the addition of ethyl acetate, the aqueous layer was made acidic (pH 2—3) by the addition of 1% HCl with vigorous stirring. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo* to give (*S*)-**19** (0.78 g, 81%) as a colorless solid. This product was subjected to the formation of a salt with (*S*)-phenylethylamine (*vide infra*).

(b) From the Optically Pure Salt (**20**): To a stirred suspension of optically pure **20** (70 mg, 0.16 mmol) in ethyl acetate (10 ml) was added 1% HCl (5 ml) at 0 °C, and the mixture was stirred at room temperature for 10 min. The organic layer was separated and worked up as usual to give optically pure (*S*)-**19** (51 mg, quant.) as a colorless solid, mp 122—125 °C (ethyl acetate–hexane), $[\alpha]_D^{20}$ −93.6° (*c*=0.5, MeOH). ^{1}H-NMR (dimethylsulfoxide-d_6) δ: 2.25—2.65 (2H, m), 2.95—3.10 (2H, m), 3.73 (3H, s), 4.57 (1H, d, *J*=11.0 Hz), 4.76 (1H, d, *J*=11.0 Hz), 6.79 (1H, d, *J*=8.5 Hz), 6.87 (1H, d, *J*=8.0 Hz), 7.21 (1H, t, *J*=8.0 Hz), 7.47 (2H, t, *J*=7.5 Hz), 7.62 (1H, t, *J*=7.0 Hz), 7.76 (2H, d, *J*=7.5 Hz), 12.53 (1H, br s). IR (KBr) cm^{-1}: 3500—2500, 1735, 1715, 1700, 1595. *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.78; H, 5.63.

(*S*)-1-Phenylethylammonium (*S*)-1-Benzoyloxymethyl-7-methoxyindan-1-carboxylate (20) To a solution of (*S*)-**19** (1.8 g, 5.8 mmol) in dry CH_2Cl_2 (18 ml) was added (*S*)-1-phenylethylamine (99% ee) (0.75 ml, 5.8 mmol). After being stirred for 20 min, the reaction mixture was concentrated *in vacuo*. The residual solid was recrystallized from ethyl acetate twice to give the optically pure **20** (1.0 g, 40%) as colorless crystals, mp 165—170 °C (ethyl acetate), $[\alpha]_D^{20}$ −83.0° (*c*=0.5, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, d, *J*=7.0 Hz), 2.35—2.45 (1H, m), 2.60—2.75 (1H, m), 3.08 (2H, t, *J*=7.5 Hz), 3.77 (3H, br s), 4.11 (1H, q, *J*=7.0 Hz), 4.69 (1H, d, *J*=11.0 Hz), 4.95 (1H, d, *J*=11.0 Hz), 6.67 (1H, d, *J*=7.5 Hz), 6.87 (1H, d, *J*=7.5 Hz), 7.18—7.39 (9H, m), 7.51 (1H, tt, *J*=7.5, 1.0 Hz), 7.85 (1H, dd, *J*=8.5, 1.0 Hz). IR (KBr) cm^{-1}: 3500—2500, 1710, 1560. *Anal.* Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.32; H, 6.55; N, 3.08.

Crystallography of 20 A single crystal (0.30×0.20×0.10 mm) of **20** was obtained by recrystallization from EtOH. Crystal data of **20**: $C_{27}H_{29}NO_5$, M.W.=447, monoclinic, space group $P2_1$, a=14.574(2) Å, b=7.014(2) Å, c=11.641(2) Å, β=102.17(1)°, V=1163.3(4) Å, Z=2, D_{calc}=1.28 g/cm^3, λ(Cu-$K\alpha$)=1.54178 Å, μ=6.28 cm^{-1}, R=0.029 and R_w=0.032 for 2079 reflections. All measurements were carried out with a Mac Science MXC 18 four-circle automated diffractometer with graphite monochromated Cu-$K\alpha$ radiation and an 18 kW rotating anode generator. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement. The data were collected at 288 K using the ω–2θ scan technique to an above maximum 2θ value of 130°. All intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SHELXS86.[14] The non-hydrogen atoms were refined anisotropically, while only the coordinates of the hydrogen atoms were refined. All calculations were performed using CRYSTAN-G crystallographic software from Mac Science. Tables of fractional atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC-137241).

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