Efficient Lipase-Catalyzed Enantioselective Desymmetrization of Prochiral 2,2-Disubstituted 1,3-Propanediols and Meso 1,2-Diols Using 1-Ethoxyvinyl 2-Furoate

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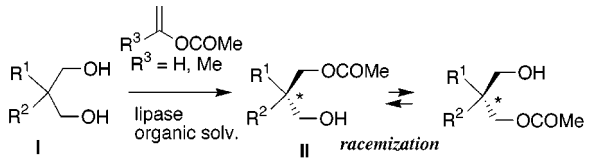
An efficient lipase-catalyzed desymmetrization of prochiral 2,2-disubstituted 1,3-propanediols was developed using 1-ethoxyvinyl 2-furoate **1b**, for which the well-known method using vinyl or isopropenyl acetate has had limited success due to low reactivity and easy racemization of the products through acyl group migration. The reagent **1b** is highly reactive and converts various prochiral 1,3-diols to the monoesters having a chiral quaternary carbon center with 82−99% ee. These products were stable against racemization under acidic conditions, and their furoyl groups were compatible with oxidative conditions. Prolonging the reaction time led to the kinetic resolution of the monoesters resulting in an increase of their optical purity. The similar desymmetrization of meso *cis*-1,2-cycloalkanediols gave the monoesters with 82−97% ee without racemization.

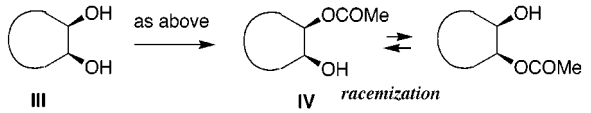
Introduction

A number of biologically important natural products contain optically active quaternary carbon center(s). Highly enantioselective, catalytic syntheses of these carbon centers have been a challenging area of research in this decade.[1] Though a variety of methods using metal catalysts have been reported, the enzyme-catalyzed enantioselective desymmetrization of symmetric compounds are also attractive and have intensively been investigated.[2] The examples include the hydrolysis of disubstituted malonates,[3] the hydrolysis of diesters derived from diols,[4] the hydrolysis of diesters of bis-enols,[5] and the reduction of 2,2-disubstituted 1,3-diones.[6] Whereas these are performed in aqueous media, the enantioselective transesterification of the 2,2-disubstituted 1,3-propanediols **I** (Scheme 1) seems to be efficient because of easy operation in organic solvents, simple workup, reuse of the lipases, and facile preparation of **I**. However, this approach has rarely been reported due to low reactivity of sterically congested substrates and the easy racemization of products **II** through the acyl group migration.[7−9] For instance, the reported enzymatic desymmetrization reactions of a few diols **I** using well-known acyl donors, i.e., vinyl and isopropenyl acetates, took several days or more and suffered from the partial racemization of **II** in some cases under acidic[7a] or hydrogenolysis conditions.[9] Likewise meso 1,2-diols **III** are suitable substrates of

Scheme 1



Scheme 2



(1) For reviews, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388−401.

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(4) (a) Suemune, H.; Harabe, T.; Xie, Z.-F.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 4337−4344. For related examples having a heteroatom-substituent, see: (b) Prasad, K.; Estermann, H.; Chen, C.-P.; Repic, O.; Hardtmann, G. E. *Tetrahedron: Asymmetry* **1990**, *1*, 421−424. (c) Estermann, H.; Prasad, K.; Shapiro, M. J. *Tetrahedron Lett.* **1990**, *31*, 445−448. (d) Watanabe, N.; Sugai, T.; Ohta, H. *Chem. Lett.* **1992**, 657−660. (e) Ito, T.; Takagi, Y.; Tsukube, H. *J. Mol. Catal. B* **1997**, 3, 259−270.

(5) Renouf, P.; Poirier, J.-M.; Duhamel, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1739−1745.

(6) Kitahara, T.; Miyake, M.; Kido, M.; Mori, K. *Tetrahedron: Asymmetry* **1990**, *1*, 775−782. Watanabe, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2919−2934. See also ref 1a.

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(8) For similar desymmetrizations of meso 1,5-diols, see: Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164−1171. Toyooka, N.; Nishino, A.; Momose, T. *Tetrahedron Lett.* **1993**, *34*, 4539−4540.

(9) Racemization of an optically acitve monoacetate like **II**, obtained by the enzymatic hydrolysis, was observed during hydrogenolysis using Pd/C in MeOH.[4a]

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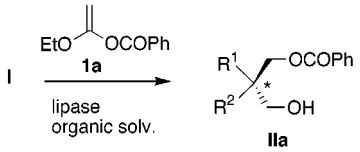
Scheme 3



lipase-catalyzed desymmetrization reactions; however, easy racemization of products **IV** has also been an annoying problem (Scheme 2).[10,11]

Therefore, to solve these problems, the development of an acyl donor exhibiting high reactivity and enantiotopic selectivity and generating products stable against racemization was necessary.

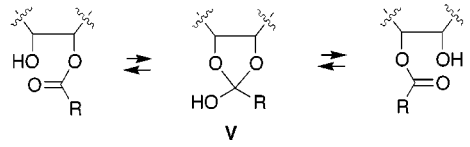
During the course of our research on the lipase-catalyzed transesterification of alcohols with novel acyl donors, 1-ethoxyvinyl esters **1**,[12] we developed 1-ethoxyvinyl benzoate **1a** as an effective reagent for the desymmetrization of **I**.[13] The reagent **1a** is more useful than the corresponding reagents having an aliphatic acyl group in terms of optical purity of the products **IIa** and their stability against racemization (Scheme 3). However, this method was still unsatisfactory for the sterically congested 1,3-diols such as **2A**−**D**, because the reactions took 4−7 days and the enantiotopic selectivity was not very high (up to 70's % ee) (see Table 2, right column).

Encouraged by our results with the benzoyl donor **1a**, we continued to search for an ethoxyvinyl aromatic ester for the desymmetrization of both 1,3-diols **I** and 1,2-diols **III** with improved performance characteristics. Very recently, we briefly communicated that 1-ethoxyvinyl 2-furoate **1b** was such a reagent with satisfactory performance.[14] In this paper, we describe the details of our results with some additional features of **1b** about an increase of the optical purity of the products through kinetic amplification.

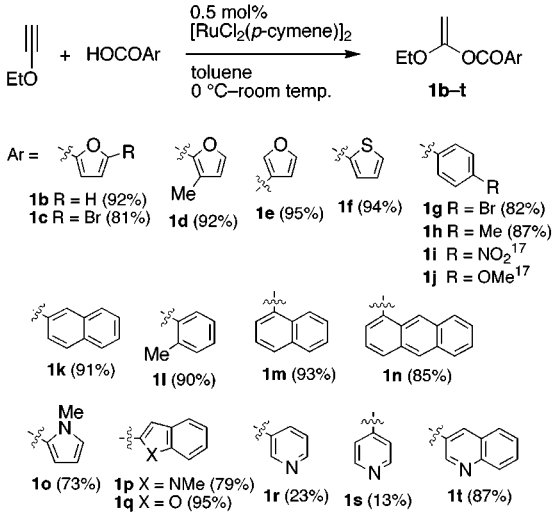
Results and Discussion

Preparation of Various 1-Ethoxyvinyl Aromatic Esters 1. It is well-known that the structure of the acyl moiety of an acyl donor highly affects both of the selectivity and the reactivity of the lipase-catalyzed transesterification reactions.[15] It is also reported that a benzoyl group migrates from one hydroxyl group of a monosaccharide to a neighboring hydroxyl group less readily than an acetyl group since the formation of the ortho ester intermediate **V** from the benzoate involves a greater loss in resonance energy (Scheme 4).[16] Therefore, we focused our attention to find a highly efficient ethoxyvinyl aromatic ester.

Scheme 4



Scheme 5



According to our method for preparation of the ethoxyvinyl esters **1**,[17] we prepared 19 aromatic esters **1b**−**t**, most of which were unknown, from commercial carboxylic acids (Scheme 5). Thus, a mixture of a carboxylic acid (1.0 equiv), ethoxyacetylene (1.5 equiv), and $[RuCl_2(p\text{-cymene})]_2$ (0.005 equiv) was stirred in toluene at 0 °C to room temperature for several hours followed by flash column chromatography on SiO_2 to give **1** in more than 80% yield in most cases. The isolated yields of **1r** and **1s** were low due to the poor solubility of the carboxylic acid and the instability of **1r** and **1s** to the chromatographic purification conditions.

Enantioselective Desymmetrization of Prochiral 2,2-Disubstituted 1,3-Propanediols 2. The preliminary evaluation of these aroyl reagents **1b**−**t** was performed on the desymmetrization of the congested diol **2A** using lipase MY (from *Candida rugosa*) under the same conditions as the previous desymmetrization of **2A** by **1a**.[13] Each reaction was quenched when **2A** was consumed. The reaction time, the optical purity, and the isolated yield of the product **3A** are summarized in Table 1. These results revealed that 1-ethoxyvinyl 2-furoate **1b** was the best reagent in terms of the reactivity, the enantioselectivity, and the yield. The 2-furoyl derivatives

(10) (a) Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron: Asymmetry* **1994**, *5*, 283−288. (b) *Idem Tetrahedron: Asymmetry* **1995**, *6*, 519−524. (c) Bremen, U.; Gais, H.-J. *Tetrahedron: Asymmetry* **1996**, *7*, 3063−3066. (d) Patti, A.; Sanfilippo, C.; Piattelli, M.; Nicolosi, G. *J. Org. Chem.* **1996**, *61*, 6458−6461.

(11) The the optically active monoacetates **IV**, obtained by the enzyme-catalyzed hydrolysis of the diacetates of **III**, have been reported to suffer from racemization during the enzymatic reaction and workup; see: (a) Crout, D. H. G.; Gaudet, V. S. B.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 808−810. (b) Xie, Z.-F.; Nakamura, I.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 966−967.

(12) Kita, Y.; Takebe, Y.; Murata, K.; Naka, T.; Akai, S. *Tetrahedron Lett.* **1996**, *37*, 7369−7372. Kita, Y.; Naka, T.; Imanishi, M.; Akai, S.; Takebe, Y.; Matsugi, M. *Chem. Commun.* **1998**, 1183−1184. Kita, Y.; Takebe, Y.; Murata, K.; Naka, T.; Akai, S. *J. Org. Chem.* **2000**, *65*, 83−88.

(13) Akai, S.; Naka, T.; Takebe, Y.; Kita, Y. *Tetrahedron Lett.* **1997**, *38*, 4243−4246; *Chem. Pharm. Bull.* **2000**, *48*, 1519−1523.

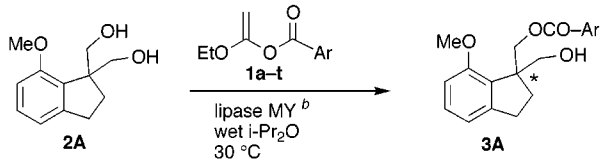
(14) Akai, S.; Naka, T.; Fujita, T.; Takebe, Y.; Kita. Y. *Chem. Commun.* **2000**, 1461−1462. In part, see also: Akai, S.; Tsujino, T.; Fukuda, N.; Iio, K.; Takeda, Y.; Kawaguchi, K.; Naka, T.; Higuchi, K.; Kita, Y. *Org. Lett.* **2001**, *3*, 4015−4018.

(15) For recent examples, see: Ema, T.; Maeno, S.; Takaya, Y.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1996**, *61*, 8610−8616. Nakamura, K.; Takenaka, K.; Ohno, A. *Tetrahedron: Asymmetry* **1998**, *9*, 4429−4439. Kawasaki, M.; Goto, M.; Kawabata, S.; Kometani, T. *Tetrahedron: Asymmetry* **2001**, *12*, 585−596.

(16) Hough, L.; Richardson, A. C. In *Rodd's Chemistry of Carbon Compounds*; Coffey, S., Ed.; Elsevier: New York, 1967; Vol. I, Part F, pp 382−386. Fromageot, H. P. M.; Reese, C. B.; Sulston, J. E. *Tetrahedron* **1968**, *24*, 3533−3540.

(17) Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2999−3005. Shibata, N.; Matsugi, M.; Kawano, N.; Fukui, S.; Fujimori, C.; Gotanda, K.; Murata, K.; Kita, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 303−310.

Table 1. Desymmetrization of 1,3-Diols 2A Using a Variety of Aroyl Donors 1a−t[a]



1, Ar =	time	3A	ee (%)[c]	yield (%)[d]
1b R = H	5 h	**3Ab**	81	69
1c R = Br	1 d	**3Ac**	81	46
1d	1 d	**3Ad**	62[f]	41
1e	1 d	**3Ae**	72	23
1f	1 d	**3Af**	75	60

1, Ar =	time	3A	ee (%)[c]	yield (%)[d]
1a R = H[e]	4 d	**3Aa**	71	82
1g R = Br	1 d	**3Ag**	86	50
1h R = Me	3 d	**3Ah**	82[f]	51
1i R = NO_2	1 d	**3Ai**	67	36
1j R = OMe	1 d	**3Aj**	80	25
1k	7 h	**3Ak**	50	22

Poorly reactive **1** (<ca.10% conversion after 7 d):

Ar = **1l**, **1m**, **1n**, **1o**, **1p** X = NMe, **1q** X = O, **1r**, **1s**, **1t**

[a] The reaction was run using **1** (3.0 equiv) under the identical reaction conditions (for details, see the typical procedure in the Experimental Section) and was quenched when **2A** was consumed. [b] Lipase from *Candida rugosa*. [c] Determined by HPLC using Daicel CHIRALCEL OD (hexane−*i*-PrOH), unless otherwise noted. [d] Isolated by flash column chromatography on SiO_2. The rest of the product was the corresponding diester. [e] Cited from ref 13. [f] Daicel CHIRALPAK AD (hexane−*i*-PrOH) was used.

1c,**d** having a substituent as well as the 3-furoyl **1e** and the 2-thienyl **1f** derivatives were also effective, giving the corresponding products **3Ac**−**3Af** with good enantioselectivity (62−81% ee); however, the reactions took 1 day, and their yields were not very high (23−60%). The benzoyl derivatives **1g**−**j**, having a substituent at the para-position, were also found to give the products **3Ag**−**3Aj** with good optical purity (67−86% ee) but with unsatisfactory reactivity (1−3 days) and yield (25−51%). 2-Naphthoyl derivative **1k** was reactive, but the selectivity was not sufficient. Other benzoyl derivatives **1l**−**n** having a substituent at the ortho-position and some heteroaromatic derivatives **1o**−**t** were poorly reactive.

Further investigation disclosed more advantages of **1b**, viz., (i) applicability to various substrates, (ii) increase of the optical purity of **3** through kinetic amplification, (iii) high stability of **3** against racemization, and (iv) inertness of **3** under oxidative conditions, as follows.

(i) High Applicability to Various 1,3-Diols 2 and (ii) Increase of the Optical Purity of 3 through Kinetic Amplification. The applicability of **1b** to various diols **2B**−**H** was examined under similar conditions, and the results are summarized in Table 2. Some of the results were compared with similar reactions using **1a** or a substituted benzoate **1g** (Table 2). Several features of **1b** are noteworthy: First, in all cases, **2B**−**H** were consumed within 5 h when **1b** was employed, whereas the reactions using **1a** and **1g** required at least 24 h and usually 100 h or more to consume the diols. Second, the optical purities and the yields of the products **3Ab**−**3Hb** were good-to-very high, which were similar to or higher than those obtained using **1g** and generally higher than those obtained using **1a**. Third, increase of the optical purity of **3** by prolonging the reaction time beyond the complete mono acylation of **2** was observed when **1b** was used. For instance, the optical purity of **3Ab** (81% ee) at 5 h was improved to 96% ee at 30 h, although the yield decreased (Table 2). The time course of this reaction shown in Figure 1 revealed that even if the enantiotopic selectivity was not high at the initial stage (63% ee at 15 min), the optical purity easily went up along the reaction time. Some other examples were obtained in the cases of **3Bb** and **3Db**. These results were ascribed to lipase-catalyzed kinetic resolution of **3**,[18] which was confirmed by the reaction of racemic **3Ab** with **1b** under similar conditions (Table 3 and Figure 2). Thus, the reaction proceeded quickly to give (*R*)-**3Ab** (51% ee, 44%

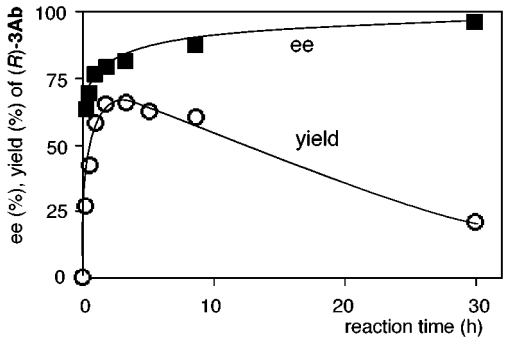
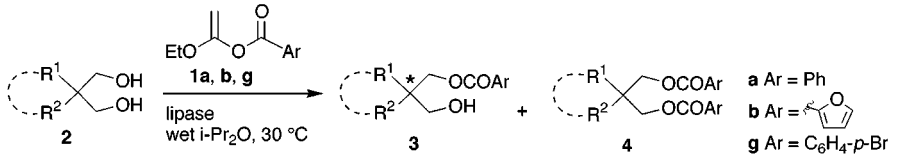
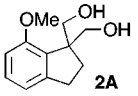
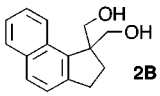
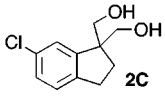
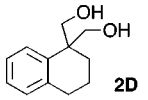
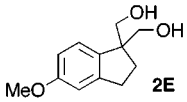
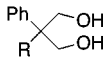


Figure 1. Time course of the reaction of **2A** with **1b**.

(18) Similar phenomena have been reported on the lipase-catalyzed transesterification of prochiral 2-monosubstituted 1,3-propanediols and hydrolysis of meso diacetates.[2,18a] However, opposite results were also reported.[18b] (a) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Gergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200−7205. (b) Guanti, G.; Banfi, L.; Brusco, S.; Narisano, E. *Tetrahedron: Asymmetry* **1994**, *5*, 537−540.

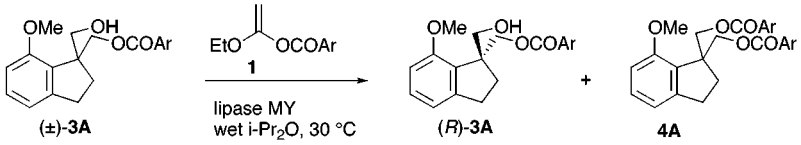
Table 2. Desymmetrization of Various 1,3-Diols 2 Using 1a,b,g[a]



2	lipase	using **1b**						using **1a**[b] or **1g**				
		3	time (h)	ee (%)[c]	yield (%)[d]	abs. config.	$[\alpha]_D$[e]	**1**	**3**	time (h)	ee (%)[c]	yield (%)[d]
 **2A**	MY	**3Ab**	5	81	69			**1a**	**3Aa**	100	71	82
	MY	**3Ab**	30	96	21	*R*	−39.5	**1g**	**3Ag**	24	86	50
 **2B**	MY	**3Bb**	5	79	93			**1a**	**3Ba**	170	73	53
	MY	**3Bb**	48	91	78	ND[f]	−16.5	**1g**	**3Bg**	120	81	74
 **2C**	MY	**3Cb**	5	85	71	ND[f]	+18.6	**1a**	**3Cb**	100	74	71
								1g	**3Cg**	100	71	81
 **2D**	MY	**3Db**	5	61	84			**1a**	**3Da**	170	46	74
	MY	**3Db**	48	83	25	ND[f]	+14.5					
 **2E**	MY	**3Eb**	5	92	35	ND[f]	+30.8					
 **2F** R = Me	CRL/HSC[g]	**3Fb**	5	>99	66	*S*	−4.9					
2G R = Et	CRL/HSC[g]	**3Gb**	2	89	87	*S*	−10.3					
2H R = allyl	CRL/HSC[g]	**3Hb**	2	82	72	*S*	−19.3					

[a] The reaction was run using **1** (3.0 equiv for **2A**−**E** or 1.5 equiv for **2F**−**H**) and was quenched when **2** was consumed. For **3Ab**, **3Bb**, and **3Db**, the result of the prolonged reaction is shown in the second line. [b] Cited from ref 13. [c] Determined by HPLC using Daicel CHIRALCEL OD (hexane−*i*-PrOH). [d] Isolated by flash column chromatography on SiO_2. [e] For the temperature and the concentration, see the Experimental Section. [f] Not determined. [g] CRL (from *Candida rugosa*) immobilized on Hyflo Super Cell.

Table 3. Kinetic Resolution of (±)-3Aa, 3Ab, and 3Ag Using 1a,b,g[a]



(±)-3A	1, Ar =	time(h)	conv. (%)	(*R*)-3A ee (%)[b]	(*R*)-3A yield (%)[c]	4A	4A, yield(%)[c]
(±)-**3Ab**	 **1b**	2	~50	(*R*)-**3Ab**	51	44	**4Ab** 47
(±)-**3Aa**	 **1a**	250	<10	(*R*)-**3Aa**	<10	>90	**4Aa** <10
(±)-**3Ag**	 **1g**	250	—	(*R*)-**3Ag**	—	100	**4Ag** —

[a] For the reaction conditions, see the Experimental Section. [b] Determined by HPLC using Daicel CHIRALCEL OD (hexane−i-PrOH). [c] Isolated by flash column chromatography on SiO_2.

yield), the same enantiomer obtained by the above-mentioned desymmetrization of **2A**, and the diester **4Ab** (47% yield) for 2 h. It is worth noticing that the similar reaction of the monobenzoate (±)-**3Aa** with the corresponding benzoyl donor **1a** was very tardy, resulting in less than 10% conversion after 250 h, although we previously observed a similar kinetic amplification by **1a** for the less congested acyclic 1,3-diol **2G**.[13] In addition, the reaction of (±)-**3Ag** with **1g** did not proceed at all. All these results disclosed that the quite high reactivity and the kinetic resolution of the monofuroate **3b** are the distinguishing features of **1b**, affording the highly optically pure **3b** within a reasonable reaction time.

In every case, the diester **4** was the only side product, which was quantitatively hydrolyzed to the starting diol **2** by alkaline hydrolysis. Therefore, the overall reaction

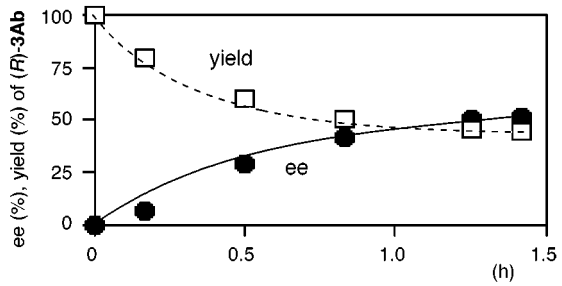
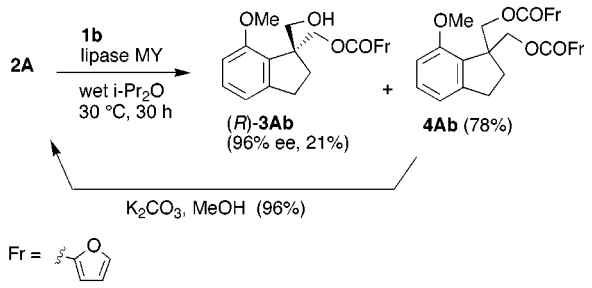


Figure 2. Time course of the kinetic resolution of (±)-**3Ab** with **1b**.

Scheme 6



provides preparation of optically active **3** without any significant loss of chemical yield. An example is shown in Scheme 6.

(iii) Stability of the Monofuroates 3b under Acidic Conditions. The stability of the furoate **3b** under acidic conditions was very much improved as noted from the following example. Thus, **3Gb** was inert to racemization in an acidic medium (0.1 equiv of camphorsulfonic acid, 4×10^{-4} M in CH_2Cl_2) at room temperature after 1 day, whereas the same treatment of the corresponding benzoate **3Ga** resulted in gradual racemization ($t_{1/2} = 18$ h) (Figure 3).[13] All the products **3Ab**−**3Hb** were easily isolated by standard column chromatography on SiO_2 with retention of the optical purity.

(iv) Stability of the Monofuroates 3b under Oxidative Conditions. The furoate moiety was preserved under oxidizing conditions. For instance, neither a decrease in optical purity nor decomposition of the furan ring was observed in the treatment of **3Gb** (88% ee) with the Dess−Martin periodinane leading to the corresponding aldehyde **5b** (88% ee, quant). Further treatment of **5b** with $NaClO_2$ afforded the carboxylic acid **6b** (quant), which was subjected to methanolysis giving the hydroxyl carboxylic acid **7b** (89%; Scheme 7).

(v) The Absolute Stereochemistry of 3. The absolute stereochemistry of **7b** was determined to be *R* by comparison of its specific rotation {$[\alpha]_D^{22} = +14.3$ (c = 0.8, $CHCl_3$)} with the reported value for 97% ee of the (*S*)-form {$[\alpha]_D^{20} = -16.5$ (c 1.0, $CHCl_3$)},[3c] and thereby that of **3Gb** to be *S*. Similarity of the specific rotations of **3Fb** and **3Hb** with that of (*S*)-**3Gb** estimated their absolute stereochemistry to be *S*.

The absolute stereochemistries of **3Ab** and **3Ag** were determined to be the same as that of the known compound (*R*)-**3Aa**[13] as follows: Silylation of **3Ab** with (*t*-Bu)Me_2SiCl−pyridine followed by either methanolysis (method A) or reduction (method B) gave the monosilyl ether **8** in 88−95% yields. Similarly, (*R*)-**3Aa** was converted to (*S*)-**8** by method B. These two products were found to have the same absolute configuration based on

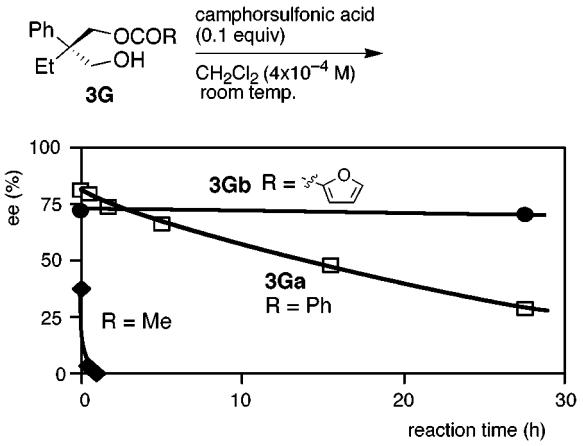
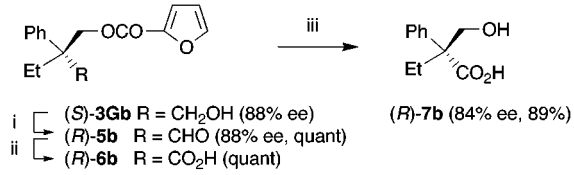


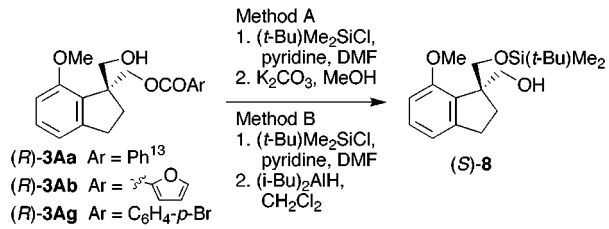
Figure 3. Stability of **3G** under acidic conditions. Results of the acetate (R = Me) and the benzoate **3Ga** are cited from ref 13.

Scheme 7[a]

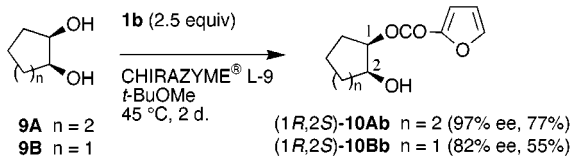


[a] Reagents and conditions: i, Dess−Martin periodinane, CH_2Cl_2; ii, $NaClO_2$, NaH_2PO_4, *t*-BuOH−H_2O; iii, NaOMe, MeOH.

Scheme 8



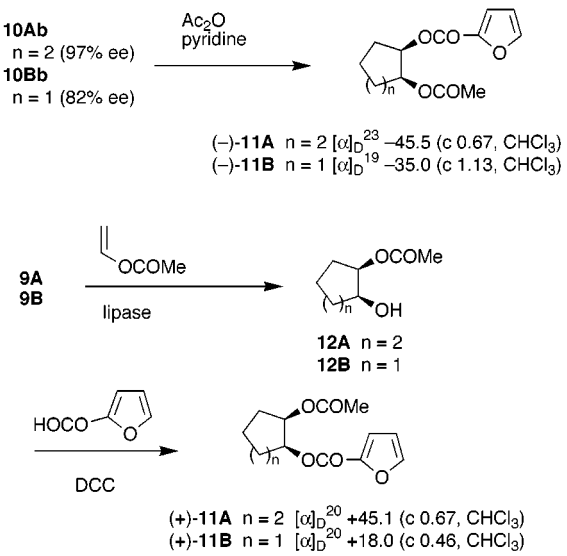
Scheme 9



the HPLC analysis using a chiral column, and thereby, the absolute stereochemistry of **3Ab** was determined to be *R*. In a similar manner, that of **3Ag** was found to be *R* (Scheme 8). The absolute stereochemistry of **3Bb**−**3Eb** has not been established yet.

Enantioselective Desymmetrization of Meso *cis*-1,2-Cycloalkanediols 9 Using 1b. The high utility of **1b** was also apparent in the desymmetrization of the meso *cis*-1,2-cycloalkanediols (**9A**,**B**). The reaction of **9A** with **1b** using CHIRAZYME L-9 (from *Mucor miehei*) provided the monofuroate (1*R*,2*S*)-**10Ab** (97% ee, 77% yield) (Scheme 9). Likewise, the desymmetrization of the cyclopentanediol **9B** gave (1*R*,2*S*)-**10Bb** (82% ee, 55% yield). A similar enantioselective desymmetrization of **9A**,**B** was reported using vinyl acetate; however, column chromatography on SiO_2 of the products often suffered from a decrease of the optical purity.[10b] On the other

Scheme 10



hand, the optical purity of **10Ab** and **10Bb** did not change at all during the standard SiO_2 column chromatography.

Determination of the absolute stereochemistry of **10Ab** and **10Bb** was performed by their derivatization to the compounds (**11A** and **11B**) and the comparison of their specific rotations with those of the compounds derived from the authentic samples (**12A,B**) prepared by the reported method[10b] (Scheme 10).

Conclusions

The above-mentioned procedure using **1b** features the following four advantages: (1) **1b** is readily prepared from commercially available ethoxyacetylene and 2-furoic acid in a large scale (20 g or more) in high yield (in detail, see the Experimental Section). Compound **1b** can be stored in a refrigerator for more than 1 year. (2) The reaction using **1b** is usually complete within several hours to give the products in high optical and chemical yields. If necessary, the only side products, diesters, can be recycled to the starting diols quantitatively. (3) Prolonging the reaction time increases the optical purity of the products through kinetic amplification. (4) Products are sufficiently stable under acidic and/or oxidative conditions. Therefore, the present procedure provides a novel, promising synthetic method of optically active compounds having a quaternary carbon center at the benzylic position and the optically active cycloalkane 1,2-diol derivatives.

From a mechanistic point of view, the quite high reactivity and high enantiotopic selectivity of **1b** are outstanding among a large number of acyl donors. An evaluation study on the mechanism and its synthetic application is now in progress in our laboratory.

Experimental Section

General Methods. All melting points (mp) and boiling points are uncorrected. Gas−liquid chromatography (GLC) analyses were carried out using a Hewlett Packard HP-5 column (Crosslinked 5% PH ME siloxane, 30 m × 0.32 mm, 0.25 μm film thickness). ^{1}H NMR spectra were measured at 300 MHz with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded by diffuse reflectance measurement of samples dispersed in a KBr powder or as a $CHCl_3$ solution. Chiral HPLC analyses were carried out using Daicel CHIRALCEL OD (250 mm × 4.6 mm, eluent: hexane−*i*-PrOH), Daicel CHIRALPAK AD (250 mm × 4.6 mm, eluent: hexane−*i*-PrOH), and Daicel CHIRALCEL OJ (250 mm × 4.6 mm, eluent: hexane−*i*-PrOH) columns. 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.). Lipase MY (from *Candida rugosa*) was a gift from Meito Sangyo Co., Ltd.. CHIRAZYME L-9 (from *Mucor miehei*) was a gift from Roche Diagnotics. CRL (0.30 g, from *Candida rugosa*, Lipase Type VII, Sigma) was immobilized on Hyflo Super Cell (HSC) (0.30 g) using deionized water (20 mL) by a standard freeze-drying method. Enzymes were dried (0.5 mmHg, room temperature, overnight) prior to use. Wet *i*-Pr_2O was prepared by vigorously stirring a 1000:1 mixture of distilled *i*-Pr_2O and water for 20−30 min using a magnetic stirrer and decanting the ether layer after settling down. Yields refer to isolated material of ≥95% purity as determined by ^{1}H NMR.

Preparation of the Reagents and the Diols. Known ethoxyvinyl esters (**1a**,**i**,**j**)[17] and diols (**2A**−**D**,[13] **2F**,[13] **2G**,[13] and **2H**[19]) were prepared by the reported method. Unknown esters (**1b**−**h**,**k**−**t**) and diol **2E** were similarly prepared as follows. We used ethoxyacetylene prepared by the literature method[20] (*Caution: Quenching the reaction by addition of brine as is mentioned in the literature is very dangerous. This may cause ignition even when one adds brine dropwise at −78 °C. We recommend quenching the reaction with EtOH or a 1:1 mixture of EtOH and 1,2-propanediol at −78 °C followed by dropwise addition of brine.*). Ethoxyacetylene is available from Acros as a 50 wt % solution in hexanes, and the use of this solution as such without purification gave similar results. [$RuCl_2$(*p*-cymene)]$_2$ is commercially available from Aldrich and used as such without purification.

1-Ethoxyvinyl 2-Furoate (1b). A Typical Procedure for the Preparation of the Ethoxyvinyl Esters. Under a nitrogen atmosphere, a solution of ethoxyacetylene (0.60 mL, 7.2 mmol) in anhydrous toluene (1.5 mL) was added to an ice-cooled mixture of 2-furoic acid (0.46 g, 4.1 mmol) and [$RuCl_2$(*p*-cymene)]$_2$ (13 mg, 0.020 mmol) in anhydrous toluene (8.0 mL). The reaction mixture was stirred at room temperature. The remaining carboxylic acid was monitored by SiO_2 TLC (it usually takes about 5 h to consume the carboxylic acid). The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (hexanes−EtOAc−Et_3N = 100:10:1) to give **1b** (0.68 g, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, t, J = 7.0 Hz), 3.88 (1H, d, J = 3.5 Hz), 3.92 (2H, q, J = 7.0 Hz), 3.97 (1H, d, J = 3.5 Hz), 6.56 (1H, dd, J = 2.0, 3.5 Hz), 7.31 (1H, dd, J = 1.0, 3.5 Hz), 7.65 (1H, dd, J = 1.0, 2.0 Hz). IR ($CHCl_3$): 1744, 1674 cm^{-1}. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.37; H, 5.55.

Large-Scale Preparation of 1b. Similarly to the above procedure, a mixture of ethoxyacetylene (20 mL, 0.24 mol), 2-furoic acid (18.0 g, 0.16 mol), and [$RuCl_2$(*p*-cymene)]$_2$ (0.20 g, 0.33 mmol) in anhydrous toluene (350 mL) was stirred at room temperature overnight and concentrated in vacuo. Distillation of the residue gave **1b** (22.5 g, 77%). Bp 80−83 °C/0.35 mmHg.

1-Ethoxyvinyl 5-Bromo-2-furoate (1c). A colorless oil: 81% yield. ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, t, J = 7.0 Hz), 3.87 (1H, d, J = 4.0 Hz), 3.93 (2H, q, J = 7.0 Hz), 3.97 (1H, d, J = 4.0 Hz), 6.50 (1H, d, J = 3.5 Hz), 7.24 (1H, d, J = 3.5 Hz). IR ($CHCl_3$): 1746, 1678 cm^{-1}. HRMS. Calcd for $C_9H_9{}^{81}BrO_4$ (M^+): 259.9684. Found: 259.9649.

1-Ethoxyvinyl 3-Methyl-2-furoate (1d). A colorless oil: 92% yield. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, t, J = 7.0 Hz), 2.39 (3H, s), 3.87 (1H, d, J = 3.5 Hz), 3.94 (2H, q, J = 7.0 Hz), 3.97 (1H, d, J = 3.5 Hz), 6.40 (1H, d, J = 1.5 Hz), 7.49 (1H, d, J = 1.5 Hz). IR ($CHCl_3$): 1736, 1676 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.13; H, 6.19.

(19) Monkovic, I.; Perron, Y. G.; Martel, R.; Simpson, W. J. *J. Med. Chem.* **1973**, *16*, 403−407.
(20) Jones, E. R. H.; Eglinton, G.; Whiting, M. C.; Shaw, B. L. *Org. Synth.* **1954**, *34*, 46−49.

1-Ethoxyvinyl 3-Furoate (1e). A colorless oil: 95% yield. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, t, J = 7.0 Hz), 3.85 (1H, d, J = 3.5 Hz), 3.92 (2H, q, J = 7.0 Hz), 3.93 (1H, d, J = 3.5 Hz), 6.80 (1H, dd, J = 1.0, 2.0 Hz), 7.45 (1H, t, J = 1.5 Hz), 8.10 (1H, dd, J = 1.0, 1.5 Hz). IR ($CHCl_3$): 1740, 1676 cm^{-1}. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.30; H, 5.79.

1-Ethoxyvinyl Thiophene-2-carboxylate (1f). A colorless oil: 94% yield. ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, J = 7.0 Hz), 3.87 (1H, d, J = 3.5 Hz), 3.94 (2H, q, J = 7.0 Hz), 3.98 (1H, d, J = 3.5 Hz), 7.14 (1H, dd, J = 4.0, 5.0 Hz), 7.31 (1H, dd, J = 1.5, 5.0 Hz), 7.90 (1H, dd, J = 1.5, 4.0 Hz). IR ($CHCl_3$): 1734, 1676 cm^{-1}. HRMS. Calcd for $C_9H_{10}O_3S$ (M^+): 198.0351. Found: 198.0342.

1-Ethoxyvinyl 4-Bromobenzoate (1g). A colorless oil: 82% yield. ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, J = 7.0 Hz), 3.88 (1H, d, J = 3.5 Hz), 3.95 (2H, q, J = 7.0 Hz), 3.96 (1H, d, J = 3.5 Hz), 7.61 (2H, d, J = 8.5 Hz), 7.96 (2H, d, J = 8.5 Hz). IR ($CHCl_3$): 1746, 1676 cm^{-1}. HRMS. Calcd for $C_{11}H_{11}{}^{81}BrO_3$ (M^+): 269.9891. Found: 269.9904.

1-Ethoxyvinyl 4-Methylbenzoate (1h). A colorless oil: 87% yield. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, t, J = 7.0 Hz), 2.42 (3H, s), 3.87 (1H, d, J = 3.5 Hz), 3.95 (2H, q, J = 7.0 Hz), 3.96 (1H, d, J = 3.5 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.99 (2H, d, J = 8.0 Hz). IR ($CHCl_3$): 1744, 1674 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.84; H, 6.90.

1-Ethoxyvinyl Naphthalene-2-carboxylate (1k). Colorless powder: 91% yield. Mp 51−52 °C. ^{1}H NMR ($CDCl_3$): δ 1.39 (3H, t, J = 7.0 Hz), 3.92 (1H, d, J = 3.5 Hz), 3.99 (2H, q, J = 7.0 Hz), 4.02 (1H, d, J = 3.5 Hz), 7.53−7.68 (2H, m), 7.89 (1H, d, J = 8.0 Hz), 7.90 (1H, d, J = 8.0 Hz), 7.97 (1H, d, J = 7.5 Hz), 8.10 (1H, dd, J = 1.0, 8.0 Hz), 8.69 (1H, s). IR ($CHCl_3$): 1742, 1674 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.45; H, 5.90.

1-Ethoxyvinyl 2-Methylbenzoate (1l). A colorless oil: 90% yield. ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, J = 7.5 Hz), 2.64 (3H, s), 3.87 (1H, d, J = 3.5 Hz), 3.95 (2H, q, J = 7.5 Hz), 3.96 (1H, d, J = 3.5 Hz), 7.25−7.29 (2H, m), 7.42−7.48 (1H, m), 8.03−8.06 (1H, m). IR ($CHCl_3$): 1752, 1674 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.80 H, 6.98.

1-Ethoxyvinyl Naphthalene-1-carboxylate (1m). Colorless powder: 93% yield. Mp 53−54 °C. ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, t, J = 7.0 Hz), 3.93 (1H, d, J = 3.5 Hz), 4.00 (2H, q, J = 7.0 Hz), 4.03 (1H, d, J = 3.5 Hz), 7.61−7.67 (3H, m), 7.90 (1H, d, J = 8.0 Hz), 8.08 (1H, d, J = 8.5 Hz), 8.36 (1H, d, J = 8.5 Hz), 9.02 (1H, d, J = 8.5 Hz). IR ($CHCl_3$): 1742, 1674 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.87.

1-Ethoxyvinyl Anthracene-1-carboxylate (1n). Colorless powder: 85% yield. Mp 77−79 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (3H, t, J = 7.0 Hz), 3.99 (1H, d, J = 4.0 Hz), 4.06 (2H, q, J = 7.0 Hz), 4.16 (1H, d, J = 4.0 Hz), 7.48−7.61 (4H, m), 8.01−8.22 (4H, m), 8.56 (1H, s). IR ($CHCl_3$): 1752, 1676 cm^{-1}. Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.21; H, 5.65.

1-Ethoxyvinyl 1-Methylpyrrole-2-carboxylate (1o). A colorless oil: 73% yield. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, t, J = 7.0 Hz), 3.84 (1H, d, J = 3.5 Hz), 3.91 (2H, q, J = 7.0 Hz), 3.93 (3H, s), 3.96 (1H, d, J = 3.5 Hz), 6.14 (1H, dd, J = 2.5, 4.0 Hz), 6.85 (1H, dd, J = 1.5, 2.5 Hz), 7.07 (1H, dd, J = 1.5, 4.0 Hz). IR ($CHCl_3$): 1727, 1674 cm^{-1}. HRMS. Calcd for $C_{10}H_{13}NO_3$ (M^+): 195.0895. Found: 195.0915.

1-Ethoxyvinyl 1-Methylindole-2-carboxylate (1p). Pale brown powder: 79% yield. Mp 84−86 °C. ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, t, J = 7.0 Hz), 3.89 (1H, d, J = 3.5 Hz), 3.96 (2H, q, J = 7.0 Hz), 3.99 (1H, d, J = 3.5 Hz), 4.09 (3H, s), 7.13−7.19 (1H, m), 7.31−7.47 (2H, m), 7.44 (1H, s), 7.69 (1H, d, J = 8.0 Hz). IR ($CHCl_3$): 1727, 1674 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N 5.71. Found: C, 68.53; H, 6.18; N 5.71.

1-Ethoxyvinyl Benzofuran-2-carboxylate (1q). White powder: 95% yield. Mp 44−45 °C. ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, t, J = 7.0 Hz), 3.92 (1H, d, J = 3.5 Hz), 3.97 (2H, q, J = 7.0 Hz), 4.03 (1H, d, J = 3.5 Hz), 7.32 (1H, t, J = 7.0 Hz), 7.48 (1H, t, J = 7.0 Hz), 7.52−7.82 (3H, m). IR ($CHCl_3$): 1746, 1678 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.99; H, 5.26.

1-Ethoxyvinyl Pyridine-3-carboxylate (1r). A brown oil: 23% yield. ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, t, J = 7.0 Hz), 3.91 (1H, d, J = 4.0 Hz), 3.97 (2H, q, J = 7.0 Hz), 3.99 (1H, d, J = 4.0 Hz), 7.41−7.45 (1H, m), 8.34−8.38 (1H, m), 8.83 (1H, dd, J = 2.0, 5.0 Hz), 9.29 (1H, dd, J = 1.0, 2.5 Hz). IR ($CHCl_3$): 1746, 1678 cm^{-1}. HRMS. Calcd for $C_{10}H_{11}NO_3$ (M^+): 193.0737. Found: 193.0742.

1-Ethoxyvinyl Pyridine-4-carboxylate (1s). A brown oil: 13% yield. ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, t, J = 7.0 Hz), 3.90 (1H, d, J = 4.0 Hz), 3.96 (2H, q, J = 7.0 Hz), 3.99 (1H, d, J = 4.0 Hz), 7.90 (1H, dd, J = 1.5, 4.5 Hz), 8.82 (1H, dd, J = 1.5, 4.5 Hz). IR ($CHCl_3$): 1755, 1676 cm^{-1}. HRMS. Calcd for $C_{10}H_{11}NO_3$ (M^+): 193.0748. Found: 193.0742.

1-Ethoxyvinyl Quinoline-3-carboxylate (1t). Pale brown powder: 87% yield. Mp 71−72 °C. ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, t, J = 7.0 Hz), 3.94 (1H, d, J = 4.0 Hz), 3.98 (2H, q, J = 7.0 Hz), 4.05 (1H, d, J = 4.0 Hz), 7.65 (1H, t, J = 7.5 Hz), 7.87 (1H, t, J = 7.5 Hz), 7.96 (1H, d, J = 7.5 Hz), 8.19 (1H, d, J = 7.5 Hz), 8.93 (1H, s), 9.49 (1H, s). IR ($CHCl_3$): 1748, 1676 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N 5.76. Found: C, 69.07; H, 5.45; N 5.70.

1,1-Bis(hydroxymethyl)-5-methoxyindan (2E) was prepared by a standard reduction of the corresponding malonate[21] using $LiAlH_4$. Colorless crystals. Mp 118−119 °C. ^{1}H NMR ($CDCl_3$): δ 1.97 (2H, t, J = 5.5 Hz), 2.10 (2H, t, J = 7.5 Hz), 2.92 (2H, t, J = 7.5 Hz), 3.73−3.88 (4H, m), 3.79 (3H, s), 6.72−6.81 (2H, m), 7.16 (1H, d, J = 8.5 Hz). HRMS. Calcd for $C_{12}H_{16}O_3$ (M^+): 208.1094. Found: 208.1099. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.27; H, 7.69.

Enzymatic Desymmetrization of the 1,3-Diols (2A−H). A General Procedure. To a mixture of **1** (0.60 mmol) and **2A−E** (0.20 mmol) in wet *i*-Pr_2O (3.0 mL) was added lipase MY (125 mg). The reaction of **2F,G** was run using **1** (0.26 mmol), **2F−H** (0.17 mmol), and CRL/HSC (100 mg) in wet *i*-Pr_2O (2.0 mL). The reaction mixture was stirred at 30 °C for the time shown in Tables 1 and 2 and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−ethyl acetate) to give the monoester **3** and the diester **4**. The isolated yield and the optical purity of the products are listed in Tables 1 and 2. The optical purity of **3** was determined by HPLC using CHIRALCEL OD or CHIRALPAK AD.

(*R*)−(1-Hydroxymethyl-7-methoxyindan-1-yl)methyl 2-Furoate (3Ab). A colorless oil: 96% ee; $[\alpha]_D^{28} = -39.5$ (c = 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.00−2.23 (2H, m), 2.83−3.03 (3H, m), 3.83 (3H, s), 3.90−3.99 (2H, m), 4.49 (1H, d, J = 10.5 Hz), 4.66 (1H, d, J = 10.5 Hz), 6.48 (1H, dd, J = 2.0, 3.5), 6.73 (1H, d, J = 8.0 Hz), 6.87 (1H, d, J = 8.0 Hz), 7.08 (1H, dd, J = 1.0, 3.5), 7.21 (1H, t, J = 8.0 Hz), 7.56 (1H, dd, J = 1.0, 2.0 Hz). IR (KBr): 3600−3200, 1719, 1588 cm^{-1}. HRMS. Calcd for $C_{17}H_{18}O_5$ (M^+): 302.1154. Found: 302.1153.

[1-(Hydroxymethyl)benz[*e*]indan-1-yl]methyl 2-Furoate (3Bb). A colorless oil: 91% ee; $[\alpha]_D^{23} = -16.5$ (c = 0.68, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.76 (1H, t, J = 6.5 Hz), 2.29−2.51 (2H, m), 3.09−3.15 (2H, m), 4.15−4.31 (2H, m), 4.65 (1H, d, J = 11.0 Hz), 4.88 (1H, d, J = 11.0 Hz), 6.48 (1H, dd, J = 2.0, 3.5 Hz), 7.05 (1H, d, J = 3.5 Hz), 7.38−7.50 (3H, m), 7.57 (1H, dd, J = 1.0, 2.0 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.87 (1H, d, J = 8.0 Hz), 8.18 (1H, d, J = 8.0 Hz). IR (KBr): 3750−3250, 1732, 1582 cm^{-1}. HRMS. Calcd for $C_{20}H_{18}O_4$ (M^+): 322.1205. Found: 322.1204.

[(6-Chloro-1-(hydroxymethyl)indan-1-yl]methyl 2-Furoate (3Cb). A colorless oil: 85% ee; $[\alpha]_D^{23} = +18.6$ (c = 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.02−2.21 (2H, m), 2.30 (1H, t, J = 6.0 Hz), 2.95 (2H, t, J = 7.5 Hz), 3.66−3.77 (2H, m), 4.42 (1H, d, J = 11.0 Hz), 4. 50 (1H, d, J = 11.0 Hz), 6.55 (1H, dd, J = 2.0, 3.5 Hz), 7.15−7.22 (3H, m), 7.37 (1H, d, J = 3.5 Hz), 7.62 (1H, dd, J = 1.0, 2.0 Hz). IR (KBr): 3700−3200, 1715,

(21) Citterio, A.; Fancelli, D.; Finzi, C.; Pesce, L. *J. Org. Chem.* **1989**, *54*, 2713−2718.

1601 cm^{-1}. HRMS. Calcd for $C_{16}H_{15}ClO_4$ (M^+): 306.0659. Found: 306.0677.

(1-Hydroxymethyl-1,2,3,4-tetrahydro-1-naphthyl)methyl 2-Furoate (3Db). A colorless oil: 83% ee; $[\alpha]_D^{23} = +14.5$ ($c = 0.52$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.84−1.93 (5H, m), 1.98 (1H, t, $J = 7.0$ Hz), 2.81 (2H, t, $J = 6.0$ Hz), 3.83 (2H, d, $J = 7.0$ Hz), 4.45 (1H, d, $J = 11.0$ Hz), 4.51 (1H, d, $J = 11.0$ Hz), 6.52 (1H, dd, $J = 2.0$, 3.5 Hz), 7.15−7.29 (4H, m), 7.45−7.48 (1H, m), 7.60 (1H, dd, $J = 1.0$, 2.0 Hz). IR (KBr): 3700−3200, 1715, 1582 cm^{-1}. HRMS. Calcd for $C_{17}H_{18}O_4$ (M^+): 286.1205. Found: 286.1186.

(1-Hydroxymethyl-5-methoxyindan-1-yl)methyl 2-Furoate (3Eb). A colorless oil: 92% ee; $[\alpha]_D^{23} = +30.8$ ($c = 0.96$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.01−2.22 (3H, m), 2.96 (2H, t, $J = 7.5$ Hz), 3.65−3.76 (2H, m), 3.79 (3H, s), 4.42 (1H, d, $J = 11.0$ Hz), 4.48 (1H, d, $J = 11.0$ Hz), 6.53 (1H, dd, $J = 2.0$, 3.5 Hz), 6.74 (1H, dd, $J = 2.0$, 8.0 Hz), 6.80 (1H, d, $J = 2.0$ Hz), 7.20 (1H, br d, $J = 3.5$ Hz), 7.26 (1H, d, $J = 8.0$ Hz), 7.61 (1H, dd, $J = 1.0$, 2.0 Hz). IR (KBr): 3600−3200, 1732, 1580 cm^{-1}. HRMS. Calcd for $C_{17}H_{18}O_5$ (M^+): 302.1154. Found: 302.1155.

(*S*)-3-Hydroxy-2-methyl-2-phenyl-1-propyl 2-Furoate (3Fb). A colorless oil: >99% ee; $[\alpha]_D^{20} = -4.9$ ($c = 0.86$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.43 (3H, s), 1.98 (1H, t, $J = 6.5$ Hz), 3.83 (2H, d, $J = 6.5$ Hz), 4.55 (1 H, d, $J = 11.0$ Hz), 4.60 (1H, d, $J = 11.0$ Hz), 6.50 (1H, dd, $J = 2.0$, 3.5), 7.13 (1H, dd, $J = 1.0$, 3.5), 7.29−7.46 (5H, m), 7.57 (1H, dd, $J = 1.0$, 2.0 Hz). IR ($CHCl_3$): 3700−3200, 1728, 1640, 1582 cm^{-1}. HRMS. Calcd for $C_{15}H_{16}O_4$ (M^+): 260.0777. Found: 260.0772.

(*S*)-2-Ethyl-3-hydroxy-2-phenyl-1-propyl2-Furoate(3Gb). A colorless oil: 89% ee; $[\alpha]_D^{20} = -10.3$ ($c = 0.93$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.74 (3H, t, $J = 7.5$ Hz), 1.83 (2H, q, 7.5 Hz), 2.01 (1H, t, $J = 6.5$ Hz), 3.80−3.96 (2H, m), 4.67 (1H, d, $J = 11.0$ Hz), 4.72 (1H, d, $J = 11.0$ Hz), 6.50 (1H, dd, $J = 1.5$, 3.0 Hz), 7.14 (1H, d, $J = 3.0$ Hz), 7.24−7.41 (5H, m), 7.58 (1H, d, $J = 1.5$ Hz). IR ($CHCl_3$): 3700−3200, 1720, 1580 cm^{-1}. HRMS. Calcd for $C_{16}H_{18}O_4$ (M^+): 274.1045. Found: 274.1048.

(*S*)-2-Allyl-3-hydroxy-2-phenyl-1-propyl2-Furoate(3Hb). A colorless oil: 82% ee; $[\alpha]_D^{20} = -19.3$ ($c = 0.54$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.07 (1H, t, $J = 7.0$ Hz), 2.58 (2H, d, $J = 7.0$ Hz), 3.82−3.91 (2H, m), 4.64 (1H, d, $J = 11.0$ Hz), 4.69 (1H, d, $J = 11.0$ Hz), 4.99−5.09 (2H, m), 5.47−5.60 (1H, m), 6.49 (1H, dd, $J = 1.5$, 3.5), 7.13 (1H, dd, $J = 1.0$, 3.5 Hz), 7.23−7.44 (5H, m), 7.57 (1H, dd, $J = 1.0$, 1.5 Hz). IR ($CHCl_3$): 3700−3200, 1728, 1640, 1582 cm^{-1}. HRMS. Calcd for $C_{17}H_{18}O_4$ (M^+): 286.1155. Found: 286.1152.

(*R*)−(1-Hyroxymethyl-7-methoxyindan-1-yl)methyl 4-Bromobenzoate (3Ag). A colorless oil: 86% ee; $[\alpha]_D^{28} = -1.7$ ($c = 1.1$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.04−2.21 (3H, m), 2.96 (2H, t, $J = 7.5$ Hz), 3.69 (1H, d, $J = 10.5$ Hz), 3.73 (1H, d, $J = 10.5$ Hz), 3.79 (3H, s), 4.45 (1H, d, $J = 11.0$ Hz), 4.49 (1H, d, $J = 11.0$ Hz), 6.72−6.90 (2H, m), 7.21−7.26 (1H, m), 7.60 (2H, d, $J = 8.5$ Hz), 7.89 (2H, d, $J = 8.5$ Hz). IR ($CHCl_3$): 3700−3200, 1730, 1580 cm^{-1}. HRMS. Calcd $C_{19}H_{19}{}^{81}BrO_4$ (M^+): 392.0422. Found: 392.0446.

[1-(Hydroxymethyl)benz[*e*]indan-1-yl]methyl 4-Bromobenzoate (3Bg). A colorless oil: 81% ee; $[\alpha]_D^{23} = -31.2$ (c 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.33−2.47 (2H, m), 3.12 (2H, t, $J = 7.5$ Hz), 4.07−4.15 (1H, m), 4.12 (1H, d, $J = 11.5$ Hz), 4.29 (1H, d, $J = 11.5$ Hz), 4.69 (1H, d, $J = 11.0$ Hz), 4.94 (1H, d, $J = 11.0$ Hz), 7.39−7.48 (3H, m), 7.52 (2H, d, $J = 8.5$ Hz), 7.71−7.77 (1H, m), 7.73 (2H, d, $J = 8.5$ Hz), 7.87 (1H, dd, $J = 2.0$. 8.0 Hz), 8.15 (1H, d, $J = 8.0$ Hz). IR (KBr): 3750−3250, 1742 cm^{-1}. HRMS. Calcd for $C_{22}H_{19}{}^{81}BrO_3$ (M^+): 412.0471. Found: 412.0497.

[(6-Chloro-1-(hydroxymethyl)indan-1-yl]methyl 4-Bromobenzoate (3Cg). A colorless oil: 71% ee; $[\alpha]_D^{23} = +7.7$ ($c = 1.4$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.01−2.21 (3H, m), 2.95 (2H, t, $J = 7.5$ Hz), 3.70 (1H, d, $J = 12.5$ Hz), 3.74 (1H, d, $J = 12.5$ Hz), 4.46 (1H, d, $J = 12.5$ Hz), 4.50 (1H, d, $J = 12.5$ Hz), 7.16−7.23 (2H, m), 7.33 (1H, d, $J = 2.0$ Hz), 7.61 (2H, d, $J = 8.5$ Hz), 7.88 (2H, d, $J = 8.5$ Hz). IR (KBr): 3700−3200, 1725 cm^{-1}. HRMS. Calcd for $C_{18}H_{16}{}^{81}BrClO_3$ (M^+): 395.9969. Found: 359.9951.

Typical Procedure for the Kinetic Resolution of (±)-3Aa, 3Ab, 3Ag Using 1a, 1b, 1g. To a solution of **1b** (46 mg, 0.25 mmol) and **3Ab** (76 mg, 0.25 mmol) in wet *i*-Pr_2O (4.0 mL) was added lipase MY (150 mg). The reaction mixture was stirred at 30 °C for 2 h and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−ethyl acetate) to give the mono ester (*R*)-**3Ab** (33 mg, 44%, 51% ee) and the diester **4Ab** (52 mg, 47%).

Enzymatic Desymmetrization of 2A Using 1b for Prolonged Time (Scheme 4). To a solution of **1b** (14.6 g, 80 mmol) and **2A** (3.3 g, 16 mmol) in wet *i*-Pr_2O (1.0 L) was added lipase MY (10 g). The reaction mixture was stirred at 30 °C for 30 h and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−ethyl acetate = 3:1) to give (*R*)-**3Ab** (1.0 g, 21%, 96% ee) and **4Ab** (4.9 g, 78%).

Hydrolysis of 4Ab. To a solution of **4Ab** (95 mg, 0.24 mmol) in MeOH (1.5 mL) and water (0.5 mL) was added K_2CO_3 (166 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated in vacuo. The residue was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexanes−ethyl acetate = 1:1) to give **2A** (48 mg, 96%).

(*R*)-2-Hydroxymethyl-2-phenylbutanoic Acid (7b). Under a nitrogen atmosphere, Dess−Martin periodinane (62 mg, 0.15 mmol) was added to a solution of (*S*)-**3Gb** (88% ee, 33 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (4.0 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. Saturated aqueous $Na_2S_2O_3$ was added to it. The mixture was extracted with CH_2Cl_2. The organic layer was successively washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give (*R*)-**5b** (32 mg, quant, 88% ee). The optical purity of the product was determined by HPLC using CHIRALCEL OD. A colorless oil: $[\alpha]_D^{22} = +3.0$ ($c = 3.6$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.87 (3H, t, $J = 7.5$ Hz), 2.04−2.24 (2H, m), 4.78 (1H, d, $J = 11.5$ Hz), 4.86 (1H, d, $J = 11.5$ Hz), 6.47 (1H, dd, $J = 2.0$, 3.5 Hz), 7.07 (1H, br d, $J = 3.5$ Hz), 7.24−7.44 (5H, m), 7.56 (1H, dd, $J = 1.0$, 2.0 Hz), 9.65 (1H, s). IR ($CHCl_3$): 1728 cm^{-1}.

NaH_2PO_4 (44 mg, 0.37 mmol), 2-methyl-2-butene (0.070 mL, 0.66 mmol), and $NaClO_2$ (20 mg, 0.18 mmol) were successively added to a solution of (*R*)-**5b** (32 mg, 0.12 mmol) in *tert*-BuOH (5.0 mL) and water (1.0 mL). The reaction mixture was stirred at room temperature for 10 min and concentrated in vacuo to one-fifth of the original volume. The residue was extracted with CH_2Cl_2, and the organic layer was concentrated in vacuo to give (*R*)-**6b** (34 mg, quant.). A colorless oil. ^1H NMR ($CDCl_3$): δ 0.88 (3H, t, $J = 7.5$ Hz), 2.04−2.24 (2H, m), 4.78 (1H, d, $J = 11.0$ Hz), 4.86 (1H, d, $J = 11.0$ Hz), 6.46 (1H, dd, $J = 2.0$, 3.5 Hz), 7.06 (1H, br d, $J = 3.5$ Hz), 7.25−7.42 (5H, m), 7.57 (1H, dd, $J = 1.0$, 2.0 Hz). IR ($CHCl_3$): 3400−2500, 1723 cm^{-1}.

NaOMe (35 mg, 0.88 mmol) was added to (*R*)-**6b** (34 mg, 0.12 mmol) in MeOH (2.0 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was purified by column chromatography (CH_2Cl_2-MeOH = 5:1) to give (*R*)-**7b** (20 mg, 89%). A colorless oil: $[\alpha]_D^{22} = +14.3$ ($c = 0.8$, $CHCl_3$) [lit.[3c] $[\alpha]_D^{20} = -16.5$ ($c = 1.0$, $CHCl_3$) for 97% ee of the (*S*)-form]. ^1H NMR ($CDCl_3$): δ 0.94 (3H, t, $J = 7.5$ Hz), 2.17 (2H, q, $J = 7.5$ Hz), 3.92 (1H, d, $J = 12$ Hz), 3.99 (1H, d, $J = 12$ Hz), 4.50−6.50 (2H, m), 7.20−7.50 (5H, m). IR ($CHCl_3$): 3400−3100, 1713 cm^{-1}.

Conversion of (*R*)-3Ab to (*S*)-8. (i) Method A. Under a nitrogen atmosphere, pyridine (6.6 mL, 82 mmol) and (*t*-Bu)-Me_2SiCl (2.2 g, 15 mmol) were added to an ice-cooled solution of (*R*)-**3Ab** (96% ee, 1.8 g, 5.8 mmol) in anhydrous dimethylformamide (DMF) (4 mL). The reaction mixture was stirred at room temperature for 2 h, to which were added water and Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with water, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2) to give (*S*)-[1-(*tert*-butyldimethylsiloxy)methyl-7-methoxyindan-1-yl]methyl 2-furoate (2.4 g, quant.). Colorless crystals: Mp 50−51 °C. $[\alpha]_D^{27} = +15.9$ ($c = 2.2$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ −0.08, (3H, s), −0.01, (3H, s), 0.82 (9H, s),

2.14−2.32 (2H, m), 2.94 (2H, t, J = 7.5 Hz), 3.75 (3H, s), 3.80 (1H, d, J = 9.5 Hz), 4.04 (1H, d, J = 9.5 Hz), 4.68 (2H, s), 6.44 (1H, dd, J = 2.0, 3.5 Hz), 6.64 (1H, d, J = 7.5 Hz), 6.81 (1H, dd, J = 1.0, 7.5 Hz), 6.95 (1H, dd, J = 1.0, 3.5 Hz), 7.15 (1H, t, J = 7.5 Hz), 7.53 (1H, dd, J = 1.0, 2.0 Hz). IR ($CHCl_3$): 1734, 1590 cm^{-1}. Anal. Calcd for $C_{23}H_{32}O_5Si$: C, 66.31; H, 7.74. Found: C, 66.43; H, 7.68.

Under a nitrogen atmosphere, K_2CO_3 (20 mg, 0.15 mmol) was added to an ice-cooled solution of the above compound (50 mg, 0.12 mmol) in anhydrous MeOH (1 mL). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 3 h and filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (benzene) to give (*S*)-**8** (37 mg, 95%). The optical purity was determined to be 96% ee by HPLC using CHIRALPAK AD. A colorless oil: $[\alpha]_D^{28}$ = +15.9 (c = 2.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ −0.01 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 2.06−2.24 (2H, m), 2.87−2.93 (2H, m), 3.20 (1H, dd, J = 3.0, 9.0 Hz), 3.63 (1H, d, J = 9.5 Hz), 3.74 (1H, dd, J = 9.0, 10.5 Hz), 3.81 (3H, s), 4.11 (1H, dd, J = 3.0, 10.5 Hz), 4.15 (1H, d, J = 9.5 Hz), 6.68 (1H, d, J = 7.5 Hz), 6.84 (1H, d, J = 7.5 Hz), 7.16 (1H, t, J = 7.5 Hz). IR (KBr): 3500−3400, 1590 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.93; H, 9.26.

(ii) Method B. Under a nitrogen atmosphere, to a solution of the silyl ether (10.3 mg, 0.025 mmol), obtained by the above method, in anhydrous CH_2Cl_2 (0.25 mL) was added $(i\text{-}Bu)_2AlH$ (0.95 M solution in hexane, 0.80 mL, 0.76 mmol) over a period of 5 min at −60 °C. The reaction mixture was stirred for 1.5 h at −60 °C and concentrated in vacuo. The residue was purified by column chromatography (benzene) to give (*S*)-**8** (7.1 mg, 88%).

Conversion of (*R*)-3Aa, (*R*)-3Ag to (*S*)-8. According to the method B, (*R*)-**3Aa** (71% ee, 10 mg, 0.032 mmol) was converted to (*S*)-**8** (8.8 mg, 85%, 70% ee), and (*R*)-**3Ag** (86% ee, 12 mg, 0.031 mmol), to (*S*)-**8** (7.9 mg, 80%, 85% ee). IR and ^{1}H NMR data of these compounds were in accord with those of the products obtained from (*R*)-**3Ab**.

Enzymatic Desymmetrization of the Meso 1,2-Diols 9. A Typical Procedure. To a mixture of **1b** (196 mg, 1.08 mmol) and **9A** (50 mg, 0.43 mmol) in *t*-BuOMe (10 mL) was added CHIRAZYME L9 (450 mg). The reaction mixture was stirred at 45 °C for 2 days and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−ethyl acetate = 5:1) to give (1*R*,2*S*)-**10Ab** (70 mg, 77%, 97% ee). The optical purity of the product was determined by HPLC using CHIRALCEL OJ.

(1*R*,2*S*)-2-Hydroxycyclohexyl 2-Furoate (10Ab). A colorless oil: $[\alpha]_D^{22}$ = −2.5 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.20−2.10 (9H, m), 3.97 (1H, br d, J = 8.0 Hz), 5.16 (1H, dt, J = 3.0, 8.0 Hz), 6.51 (1H, dd, J = 1.5, 3.0 Hz), 7.17 (1H, dd, J = 1.0, 3.0 Hz), 7.59 (1H, dd, J = 1.0, 1.5 Hz); IR ($CHCl_3$): 3560, 1717 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.83; H, 6.72. Found: C, 62.57; H, 6.68.

(1*R*,2*S*)-2-Hydroxycyclopentyl 2-Furoate (10Bb). Compound **9B** (104 mg, 1.02 mmol) was converted to (1*R*,2*S*)-**10Bb** (110 mg, 55%, 82% ee). The optical purity of the product was determined by HPLC using CHIRALCEL OD. A colorless oil: $[\alpha]_D^{19}$ = −1.9 (c = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.59−2.15 (7H, m), 4.26−4.31 (1H, m), 5.16−5.22 (1H, m), 6.52 (1H, dd, J = 2.0, 3.5 Hz), 7.21 (1H, dd, J = 1.0, 3.5 Hz), 7.58 (1H, dd, J = 1.0, 2.0 Hz). IR ($CHCl_3$): 3560, 1717 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.06; H, 6.22.

Acetylation of (1*R*,2*S*)-10Ab. Under a nitrogen atmosphere, to an ice-cooled solution of (1*R*,2*S*)-**10Ab** (97% ee, 11 mg, 0.052 mmol) in pyridine (0.20 mL) was added Ac_2O (0.010 mL, 0.11 mmol). The reaction mixture was stirred at room temperature for 2 h, and water and Et_2O were added to it. The mixture was extracted with ether. The organic layer was successively washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (Et_2O−pentane = 1:1) to give (1*R*,2*S*)-**11A** (13.4 mg, quant). A colorless oil: $[\alpha]_D^{23}$ = −45.5 (c = 0.67, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.38−2.15 (8H, m), 2.05 (3H, s), 5.02−5.12 (1H, m), 5.25−5.29 (1H, m), 6.51 (1H, dd, J = 1.5, 3.5 Hz), 7.17 (1H, dd, J = 1.0, 3.5 Hz), 7.59 (1H, dd, J = 1.0, 1.5 Hz). IR ($CHCl_3$): 1717 cm^{-1}. HRMS. Calcd for $C_{13}H_{16}O_5$ (M^+): 252.0998. Found: 252.0996.

Acetylation of (1*R*,2*S*)-10Bb. Similarly to the acetylation of (1*R*,2*S*)-**10Ab,** (1*R*,2*S*)-**10Bb** (18.1 mg, 0.092 mmol) was converted to (1*R*,2*S*)-**11B** (22.0 mg, quant). A colorless oil: $[\alpha]_D^{19}$ = −35.0 (c = 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.63−2.12 (6H, m), 2.03 (3H, s), 5.23 (1H, dt, J = 4.5, 6.0 Hz), 5.36 (1H, dt, J = 4.5, 6.0 Hz), 6.51 (1H, dd, J = 2.0, 3.5 Hz), 7.15 (1H, dd, J = 1.0, 3.5 Hz), 7.58 (1H, dd, J = 1.0, 2.0 Hz). IR ($CHCl_3$): 1717 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.73; H, 6.00.

Furoylation of 12A. Under a nitrogen atmosphere, a mixture of DCC (62 mg, 0.30 mmol), DMAP (3.0 mg, 0.02 mmol), and 2-furoic acid (34 mg, 0.30 mmol) in CH_2Cl_2 (2.0 mL) was stirred at 0 °C for 30 min, and a solution of **12A** (29 mg, 0.18 mmol), prepared by the reported method,[10b] in CH_2Cl_2 (1.0 mL) was added to it. The reaction mixture was stirred at room temperature for 4 h and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−ethyl acetate = 5:1) to give (1*S*,2*R*)-**11A** (26 mg, 56%). A colorless oil: $[\alpha]_D^{20}$ = +45.1 (c = 0.67, $CHCl_3$).

Furoylation of 12B. Similarly to the furoylation of **12A**, **12B** (21 mg, 0.15 mmol), prepared by the reported method,[10b] was converted to (1*S*,2*R*)-**11B** (9.3 mg, 28%). A colorless oil: $[\alpha]_D^{20}$ = +18.0 (c = 0.46, $CHCl_3$).

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