JOC Article

Enantiodivergent Preparation of Optically Active Oxindoles Having a Stereogenic Quaternary Carbon Center at the C3 Position via the Lipase-Catalyzed Desymmetrization Protocol: Effective Use of 2-Furoates for Either Enzymatic Esterification or Hydrolysis

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Both enantiomers of oxindoles **2a**−**h**, having a stereogenic quaternary carbon center at the C3 position and a different *N*-protective group, were readily prepared by the lipase-catalyzed desymmetrization protocol. Thus, the transesterification of the prochiral diols **3a**−**h** with 1-ethoxyvinyl 2-furoate **5** was catalyzed by *Candida rugosa* lipase to give (*R*)-(+)-**2a**−**h** (68−99% ee), in which the use of a mixed solvent, $^{i}Pr_2O$ (diisopropyl ether)−THF, was crucial. The same lipase also effected the enantioselective hydrolysis of the difuroates **4a**−**h** in a mixture of $^{i}Pr_2O$, THF, and H_2O to provide the enantiomers (*S*)-(−)-**2a**−**h** (82−99% ee). The products **2** obtained by both methods were stable against racemization. These enzymatic desymmetrization reactions were also applicable for other typical symmetrical difuroates **12b** and **15b** to provide the racemization-resistant products **13b** and **16b**.

Introduction

Oxindole- and indoline-skeletons **1** having a stereogenic quaternary carbon center at the C3 position are found in many biologically important indole alkaloids such as spirotryprostatins A and B, (−)-physostigmine, and (−)-esermethole.[1−5] Effective construction of their stereogenic quaternary carbon center has been one of the pivotal issues for their asymmetric total synthesis, and a variety of methodologies have been developed via enantio- or diastereoselective carbon−carbon bond-forming reactions at the C3 position.[1−5]

On the other hand, the biocatalytic enantioselective desymmetrization of the prochiral substrates (**3** and **4**) by (trans)esterification and hydrolysis, respectively, could offer an attractive alternative (Scheme 1) with regard to easy and safe operations, mild reaction conditions, and high chemical and optical yields of the products.[6] However, the potential of the approaches in Scheme 1 was hardly exploited. The only successful example was the enantioselective hydrolysis of the dipropanoate **4** (R^1 = MOM, R^2 = H, R^3 = Et) in which the product **2** (R^1 = MOM, R^2 = H, R^3 = Et) (95% ee, 38% yield) was obtained after a 5 day reaction, whereas the enantioselective esterification of the corresponding diol **3** (R^1 = MOM, R^2 = H) did not proceed.[7,8]

In addition to the above-mentioned low reactivity of the sterically congested substrates (**3** and **4**), the enzymatic desymmetrization of the prochial 2,2-disubstituted 1,3-propanediols **I** and the hydrolytic desymmetrization of their diesters **II** have often suffered from the easy

(1) For recent reviews, see: Saxton, J. E. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, Chapter 1. Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, 327−340. Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209−2219.

(2) For some recent examples of the asymmetric total syntheses of spirotryprostatins, see: Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596−4599. Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249−251. Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694−696. Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135−3137.

(3) For recent examples of the asymmetric total synthesis of physostigmine, see: Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503. Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675−678.

(4) For an example of the asymmetric total synthesis of esermethole, see: Fuji, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951−964.

(5) For some other recent examples, see: (a) Lakshmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699−1704. (b) Yokoshima, S.; Tokuyama, H.; Fukuyama T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4073−4075. (c) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439−1442. (d) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921−3924. (e) Takayama, H.; Fujiwara, R.; Kasai, Y.; Kitajima, M.; Aimi, N. *Org. Lett.* **2003**, *5*, 2967−2970.

(6) For recent reviews, see: Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769−3826. Bornscheuer, U. T.; Kazlauskas, R. J. In *Hydrolases in Organic Synthesis*; Wiley: Weinheim, 1999. Theil, F. *Tetrahedron* **2000**, *56*, 2905−2919. Faber, K. In *Biotransformations in Organic Chemistry*, 4th ed.; Springer-Verlag: Berlin, 2000. Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1475−1499. Hanefeld, U. *Org. Biomol. Chem.* **2003**, *1*, 2405−2415.

(7) Nakazawa, K.; Hayashi, M.; Tanaka, M.; Aso, M.; Suemune, H. *Tetrahedron: Asymmetry* **2001**, *12*, 897−901.

(8) Nonenzymatic desymmetrization of the oxindoles or indolines having two identical substituents at the C3 position has never been reported to the best of our knowledge.

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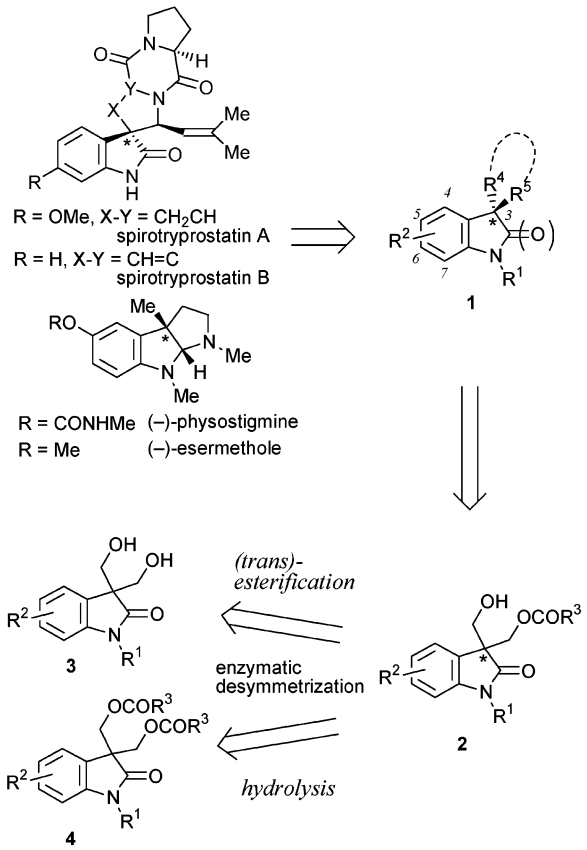
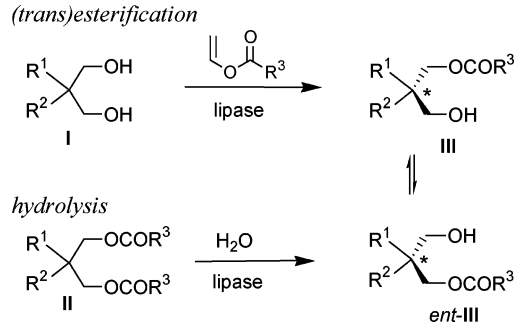
SCHEME 1



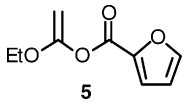
racemization of the products (**III** and *ent*-**III**). This is because lower aliphatic acyl groups (COR^3) such as an acetyl group are prone to easily migrate to the neighboring hydroxyl group under various conditions (Scheme 2).[9] Therefore, to make both approaches in Scheme 1 useful, other acyl groups (COR^3) having a high reactivity for the enzymatic reaction and resistance against the migration needed to be developed.

Recently, we have developed a new prominent acyl donor, 1-ethoxyvinyl 2-furoate **5**, for the lipase-catalyzed desymmetrization of the prochiral 2,2-disubstituted 1,3-propanediols **I**.[10] The reagent **5** offers advantages such as high reactivity, high enantioselectivity, and the production of racemization-resistant products **III** (R^3 = 2-furyl). In this paper, the successful application of **5** for the desymmetrization of **3** is presented using a mixed

SCHEME 2



solvent, $^iPr_2O$ (diisopropyl ether)−THF.[11] We also have achieved the first lipase-catalyzed hydrolysis of the prochiral difuroate **4** (R^3 = 2-furyl). By these two methods, both enantiomers of the oxindoles **2** (≥97% ee in most cases) having various types of *N*-protective groups were prepared. The efficiency of the hydrolytic desymmetrization strategy using the difuroates was also demonstrated in the typical substrates (**12**, **15**) for which the existing methods caused easy racemization of the products.



Results and Discussion

Preparation of Prochiral Diols 3 and Prochiral Difuroates 4. The core indole (or indoline) skeletons of most natural indole alkaloids are classified as either compounds having no substituent at the C4−C7 positions or those having an oxygen substituent at the C5 or C6 position. Aiming at the preparation of chiral synthons useful for the total synthesis of natural products, we planned to examine the enzymatic desymmetrization of the prochiral diols **3a**−**h** and the difuroates **4a**−**h** having various *N*-protective groups.

The diols **3a**−**h** were prepared from commercially available **6a** and **7f** or the known compounds (**6b**,[5a] **6c**,[12] **7a**,[13] **7b**,[14] **7e**,[14] **7g**,[7] and **7h**[15]). New compounds (**7c** and **7d**) were prepared by the *N*-protection of **6b** and **6c**, respectively. The bis-hydroxymethylation at the C3 position of **7** was performed with an aqueous 37% solution of formaldehyde[16] and Na_2CO_3 to give the diols **3a**−**h**.

(9) Acyl group migration was reported to proceed during the enzymatic reactions, the purification by SiO_2 chromatography, and the subsequent chemical transformations. For migrations on the hydrolysis approaches, 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. (c) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C−H. *J. Am. Chem. Soc.* **1988**, *110*, 7200−7205. (d) Suemune, H.; Harabe, T.; Xie, Z.-F.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 4337−4344. (e) Liu, K. K.-C.; Nozaki, K.; Wong, C.-H. *Biocatalysis* **1990**, *3*, 169−177. (f) Prasad, K.; Estermann, H.; Underwood, R. L.; Chen. C.-P.; Kucerovy, A.; Repic, O. *J. Org. Chem.* **1995**, *60*, 7693−7696. (g) Bódai, V.; Novák, L.; Poppe, L. *Synlett* **1999**, 759−761. (h) Egri, G.; Bálint, J.; Peredi, R.; Fogassy, E.; Novák, L.; Poppe, L. *J. Mol. Cat. B* **2000**, *10*, 583−596. For migrations on the esterification approaches, see: (i) Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron: Asymmetry* **1994**, *5*, 283−288. (j) Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron: Asymmetry* **1995**, *6*, 519−524. (k) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 283−291.

(10) (a) Akai, S.; Naka, T.; Fujita, T.; Takebe, Y.; Kita, Y. *Chem. Commun.* **2000**, 1461−1462. (b) Akai, S.; Naka, T.; Fujita, T.; Takebe, Y.; Tsujino, T.; Kita, Y. *J. Org. Chem.* **2002**, *67*, 411−419. For synthetic applications, see: (c) Akai, S.; Tsujino, T.; Fukuda, N.; Iio, K.; Takeda, Y.; Kawaguchi, K.; Naka, T.; Higuchi, K.; Kita, Y. *Org. Lett.* **2001**, *3*, 4015−4018.

(11) Part of this study was reported in a preliminary communication, see: Akai, S.; Tsujino, T.; Naka, T.; Tanimoto, K.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 7315−7317.

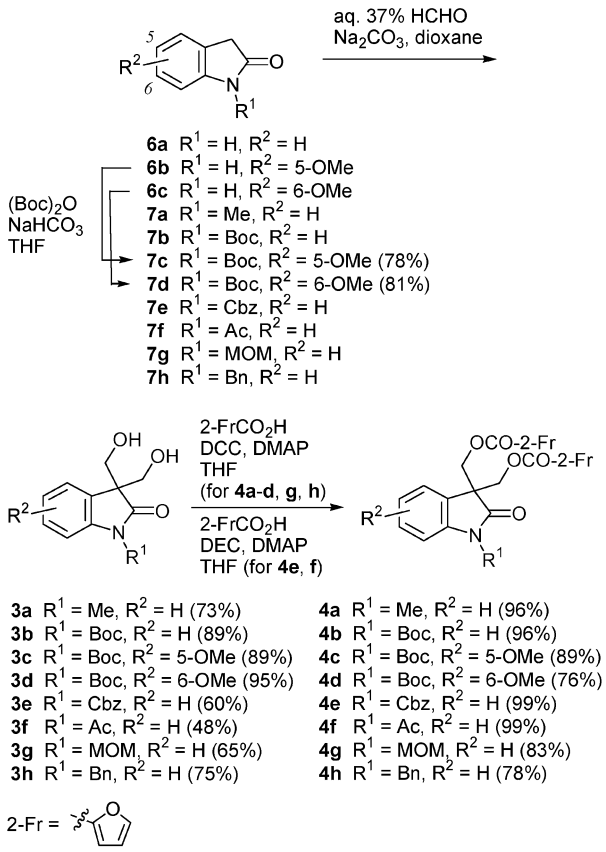
(12) Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093−6109. See also: Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084−12085.

(13) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218−4223.

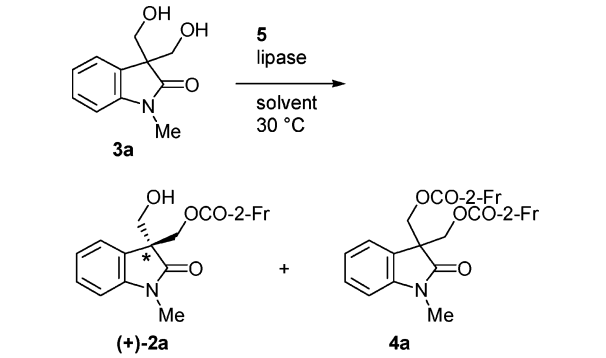
(14) Preparation of **7b** was carried out at a temperature (65 °C) higher than that in the reported method (Rajeswaran, W. G.; Cohen, L. A. *Tetrahedron* **1998**, *54*, 11375−11380) because of the tardy reaction.

(15) Crestini, C.; Saladino, R. *Synth. Commun.* **1994**, *24*, 2835−2841. For the preparation of *N*-benzylisatin, see: Singh, R. P.; Majumder, U.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 6263−6267.

SCHEME 3



SCHEME 4



The prochiral difuroates **4a**−**h** were prepared from **3a**−**h** by the condensation with 2-furoic acid using either DCC or DEC (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) and DMAP (Scheme 3).

Desymmetrization of Prochiral Diols 3 by Lipase-Catalyzed Enantioselective Transesterification. The transesterification of **3a** using **5** was at first investigated by applying the reaction conditions [*C. rugosa* lipase (Meito MY), wet $^iPr_2O$] used in our previous study.[10] However, the very poor solubility of **3a** hampered its fast esterification and resulted in enhancement of the further esterification of the soluble product **2a** to exclusively provide the diester **4a** (Scheme 4). Although **3a** was soluble in polar solvents such as THF, dioxane, and acetonitrile, the lipase MY-catalyzed reaction did not proceed. After investigation of a range of solvents, the use of a 1:1 mixture of $^iPr_2O$ and THF was found to give **2a** (33% ee) after 7 days. On the other hand, the use of a 1:1 mixture of $^iPr_2O$ and either dioxane or acetonitrile resulted in a very poor selectivity and reactivity. Next, we examined several lipases in the 1:1 mixture of $^iPr_2O$ and THF, and a *C. rugosa* lipase (Meito OF) was found to be more effective to give (+)-**2a** (77% ee, 21% yield) and **4a** (79% yield) after 4 days (Table 1, entry 2).[17] Investigation of the reaction conditions was continued by changing the ratio of $^iPr_2O$ to THF. Each reaction was carried out using a minimal volume of the solvent to dissolve **3a** and quenched by filtering the lipase through a Celite pad when **3a** was consumed (Table 1). The reaction proceeded faster in solvent mixtures with a higher ratio of $^iPr_2O$ to THF; however, a considerable amount of **4a** was produced in all cases. Good optical purities (79−87% ee) and acceptable yields (53−60%) of **2a** were obtained in a 5:1 or 10:1 mixture of $^iPr_2O$ and THF (entries 4 and 5).

With the profile of the desymmetrization reaction of **3a** in hand, various prochiral diols **3b**−**h** were next subjected to the desymmetrization. Among the different ratios of $^iPr_2O$ to THF, only a few, i.e., neat $^iPr_2O$, 10:1, 5:1, and 2:1, were examined for each substrate, and the best results are summarized in the left column of Table 2.[18] Some features are worth noticing. First, the 5:1 ratio of $^iPr_2O$ to THF was generally the best choice, while the other ratio of the solvents resulted in a decrease of both optical and chemical yields of **2**. In the case of **3c**, the best result was obtained using $^iPr_2O$ alone (entry 4), although the use of a 10:1 mixture of $^iPr_2O$ and THF also afforded a similar result (24 h, 97% ee, 75% yield). Second, the *N*-acyl derivatives **3b**−**f** generally produced (+)-**2b**−**f** with high optical (91−99% ee) and chemical yields (71−93%) irrespective of the structure of the acyl group (entries 2−7). On the contrary, the desymmetrization of the *N*-alkyl derivatives (**3g** and **3h**) resulted in lower optical and chemical yields (entries 8 and 9). Third, this method was scarcely affected by the reaction scale and was suitable for multigram synthesis of chiral products. For instance, under identical reaction conditions using the same ratio of **3b**, **5**, lipase OF, and the solvent mixture, the reactions of **3b** (100 mg and 2.0 g) afforded similar results (entries 2 and 3). Fourth, recrystallization was effective for obtaining the optically pure products **2** from those with unsatisfactory optical purities.

(16) For previous examples of bis-hydroxymethylation at the α-position of the ketones, see: Schneider, G.; Wölfling, J.; Hackler, L.; Meskó, E.; Dombi, G. *Synthesis* **1985**, 194−197.

(17) Following lipases were inactive in the 1:1 mixture of $^iPr_2O$ and THF at 30 °C: *C. rugosa* lipases (Amano AY and Roche Diagnostics CHIRAZYME L-3), *C. antarctica* lipase (Roche Diagnostics CHIRAZYME L-2), *Mucor miehei* lipase (Roche Diagnostics CHIRAZYME L-9), *Pseudomonas aeruginosa* lipase (Toyobo LIP), *Pseudomonas* sp. lipase (Amano AK), *Pseudomonas cepacia* lipases (Amano AH and PS), porcine pancreas (Amano), and pig liver esterase (Amano).

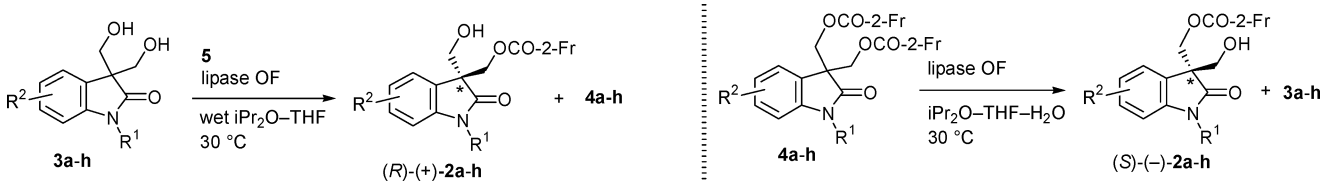
(18) ***Caution:*** During the workup of the transesterification reaction of **3**, viz., the filtration of the reaction mixture through a Celite pad followed by concentration of the filtrate in vacuo, we occasionally observed the formation of 3-acetoxymethyl-3-(furoyloxymethy)oxindoles in variable yields. This often occurred when we used a large excess of **5** (for instance, 5 equiv), which resulted in decreasing yields of **2**. The side-product seemed to be generated by the acetylation of the optically active **2**. The remaining **5** was likely to be involved to some degree, although we have not specified the exact factor that induces the undesired reaction. The side-reaction could be suppressed by stirring the above-mentioned filtrate with water for 30 min to decompose **5** and to extract the resultant 2-furoic acid with the aqueous phase (for details, see Experimental Section).

TABLE 1. Lipase OF-Catalyzed Transesterification of 3a with 5 under Various Conditions[a]

entry	ratio of $^{i}Pr_2O$ to THF (solvent volume)[b]	reaction time[c]	**2a**[d]	**4a**
1	1:2 (5 mL)	4 days	76% ee, 15%[e]	76%[e]
2	1:1 (10 mL)	4 days	77% ee, 21%[e]	79%[e]
3	2:1 (15 mL)	4 days	75% ee, 16%	76%
4	5:1 (20 mL)	22 h	79% ee, 60%	40%
5	10:1 (40 mL)	7 h	87% ee, 53%	47%
6	neat $^{i}Pr_2O$ (40 mL)	7 h	62% ee, 30%	65%

[a] Reagent amounts: **3a** (30 mg), **5** (80 mg, 3 equiv), and lipase OF (75 mg). [b] Minimal volume of the mixed organic solvent to dissolve **3a** (30 mg) was used in the presence of water (0.1 v/v % to the combined volume of the organic solvents). [c] Reaction was quenched when **3a** was consumed. [d] Optical purity was determined by HPLC using a chiral column, Daicel Chiralcel OD. [e] Yields based on ^{1}H NMR data.

TABLE 2. Enzymatic Desymmetrization of 3a−h and 4a−h[a]



(1) enzymatic transesterification of **3a−h**[a]

entry	3	R^1	R^2	ratio of $^{i}Pr_2O$ to THF	time, h[b]	(+)-**2**	ee, %	yield, %[c]	**4**,	yield, %[c]
1	**3a**	Me	H	10:1	7	(+)-**2a**	87	53	**4a**	47
2	**3b**	Boc	H	5:1	23	(+)-**2b**	97	83	**4b**	15
3[d]	**3b**	Boc	H	5:1	22	(+)-**2b**	99	93	**4b**	6
4	**3c**	Boc	5-OMe	neat $^{i}Pr_2O$	3	(+)-**2c**	98	77	**4c**	20
5	**3d**	Boc	6-OMe	5:1	19	(+)-**2d**	91	79	**4d**	13
6	**3e**	Cbz	H	5:1	58	(+)-**2e**	98	71	**4e**	28
7	**3f**	Ac	H	5:1	48	(+)-**2f**	97	90	**4f**	5
8	**3g**	MOM	H	5:1	64	(+)-**2g**	86	34	**4g**	38
9	**3h**	Bn	H	5:1	144	(+)-**2h**	68	59	**4h**	24

(2) enzymatic hydrolysis of **4a−h**

entry	**4**	time, h[b]	(−)-**2**	ee, %	yield, %[c]	**3**,	yield, %[c]
10[d]	**4a**	4.5	(−)-**2a**	>99	46	**3a**	50
11	**4b**	72	(−)-**2b**	>99	33	**3b**	63
12[d]	**4b**	24	(−)-**2b**	>99	34	**3b**	64
13	**4c**	120	(−)-**2c**	>99	40	**3c**	51
14	**4d**	72	(−)-**2d**	82	12	**3d**	79
15	**4e**	48	(−)-**2e**	>99	29	**3e**	61
16	**4f**	24	(−)-**2f**	97	34	**3f**	61
17	**4g**	39	(−)-**2g**	98	57	**3g**	43
18	**4h**	24	(−)-**2h**	98	40	**3h**	58

[a] Substrate amount was 20−100 mg unless otherwise noted. For a detailed reaction procedure and the determination of the optical purity of the product, see Experimental Section. [b] Reaction was quenched when the starting material was consumed. [c] Isolated yield by flash column chromatography on SiO_2. [d] Substrate amount was 2.0 g for entries 3 and 12 and 0.50 g for entry 10.

For instance, **2d** was obtained in >99% ee after a single recrystallization step from the optically impure (91% ee) material.

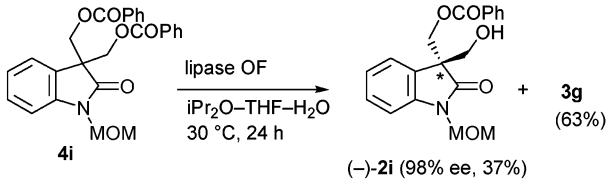
The products (+)-**2a−h** were easily isolated by standard flash column chromatography on silica gel and stored in a refrigerator for several months without any loss of optical purity.

Desymmetrization of the Prochiral Difuroates 4 by Lipase-Catalyzed Enantioselective Hydrolysis. In general, hydrolytic desymmetrization of prochiral diacetates **II** (Scheme 2) also suffers from racemization during the enzymatic resolution due to concomitant nonenzymatic acetyl group migration. This is aggravated by the phosphate buffer (pH 7) typically used as the reaction medium.[9] Although desymmetrization trials of any aromatic diesters **II** (R^3 = aryl group) have attained no success,[7] we were interested in the applicability of the difuroates **4** (R^3 = 2-furyl) for the enzymatic hydrolysis as a means to solve the above-mentioned racemization problem.

A preliminary study of the hydrolysis of **4b** was started by using lipase OF in water or an alcohol (MeOH, EtOH, *n*PrOH, ^{i}PrOH, *n*BuOH, ^{i}BuOH, and *t*BuOH) at 30 °C; however, no reaction took place over 6 days in every case. Next, the use of the mixed solvent ($^{i}Pr_2O$−THF, 5:1) in the presence of water or the above-mentioned alcohols was examined, and we found that the use of a mixture of $^{i}Pr_2O$−THF−water (5:1:6) gradually caused the hydrolysis of **4b** along with the simultaneous hydrolysis of **2b** to **3b**. When **4b** was consumed after 3 days, (−)-**2b** (99% ee, 33% yield) and **3b** (63% yield) were isolated (Table 2, entry 11). Using this solvent mixture, (−)-**2** with more than 97% ee was obtained in most cases; however, the chemical yields were always unsatisfactory due to the formation of substantial amounts of **3** (entries 10−18). The applicability of this method for multigram synthesis was also approved without any change of the optical and chemical yields of the product (entry 12). The use of a 1:1 mixture of $^{i}Pr_2O$−water caused a faster hydrolysis but gave (−)-**2** in slightly lower chemical and/or optical yields than that of a mixture of $^{i}Pr_2O$−THF−water (5:1:6) due to the rapid hydrolysis of the products **2** [for example, **4a**: 3 h, >99% ee, 22% yield, **4c**: 24 h, 80% ee, 35% yield]. On the other hand, the reaction in THF−water (1:1) did not take place. On the basis of their specific rotations, the products **2** of the hydrolysis had opposite absolute stereochemistry to those of the above-mentioned transesterification.

Remarkably, the desymmetrization of *N*-MOM difuroate **4g** proceeded faster and in higher yields of (−)-**2g** (entry 17) compared to the corresponding *N*-MOM dipropanoate.[7] Contrary to the precedent literature,[7] diben-

SCHEME 5



zoate **4i** was also susceptible to the hydrolytic desymmetrization to give (−)-**2i** (98% ee, 37% yield) (Scheme 5). Nevertheless, furoate (−)-**2g** was perfectly stable under acidic conditions (0.1 equiv of camphorsulfonic acid, 0.4 M in CH_2Cl_2, room temperature, 30 h), whereas benzoate (−)-**2i** sustained partial racemization, thus suggesting distinct advantages of using furoates instead of benzoates (Figure 1).

Determination of Absolute Stereochemistry of Products. The absolute stereochemistry of (−)-**2a** was determined to be *S* as follows. The hydroxymethyl group of (−)-**2a** was converted to the methyl group (**8**) via the radical reduction of the corresponding iodide using 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V-70L)[19] and $(Me_3Si)_3SiH$,[20] and its furoyloxy group was cleaved by Dibal-H to give **9**.[21] The hydroxyl group of **9** was converted to the nitrile group (**10**), which was in turn transformed to the known aldehyde **11** (Scheme 6). Comparison of its specific rotation ($[\alpha]_D^{29}$ +41.3 (*c* 0.35, $CHCl_3$)) with the reported value, $[\alpha]_D^{24}$ +20.2 (*c* 0.50, $CHCl_3$) for (*S*)-**11** with 45% ee,[22a] clearly disclosed that its absolute stereochemistry was *S*; therefore, (−)-**2a** has *S*-chirality at the C3 position. The optical purity of **11** was determined to be 99% by the HPLC analysis using a chiral column, Daicel Chiralcel OD, and confirmed complete retention of the chiral integrity during these transformations. The absolute stereochemistries of all other products (−)-**2b**−**h** were tentatively assigned to be *S* on the basis of the similarity of their specific rotation to that of (−)-**2a**.

Because the conversion of (*R*)-**11** to (+)-esermethole and (+)-physostigmine has already been attained,[22b] (*S*)-**11** can lead to natural (−)-esermethole and (−)-physostigmine.

Lipase-Catalyzed Hydrolytic Desymmetrization of Prochiral Propane-1,3-diyl Difuroate and *meso*-Cyclohexane-1,2-diyl Difuroate. The desymmetrization of prochiral 2-substituted propane-1,3-diyl diacetates such as **12a** has been known to be troublesome, because the racemization of the product **13a** gradually took place during the enzymatic reaction in phosphate buffer (pH 7).[9c,e,g,h] We briefly investigated the applicability of the newly developed difuroate protocol to this system. The hydrolysis of the corresponding difuroate **12b** was attained using CAL-B (*Candida antarctica* lipase, fraction B) in a 1:1 mixture of $^iPr_2O$ and water to give **13b** (75% ee, 55% yield) (Scheme 7). The comparison of the stability of **13b** and the acetate **13a** in a phosphate buffer (pH 7.2) revealed the efficacy of our furoate method (Figure 2). The superior stability of **13b** over **13a** was also apparent under acidic conditions [0.1 equiv of camphorsulfonic acid, CH_2Cl_2, room temperature, 30 h] (Figure 3).

The hydrolysis of the *meso*-diacetates **15a** is another example of the easy racemization of the product **16a**.[9a,b,j] The desymmetrization of the corresponding difuroate **15b** proceeded slowly in a 1:1 mixture of $^iPr_2O$ and water at 50 °C to give optically pure **16b** (20% yield) after 24 h (Scheme 8). The satisfactory stability of **16b** was again

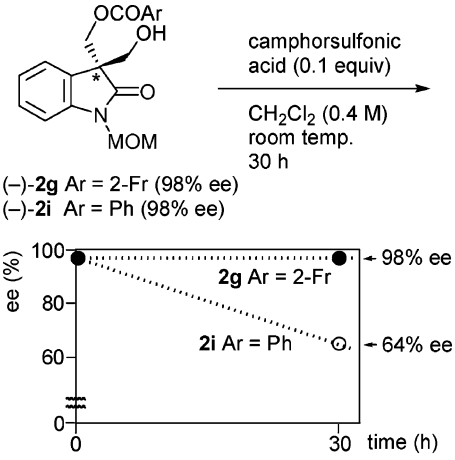
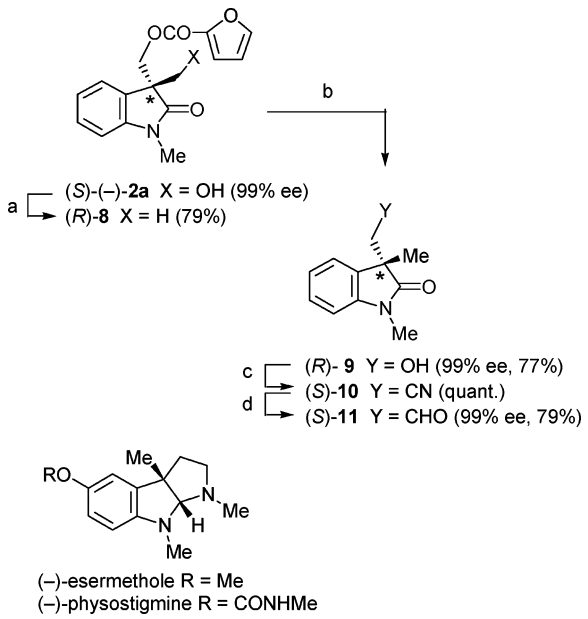


FIGURE 1. Comparison of the stability of **2g** and **2i** under acidic conditions.

SCHEME 6[a]



[a] Reagents and conditions: (a) (1) $MeP(OPh)_3I$, DMF, 120 °C; (2) 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V-70L), $(Me_3Si)_3SiH$, C_6H_6, 50 °C. (b) Dibal-H, toluene −78 °C. (c) (1) I_2, 35% NaOH, MeOH, room temp; (2) $BH_3{\cdot}Me_2S$, THF, room temp; (3) Dess−Martin periodinane, CH_2Cl_2, 0 °C.

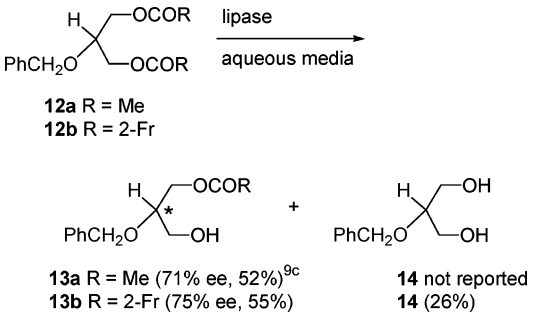
(19) Matsugi, M.; Gotanda, K.; Ohira, C.; Suemura, M.; Sano, A.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 6928−6930.

(20) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641−3642.

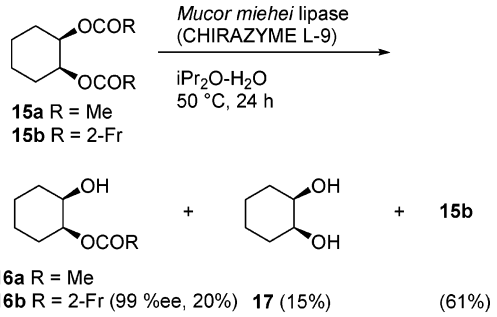
(21) Alkaline hydrolysis of **8** (99% ee) using K_2CO_3 in MeOH at room temperature caused a significant racemization of **9** (12% ee) probably via the retro-aldol−aldol reaction.[10c] The use of Dibal-H successfully cleaved the ester bonding of **8** to give **9** (99% ee, 50% yield, 77% yield based on the consumed **8**) and the recovered **8** (35% yield).

(22) (a) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477−6487. (b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499.

SCHEME 7



SCHEME 8



certified by the comparison with the acetate **16a** under acidic conditions (Figure 4).[23]

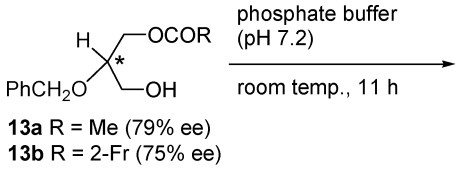
Conclusion

The efficient preparation of either enantiomer of the oxindoles **2** bearing a stereogenic quaternary carbon center at the C3 position was developed by two complementary methods, viz., the enantioselective transesterification of the prochiral diols **3** and the enantioselective hydrolysis of the prochiral difuroates **4**. These methods conveniently give access to indole derivatives **2a**−**h**, with various *N*-protective groups such as Boc, Cbz, Ac, Me, MOM, and Bn, in excellent optical purity, from readily available starting materials in few steps. The formation of the racemization-resistant monofuroates **2** is another noticeable advantage of both methods, for which the use of the furoyl donor **5** (for the transesterification) and the difuroates **4** (for the hydrolysis) is crucial.

The transesterification approach is more advantageous than the hydrolysis approach in terms of the fewer steps and generally higher chemical yields. An example is the preparation of (+)-**2b** (99% ee, 69% overall yield) in three steps from commercial **6a**. In this study, the effective use of a mixed solvent system, $^{i}Pr_2O$−THF for polar substrates was elucidated, and this method would be applicable for a wide range of substrates.

Additionally, the first successful examples of the use of aromatic diesters for the enzymatic hydrolytic desymmetrization were discovered in this study. Although the reaction is usually slow and the overhydrolysis from the monofuroates to the diols resulted in the decreased yields of the products, this method has opened an alternative approach for the preparation of racemization-resistant products by enzymatic hydrolysis.

(23) We have reported the higher stability of **16b** in comparison to that of **16a** during the standard SiO_2 column chromatography.[10b]



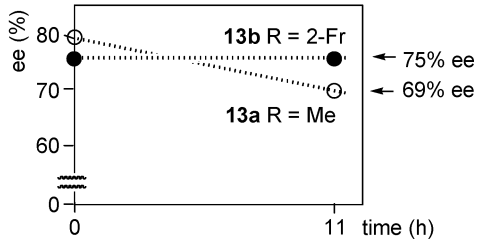


FIGURE 2. Comparison of the stability of **13a** and **13b** in phosphate buffer.

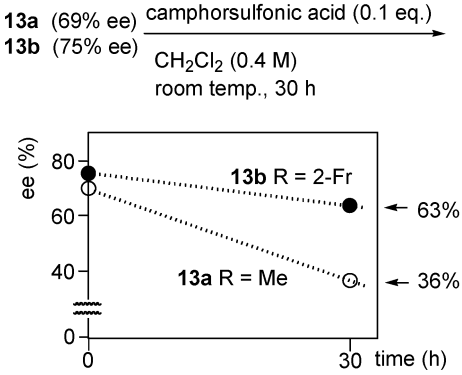


FIGURE 3. Comparison of the stability of **13a** and **13b** under acidic conditions.

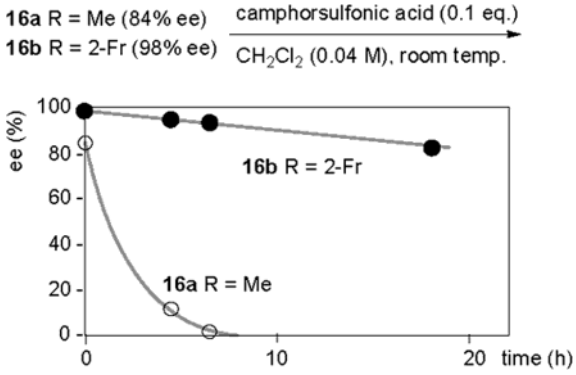


FIGURE 4. Comparison of the stability of **16a** and **16b** under acidic conditions.

Experimental Section

Materials. Lipases MY (from *C. rugosa*) and OF (from *C. rugosa*) were gifts from Meito Sangyo Co., Ltd., Japan. CAL-B (*C. antarctica* lipase, fraction B) and CHIRAZYME L-9 (from *Mucor miehei*) were gifts from Roche Diagnostics. Yields refer to the isolated material of ≥95% purity as determined by ^{1}H NMR. The known compounds (**5**,[10b] **6b**,[5a] **6c**,[12] **7a**,[13] **7b**,[14] **7e**,[14] **7g**,[7] **7h**,[15] **13a**,[9e,h] and **16a**[9b,j]) were prepared according to the reported procedure. The compounds (**6a**, **7f**, **14**, and **17**) were commercially available and used as purchased.

5-Methoxy-1-(*tert*-butoxycarbonyl)oxindole (7c). Under a nitrogen atmosphere, a mixture of **6b** (0.20 g, 1.23 mmol), $(Boc)_2O$ (0.67 g, 3.1 mmol), and $NaHCO_3$ (0.92 g, 11 mmol) in anhydrous THF (17 mL) was heated at refluxing temperature

for 2.5 h. After cooling, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 4:1) to give **7c** (0.25 g, 78% yield) as white crystals; mp 124−125 °C. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.64 (9H, s), 3.62 (2H, s), 3.80 (3H, s), 6.80−6.82 (2H, m), 7.70 (1H, d, J = 9.5 Hz). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 28.2, 36.9, 55.6, 84.1, 110.4, 112.7, 115.8, 124.4, 134.3, 149.1, 156.5, 172.9. IR (KBr): 1790−1770, 1713 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.78; H, 6.50; N, 5.30.

6-Methoxy-1-(*tert*-butoxycarbonyl)oxindole (7d). Similarly to the preparation of **7c**, **7d** (0.33 g, 81% yield) was obtained from **6c** (0.26 g, 1.56 mmol). White crystals; mp 77−78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.65 (9H, s), 3.28 (2H, s), 3.82 (3H, s), 6.67 (1H, dd, J = 2.0, 8.0 Hz), 7.11 (1H, d, J = 8.0 Hz), 7.43 (1H, d, J = 2.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.0, 35.9, 55.5, 84.3, 101.9, 109.7, 114.8, 124.6, 141.8, 149.1, 159.6, 173.7. IR (KBr): 1800−1770, 1728 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.73; H, 6.50; N, 5.14.

3,3-Bis(hydroxymethyl)-1-methyloxindole (3a). A Typical Procedure for Preparation of Diols 3 from 7. An aqueous 37% HCHO solution (1.7 mL) was added to a mixture of **7a** (1.15 g, 7.8 mmol) and Na_2CO_3 (170 mg, 1.6 mmol) in dioxane (6.5 mL). After the mixture was stirred at room temperature for 17 h, an aqueous 37% HCHO solution (0.22 mL) was added. The stirring was continued for further 2.5 h, and the reaction mixture was filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−EtOAc) to give **3a** (1.18 g, 73% yield) as white crystals; mp 161−162 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.20 (3H, s), 3.80 (2H, d, J = 11.0 Hz), 3.90 (2H, d, J = 11.0 Hz), 6.98 (1H, d, J = 7.5 Hz), 7.10 (1H, dt, J = 1.0, 7.5 Hz), 7.31 (1H, dt, J = 1.0, 7.5 Hz), 7.42 (1H, d, J = 7.5 Hz). ^{13}C NMR (CD_3OD, 75 MHz): δ 26.4, 59.2, 64.7, 109.3, 123.7, 125.0, 129.4, 130.9, 146.0, 179.6. IR (KBr): 3700−3100, 1695−1610 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.66; H, 6.32; N, 6.74.

3,3-Bis(2-furoyloxymethyl)-1-methyloxindole (4a). Typical Procedure for Preparation of Difuroates 4 from 3. Under a nitrogen atmosphere, a mixture of **3a** (0.81 g, 3.9 mmol), furan-2-carboxylic acid (1.31 g, 11.7 mmol), DCC (2.4 g, 11.7 mmol), and DMAP (0.24 g, 2.0 mmol) in anhydrous THF (23 mL) was stirred at room temperature for 15 h. Water (10 mL) was added, and the mixture was stirred vigorously. The product was extracted with EtOAc three times, and the combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 1:1) to give **4a** (1.48 g, 96% yield) as white crystals; mp 106.5−107 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.29 (3H, s), 4.55 (2H, d, J = 11.0 Hz), 4.88 (2H, d, J = 11.0 Hz), 6.47 (2H, dd, J = 2.0, 3.5 Hz), 6.90 (1H, dd, J = 1.0, 7.5 Hz), 7.05 (2H, dd, J = 1.0, 3.5 Hz), 7.06 (1H, dt, J = 1.0, 7.5 Hz) 7.33 (1H, dt, J = 1.0, 7.5 Hz), 7.45 (1H, dd, J = 1.0, 7.5 Hz). 7.56 (2H, dd, J = 1.0, 2.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.4, 51.9, 64.7, 108.2, 111.8, 118.4, 122.9, 124.6, 127.0, 129.3, 143.8, 143.9, 146.7, 157.8, 174.3. IR (KBr): 1730−1710 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_7$: C, 63.80; H, 4.33; N, 3.54. Found: C, 63.89; H, 4.52; N, 3.53.

Typical Procedure for Lipase-Catalyzed Desymmetrization of Prochiral Diols 3a−h Using 5. To a resealable vessel were added ^{i}Pr$_2$O (55 mL), THF (11 mL), and water (0.07 mL). The diol **3b** (100 mg, 0.34 mmol), **5** (187 mg, 1.0 mmol), and lipase OF (180 mg) were added in this order, and the vessel was sealed. The reaction mixture was stirred at 30 °C with monitoring the reaction by TLC. When **3b** was consumed, the reaction mixture was filtered through a Celite pad. Water (100 mL) was added to the filtrate, and the mixture was stirred vigorously at room temperature until **5** disappeared (TLC analysis; usually for 30 min to 5 h). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 3:1 to 2:1)[24] to give the monoester (*R*)-**2b** (109 mg, 83% yield) and the diester **4b** (24 mg, 15% yield). The reaction conditions, the isolated yield, and the optical purity of other products (*R*)-**2a**,**c**−**h** are listed in Table 2. The 2 g-scale reaction (entry 3) was carried out by the same procedure using the same ratio of the substrate, the reagents, and the solvent. The optical purity of (*R*)-**2** was determined by HPLC using chiral columns: Daicel Chiralcel OD for **2a**−**d**,**f**, Chiralpak AD for **2e**,**g**, and Chiralcel OJ for **2h**.

(*R*)-(+)-[3-(Hydroxymethyl)-1-methyloxindol-3-yl]methyl 2-Furoate (2a). A pale yellow oil, 87% ee; $[\alpha]_D^{27}$ +63.3 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.19 (3H, s), 3.82 (1H, d, J = 11.0 Hz), 3.99 (1H, d, J = 11.0 Hz), 4.46 (1H, d, J = 11.0 Hz), 4.77 (1H, d, J = 11.0 Hz), 6.40 (1H, d, J = 3.0 Hz), 6.83 (1H, d, J = 7.5 Hz), 6.96 (1H, d, J = 3.0 Hz), 7.01 (1H, t, J = 7.5 Hz), 7.25 (1H, d, J = 7.5 Hz), 7.29 (1H, t, J = 7.5 Hz), 7.48 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.3, 29.6, 63.8, 64.4, 108.4, 111.8, 118.3, 123.0, 124.1, 127.5, 129.1, 143.9, 144.0, 146.6, 158.0, 176.5. IR (KBr): 3700−3200, 1713, 1693 cm^{-1}. High-resolution EIMS calcd for $C_{16}H_{15}NO_5$ (M^+), 301.0950; found, 301.0979.

(*R*)-(+)-[3-(Hydroxymethyl)-1-(*tert*-butoxycarbonyl)oxindol-3-yl]methyl 2-Furoate (2b). White crystals, 97% ee; mp 125−126 °C; $[\alpha]_D^{27}$ +56.3 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.64 (9H, s), 3.96 (1H, d, J = 11.0 Hz), 4.04 (1H, d, J = 11.0 Hz), 4.57 (1H, d, J = 11.0 Hz), 4.79 (1H, d, J = 11.0 Hz), 6.45 (1H, dd, J = 1.5, 3.5 Hz), 6.99 (1H, d, J = 3.5 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.34 (1H, t, J = 7.5 Hz), 7.40 (1H, d, J = 7.5 Hz), 7.54 (1H, d, J = 1.5 Hz), 7.86 (1H, d, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.9, 54.3, 64.2, 64.9, 84.7, 111.8, 115.0, 118.4, 123.7, 124.6, 126.4, 129.0, 140.0, 143.6, 146.7, 148.8, 157.8, 175.1. IR (KBr): 3700−3200, 1790−1720 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.71; H, 5.46; N, 3.60.

(*R*)-(+)-[3-(Hydroxymethyl)-5-methoxy-1-(*tert*-butoxycarbonyl)oxindol-3-yl]methyl 2-Furoate (2c). White crystals, 98% ee; mp 140−140.5 °C; $[\alpha]_D^{27}$ +49.8 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.65 (9H, s), 3.78 (3H, s), 3.95 (1H, d, J = 11.0 Hz), 4.07 (1H, d, J = 11.0 Hz), 4.59 (1H, d, J = 11.0 Hz), 4.79 (1H, d, J = 11.0 Hz), 6.47 (1H, dd, J = 1.5, 3.5 Hz), 6.87 (1H, dd, J = 2.5, 9.0 Hz), 6.96 (1H, d, J = 2.5 Hz), 7.04 (1H, d, J = 3.5 Hz), 7.56 (1H, br s), 7.81 (1H, d, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.1, 54.4, 55.6, 64.4, 64.8, 84.7, 110.0, 111.9, 114.0, 116.0, 118.5, 127.6, 133.4, 143.8, 146.7, 148.9, 157.0, 157.9, 175.2. IR (KBr): 3625−3250, 1786, 1770, 1732 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_8$: C, 60.43; H, 5.55; N, 3.36. Found: C, 60.28; H, 5.58; N, 3.28.

(*R*)-(+)-[3-(Hydroxymethyl)-6-methoxy-1-(*tert*-butoxycarbonyl)oxindol-3-yl]methyl 2-Furoate (2d). White crystals. Recrystallization from benzene gave **2d** (99% ee); mp 136−136.5 °C; $[\alpha]_D^{26}$ +69.6 (*c* 1.0, $CHCl_3$) for 99% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.65 (9H, s), 3.83 (3H, s), 3.91 (1H, d, J = 11.0 Hz), 4.03 (1H, d, J = 11.0 Hz), 4.56 (1H, d, J = 11.0 Hz), 4.78 (1H, d, J = 11.0 Hz), 6.48 (1H, dd, J = 1.5, 3.5 Hz), 6.71 (1H, dd, J = 2.5, 8.0 Hz), 7.05 (1H, d, J = 3.5 Hz), 7.27 (1H, d, J = 8.0 Hz), 7.53 (1H, d, J = 2.5 Hz), 7.56 (1H, d, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.1, 53.8, 55.5, 64.5, 64.9, 84.9, 102.2, 110.2, 111.9, 117.6, 117.9, 118.5, 124.4, 141.2, 143.8, 146.7, 157.9, 160.6, 175.7. IR (KBr): 3625−3250, 1790, 1775, 1732 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_8$: C, 60.43; H, 5.55; N, 3.36. Found: C, 60.70; H, 5.70; N, 3.56.

(*R*)-(+)-[1-Benzyloxycarbonyl-3-(hydroxymethyl)oxindol-3-yl]methyl 2-Furoate (2e). White crystals, 98% ee; mp 136−137 °C; $[\alpha]_D^{28}$ +56.4 (*c* 1.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.89 (1H, d, J = 11.0 Hz), 4.00 (1H, d, J = 11.0 Hz), 4.53 (1H, d, J = 11.0 Hz), 4.74 (1H, d, J = 11.0 Hz), 5.39

(24) Occasionally, a product was obtained with a small amount of furan-2-carboxylic acid as a contaminant after standard SiO_2 flash chromatography. Use of the eluent containing 1 v/v % of Et_3N for the chromatography was effective to prevent the contamination.

(2H, s), 6.35 (1H, dd, J = 2.0, 3.5 Hz), 6.88 (1H, d, J = 3.5 Hz), 7.13 (1H, t, J = 7.5 Hz), 7.26−7.36 (5H, m), 7.43−7.46 (3H, m), 7.87 (1H, d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 54.5, 64.5, 64.8, 68.9, 111.9, 115.3, 118.6, 123.8, 125.1, 128.2, 128.6, 128.7, 129.4, 134.7, 139.7, 143.6, 146.8, 150.5, 157.8, 175.0. IR (KBr): 3700−3200, 1790, 1760, 1730 cm^{-1}. Anal. Calcd for $C_{23}H_{19}NO_7$: C, 65.55; H, 4.54; N, 3.32. Found: C, 65.37; H, 4.70; N, 3.30.

(*R*)-(+)-[1-Acetyl-3-(hydroxymethyl)oxindole-3-yl]methyl 2-Furoate (2f). White crystals, 97% ee; mp 122−122.5 °C; $[\alpha]_D^{27}$ +20.1 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 2.71 (3H, s), 4.00 (1H, d, J = 11.0 Hz), 4.08 (1H, d, J = 11.0 Hz), 4.61 (1H, d, J = 11.0 Hz), 4.80 (1H, d, J = 11.0 Hz), 6.46 (1H, dd, J = 1.5, 3.5 Hz), 6.70 (1H, d, J = 3.5 Hz), 7.21−7.26 (1H, m), 7.35−7.42 (2H, m), 7.55 (1H, s), 8.27 (1H, d, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 26.8, 54.8, 64.6, 64.8, 111.9, 116.7, 118.5, 123.3, 125.4, 126.3, 129.4, 140.6, 143.8, 146.7, 157.7, 170.5, 177.3. IR (KBr): 3600−3180, 1770−1740, 1725, 1713 cm^{-1}. High-resolution FABMS calcd for $C_{17}H_{16}NO_6$ [(M + H)$^+$], 330.0978; found, 330.0959.

(*R*)-(+)-[3-Hydroxymethyl-1-(methoxymethyl)oxindol-3-yl]methyl 2-Furoate (2g). Colorless oil, 86% ee; $[\alpha]_D^{27}$ +19.7 (*c* 0.89, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.34 (3H, s), 3.95 (1H, d, J = 11.0 Hz), 4.08 (1H, d, J = 11.0 Hz), 4.60 (1H, d, J = 11.0 Hz), 4.87 (1H, d, J = 11.0 Hz), 5.15 (1H, d, J = 11.0 Hz), 5.21 (1H, d, J = 11.0 Hz), 6.46 (1H, dd, J = 1.5, 3.5 Hz), 7.02 (1H, d, J = 3.5 Hz), 7.08−7.15 (2H, m), 7.34 (1H, dt, J = 1.0, 7.5 Hz), 7.39 (1H, d, J = 7.5 Hz), 7.53 (1H, d, J = 1.5 Hz). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 54.2, 56.3, 64.3, 64.6, 71.2, 109.8, 111.8, 118.3, 123.4, 123.9, 126.8, 129.1, 142.2, 143.8, 146.5, 157.8, 177.0. IR (KBr): 3600−3200, 1730−1710 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.50; H, 5.25; N, 4.16.

(*R*)-(+)-[1-Benzyl-3-(hydroxymethyl)oxindol-3-yl]methyl 2-Furoate (2h). A colorless oil, 68% ee; $[\alpha]_D^{25}$ +33.9 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (1H, d, J = 11.0 Hz), 4.08 (1H, d, J = 11.0 Hz), 4.64 (1H, d, J = 11.0 Hz), 4.83 (1H, d, J = 16.0 Hz), 4.92 (1H, d, J = 11.0 Hz), 5.08 (1H, d, J = 16.0 Hz), 6.41 (1H, dd, J = 1.5, 3.5 Hz), 6.76 (1H, d, J = 7.5 Hz), 6.87 (1H, d, J = 3.5 Hz), 7.03 (1H, t, J = 7.5 Hz), 7.19 (1H, dt, J = 1.0, 7.5 Hz), 7.24−7.31 (5H, m), 7.37 (1H, d, J = 7.5 Hz), 7.52 (1H, d, J = 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.8, 53.8, 64.3, 64.7, 109.4, 111.8, 118.3, 123.0, 127.2, 127.5, 127.6, 128.8, 128.9, 135.4, 143.1, 143.9, 146.6, 158.0, 176.7. IR (KBr): 3700−3200, 1740−1690 cm^{-1}. High-resolution FABMS calcd for $C_{22}H_{20}NO_5$ [(M + H)$^+$], 378.1342; found, 378.1342.

Typical Procedure for Lipase-Catalyzed Desymmetrization of Difuroates 4a−h. A solution of **4a** (500 mg, 1.26 mmol) in a 5:1 mixture of ^{i}Pr$_2$O−THF (50 mL) was placed in a resealable vessel, and water (50 mL) and lipase OF (500 mg) were added. The vessel was sealed, and the reaction mixture was stirred at 30 °C with monitoring the reaction by TLC. When **4a** was consumed, water (20 mL) and EtOAc (80 mL) were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc with 1 v/v % of Et_3N)[24] to give (*S*)-**2a** and **3a**. The reaction conditions, the isolated yield, and the optical purity of (*S*)-**2b**−**h** are listed in Table 2. The 2 g-scale reaction (entry 12) was carried out by the same procedure using the same ratio of substrate, reagents, and solvent. The optical purity of (*S*)-**2a**−**h** was determined as described for (*R*)-**2** obtained by the desymmetrization of **3**. The spectroscopic data of (*S*)-**2a**−**h** were identical with those of (*R*)-**2a**−**h**.

(*S*)-(−)-[3-(Hydroxymethyl)-1-methyloxindol-3-yl]methyl 2-Furoate (2a): >99% ee; $[\alpha]_D^{25}$ −66.6 (*c* 0.79, $CHCl_3$).

(*S*)-(−)-[3-(Hydroxymethyl)-1-(*tert*-butoxycarbonyl)oxindol-3-yl]methyl 2-Furoate (2b): >99% ee; $[\alpha]_D^{28}$ −53.8 (*c* 0.80, $CHCl_3$).

(*S*)-(−)-[3-(Hydroxymethyl)-5-methoxy-1-(*tert*-butoxycarbonyl)oxindol-3-yl]methyl 2-Furoate (2c): >99% ee; $[\alpha]_D^{27}$ −46.1 (*c* 1.1, $CHCl_3$).

(*S*)-(−)-[3-(Hydroxymethyl)-6-methoxy-1-(*tert*-butoxycarbonyl)oxindol-3-yl]methyl 2-Furoate (2d): 82% ee; $[\alpha]_D^{28}$ −41.4 (*c* 0.91, $CHCl_3$).

(*S*)-(−)-[1-Benzyloxycarbonyl-3-(hydroxymethyl)oxindol-3-yl]methyl 2-Furoate (2e): >99% ee; $[\alpha]_D^{28}$ −56.3 (*c* 0.97, $CHCl_3$).

(*S*)-(−)-[1-Acetyl-3-(hydroxymethyl)oxindole-3-yl]methyl 2-Furoate (2f): 97% ee; $[\alpha]_D^{27}$ −21.8 (*c* 0.63, $CHCl_3$).

(*S*)-(−)-[3-Hydroxymethyl-1-(methoxymethyl)oxindol-3-yl]methyl 2-Furoate (2g): 98% ee; $[\alpha]_D^{27}$ −26.0 (*c* 0.73, $CHCl_3$).

(*S*)-(−)-[1-Benzyl-3-(hydroxymethyl)oxindol-3-yl]methyl 2-Furoate (2h): 98% ee; $[\alpha]_D^{27}$ −45.0 (*c* 1.1, $CHCl_3$).

(*S*)-(−)-[3-(Hydroxymethyl)-1-(methoxymethyl)oxindol-3-yl]methyl 2-Benzoate (2i). Similarly to the typical procedure for the desymmetrization of **4a**−**h**, **4i** (20 mg, 0.040 mmol) and lipase OF (40 mg) were stirred in a mixture of ^{i}Pr$_2$O−THF (5:1, 4.0 mL) and water (2.0 mL) at 30 °C for 24 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 2:1) to give (*S*)-**2i** (5.8 mg, 37% yield) and **3g** (6.0 mg, 63% yield). (*S*)-**2i** was obtained as a colorless oil. The optical purity was determined to be 98% ee by HPLC using a Daicel Chiralpak AS. The absolute stereochemistry is tentatively presumed to be *S* on the basis of the similarity of its specific rotation {$[\alpha]_D^{27}$ −37.2 (*c* 1.0, $CHCl_3$)} to that of (*S*)-**2a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.32 (3H, s), 3.97 (1H, d, J = 11.0 Hz), 4.10 (1H, d, J = 11.0 Hz), 4.70 (1H, d, J = 11.0 Hz), 4.84 (1H, d, J = 11.0 Hz), 5.16 (1H, d, J = 11.0 Hz) 5.21 (1H, d, J = 11.0 Hz), 7.05 (2H, t, J = 7.5 Hz), 7.30 (4H, dt, J = 2.5, 7.5 Hz), 7.45 (1H, t, J = 7.5 Hz), 7.75 (2H, d, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 54.4, 56.4, 64.3, 64.9, 71.3, 109.9, 123.5, 123.9, 127.1, 128.4, 129.2, 129.5, 133.2, 142.4, 166.0, 177.4. IR (KBr): 3650−3200, 1724, 1614 cm^{-1}. High-resolution FABMS calcd for $C_{19}H_{20}NO_5$ [(M + H)$^+$], 342.1341; found, 342.1353.

(*S*)-(+)-3-(2-Oxoethyl)-1,3-dimethyoxindole (11). A mixture of (*S*)-**10** (100 mg, 0.50 mmol), an aqueous 35% NaOH solution (2.0 mL), and MeOH (2.0 mL) was stirred at room temperature for 3 h, which was acidified with 2 N HCl. The product was extracted with EtOAc three times, and the combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 2:1 to 1:1) to give (*S*)-1,3-dimethyloxindol-3-yl acetic acid (107 mg, 97% yield) as pale yellow crystals; mp 175−175.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (3H, s), 2.73 (1H, d, J = 16.5 Hz), 2.91 (1H, d, J = 16.5 Hz), 3.14 (3H, s), 6.78 (1H, br d, J = 7.5 Hz), 7.00 (1H, br t, J = 7.5 Hz), 7.12 (1H, br d, J = 7.5 Hz), 7.21 (1H, dt, J = 1.0 Hz, 7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.9, 26.5, 41.3, 45.3, 108.4, 122.3, 122.8, 128.3, 132.7, 143.1, 174.0, 180.3. IR (KBr): 3350−2800, 1730−1675, 1614 cm^{-1}. High-resolution FABMS calcd for $C_{12}H_{14}NO_3$ [(M + H)$^+$], 220.0974; found, 220.0974.

Under a nitrogen atmosphere, BH_3·Me_2S (2.0 M in THF, 0.070 mL, 0.14 mmol) was added to an ice-cooled solution of the above product (30 mg, 0.14 mmol) in anhydrous THF (0.3 mL). The reaction mixture was stirred at room temperature for 9 h and quenched with MeOH (1 mL). The whole mixture was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−EtOAc, 1:1 to EtOAc) to give (*S*)-3-(2-hydroxyethyl)-1,3-dimethyloxindole (25 mg, 89% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.34 (3H, s), 1.89−2.00 (1H, m), 2.04−2.14 (1H, m), 3.15 (3H, s), 3.30−3.42 (1H, m), 3.54−3.62 (1H, m), 6.79 (1H, br d, J = 8.0 Hz), 7.01 (1H, dt, J = 1.0, 8.0 Hz), 7.10 (1H, br d, J = 8.0 Hz), 7.21

(1H, dt, J = 1.0, 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.5, 26.3, 39.9, 46.9, 59.3, 108.3, 122.4, 122.8, 128.0, 134.0, 142.8, 181.6. IR (KBr): 3550−3300, 1720−1690 cm^{-1}. High-resolution FABMS calcd for $C_{12}H_{16}NO_2$ [(M + H)$^+$], 206.1181; found, 206.1191.

A mixture of the above product (20 mg, 0.10 mmol) and Dess−Martin periodinane (124 mg, 0.30 mmol) in CH_2Cl_2 (0.80 mL) was stirred at 0 °C for 30 min, and the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution. After vigorous stirring for 10 min, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 1:1) to give (*S*)-(+)-**11** (18 mg, 92% yield) as a pale yellow oil. The optical purity of the product was determined to be 99% ee on the basis of HPLC analysis using Daicel Chiralcel OD. $[\alpha]_D^{29}$ +41.3 (*c* 0.35, $CHCl_3$) {lit.[22a] $[\alpha]_D^{24}$ +20.2 (*c* 0.50, $CHCl_3$) for (*S*)-**11** with 45% ee}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (3H, s), 2.91 (2H, s), 3.20 (3H, s), 6.81 (1H, d, J = 7.5 Hz), 7.00 (1H, t, J = 7.5 Hz), 7.12 (1H, d, J = 7.5 Hz), 7.21 (1H, t, J = 7.5 Hz), 9.45 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.9, 26.4, 45.0, 50.5, 108.4, 122.4, 122.7, 128.3, 132.7, 143.2, 179.5, 198.7. IR (KBr): 1720−1690, 1614 cm^{-1}. High-resolution FABMS calcd for $C_{12}H_{14}NO_2$ [(M + H)$^+$], 204.1028; found, 204.1028.

(−)-2-Benzyloxy-3-hydroxypropan-1-yl 2-Furoate (13b). Similarly to the typical procedure for the enzymatic hydrolysis of **4**, a mixture of **12b** (40 mg, 0.108 mmol) and CALB (80 mg) was stirred in a 1:1 mixture of ^{i}Pr$_2$O and water (total 2.0 mL) at 30 °C for 84 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 2:1) to give (−)-**13b** (14.9 mg, 55% yield) and **14** (4.8 mg, 26% yield). The optical purity of (−)-**13b** was determined to be 75% ee on the basis of HPLC analysis using Daicel Chiralcel OD. Colorless oil; $[\alpha]_D^{27}$ −10.0 (*c* 0.74, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.60−3.75 (3H, m), 4.34 (1H, dd, J = 5.5, 11.5 Hz), 4.39 (1H, dd, J = 5.5, 11.5 Hz), 4.56 (1H, d, J = 11.5 Hz), 4.67 (1H, d, J = 11.5 Hz), 6.43 (1H, dd, J = 2.0, 3.5 Hz), 7.10 (H, dd, J = 1.0, 3.5 Hz), 7.18−7.26 (5H, m), 7.50 (1H, dd, J = 1.0, 2.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 61.8, 63.4, 72.2, 77.0, 111.9, 118.3, 127.8, 127.9, 128.4, 137.7, 144.2, 146.5, 158.5. IR (KBr): 3550−3200, 1730−1710 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.80; H, 5.95.

(1*S*,2*R*)-2-Hydroxycyclohex-1-yl 2-Furoate (16b). Similarly to the typical procedure for the enzymatic hydrolysis of **4**, a mixture of **15b** (40 mg, 0.13 mmol) and CHIRAZYME L-9 (80 mg) was stirred in a 1:1 mixture of ^{i}Pr$_2$O and water (total 2.0 mL) at 50 °C for 24 h. The workup and the purification were similarly performed to give **16b** (5.4 mg, 20% yield), **17** (2.3 mg, 15% yield), and recovered **15b** (24 mg, 61% yield). The optical purity of **16b** was determined to be 99% ee on the basis of HPLC analysis using Daicel Chiralcel OJ. Colorless oil; $[\alpha]_D^{27}$ +2.5 (*c* 0.79, $CHCl_3$) {lit.[10b] $[\alpha]_D^{22}$ −2.5 (*c* 1.0, $CHCl_3$) for (1*R*,2*S*)-**16b** with 97% ee}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25−2.05 (9H, m), 3.97 (1H, d, J = 6.0 Hz), 5.17 (1H, dt, J = 3.0, 8.0 Hz), 6.52 (1H, dd, J = 1.0, 3.0 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.60 (1H, d, J = 1.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 21.9, 27.1, 30.3, 69.2, 74.8, 111.8, 118.0, 144.7, 146.3, 158.3. High-resolution FABMS calcd for $C_{11}H_{15}O_4$ [(M + H)$^+$], 211.0970; found, 211.0966.

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Supporting Information Available: General methods; preparation of **3b**−**h**, **4b**−**i**, **12b**, and **15b** and the conversion of (*S*)-(−)-**2a** to (*S*)-(+)-**10**; ^{1}H NMR and ^{13}C NMR spectra for compounds **3c**,**g**, (+)-**2a**, (+)-**2f**, (+)-**2h**, (−)-**2i**, (*S*)-3-(iodomethyl)-1,3-dimethyoxindole, (*S*)-**10**, (*S*)-1,3-dimethyloxindol-3-yl acetic acid, (*S*)-3-(2-hydroxyethyl)-1,3-dimethyloxindole, (*S*)-**11**, **12b**, **15b**, and (1*S*,2*R*)-**16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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