An Efficient Enantioselective Total Synthesis of Antitumor Lignans: Synthesis of Enantiomerically Pure 4-Hydroxyalkanenitriles *via* an Enzymatic Reaction

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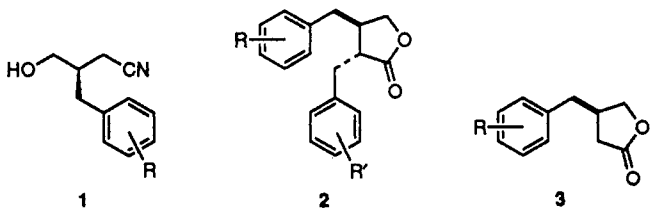
Efficient preparation of optically pure 4-hydroxyalkanenitriles, **1a–f**, was achieved *via* an enzymatic reaction using lipase PS (*Pseudomonas* sp.). Optically pure (*R*)-4-hydroxy-3-[[3,4-(methylenedioxy)phenyl]methyl]butanenitrile (**1a**) was applied to the enantioselective synthesis of three types of antitumor lignans, (−)-*hinokinin*, (−)-*isodeoxypodophyllotoxin*, and (+)-*isostegane*.

Introduction

Natural antitumor lignans have been recognized as challenging targets for organic synthesis.[1] The skeleton of 2,3-disubstituted-4-butanolide **2** is the most important feature found in lignans.[1] Optically active 4-butanolide **3** has frequently been used for the asymmetric synthesis of lignans as the key starting intermediate.[1a] Although

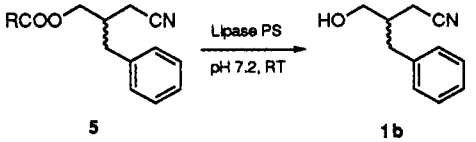


1 **2** **3**

significant success has been achieved in constructing a lignan framework from lactone **3**, important steps remained to be resolved. The key intermediate, 4-butanolide **3**, has been synthesized in multistep sequences in low overall yield.[1a] As can be seen in Figure 1, many types of optically active antitumor lignans are derived from (*R*)-3-[[3,4-(methylenedioxy)phenyl]methyl]-4-butanolide (**3a**) which is converted from (*R*)-4-hydroxy-3-[[3,4-(methylenedioxy)phenyl]methyl]butanenitrile (**1a**). Hydroxy nitriles **1** are useful building blocks in organic synthesis because both hydroxyl and cyano groups can be easily converted to broadly varied types of functional groups.[2] There has been limited work[3] reported, however, on a general method applicable to preparation of optically pure 4-hydroxyalkanenitriles **1**. The enzymatic reaction is now well recognized as an easy and dependable means of creating enantiomerically pure products.[4] In this paper, we describe the first use of a lipase to prepare optically active 4-hydroxyalkanenitriles **1** and its application for the highly efficient enantioselective total syntheses of three types of antitumor lignans, (−)-*hinokinin*,[1b-h] (−)-*isodeoxypodophyllotoxin*,[1i-k] and (+)-*isostegane*.[1d,l,n]

Results and Discussion

Synthesis of Optically Pure 4-Hydroxyalkanenitriles 1. The key intermediate of our synthesis of antitumor lignans is optically pure hydroxy nitrile **1a**. Our synthetic strategy for optically active hydroxy nitrile was based on the use of a lipase-catalyzed reaction. As shown in Scheme I, two possible ways to synthesize **1a** by an enzymatic reaction are considered. One is a kinetic resolution of racemic acetate **5a** (path A), and the other is a transformation of chiral monoacetate **7a** which is expected to be obtained from the enantioselective monoacetylation of the prochiral diol **6a** (path B). Since enzymatic resolution of a racemic ester was a well-established procedure,[4] we initially tried to resolve the racemic acetate of **1a** by lipase-catalyzed hydrolysis (path A), but we were unable to find an enzyme that hydrolyzed the acetate with enantioselectivity. In the hydrolysis of 3-cyano-2-[[3,4-(methylenedioxy)phenyl]methyl]propyl acetate (**5a**), lipases from *Aspergillus niger* (A and A-6), *Candida* sp. (MY and M10), *Rhizopus* sp. (F-AP15 and Newlase F), porcine pancreatin (PPL), hog pancreatin, pig liver esterase (PLE), and *Pseudomonas* sp. (PS) were not enantioselective. We previously reported that the stereochemical behavior of lipase PS (*Pseudomonas* sp.) is sensitive to the ester functionality, and that enantioselectivity of the lipase-catalyzed hydrolysis of 3-hydroxyalkanenitriles could be enhanced by changing the acyl residue.[5] However, the reaction of lipase PS was not enantioselective with any racemic esters **5** (eq 1).



5 **1b** (1)

• Abstract published in *Advance ACS Abstracts*, September 1, 1993.

(1) (a) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029 and refs cited therein. (b) Rehnberg, N.; Magnussen, G. *J. Org. Chem.*, **1990**, *55*, 4340. (c) Yoda, H.; Naito, S.; Takabe, K.; Tanaka, N. *Tetrahedron Lett.*, **1990**, *31*, 7623. (d) Tomioka, K.; Ishiguro, T.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 4333. (e) Belletire, J. L.; Fry, D. F. *J. Org. Chem.*, **1987**, *52*, 2549. (f) Anjaneyula, A. s. R.; Ramaiah, P. A.; Row, L. R.; Venkateswarlu, R.; Pelter, A.; Ward, R. S. *Tetrahedron* **1981**, *37*, 3641. (g) de Carvalho, M. D.; Yoshida, M.; Gottlieb, O. R.; Gottlieb, H. E. *Phytochemistry* **1987**, *26*, 265. (h) Howorth, R. D.; Woodcock, D. *J. Chem. Soc.* **1938**, 1985. (i) Brown, E.; Daugan, A. *Tetrahedron* **1989**, *45*, 141. (j) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1979**, 3315. (k) Kuhn, M.; Von Wartburg, A. *Helv. Chim. Acta* **1967**, *50*, 1546. (l) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303. (m) Tomioka, K.; Mizuguchi, M.; Koga, K. *Chem. Pharm. Bull.* **1982**, *30*, 4304. (n) Tomioka, K.; Mizuguchi, H.; Ishiguro, T.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 121. (o) Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans 1* **1989**, 935. (p) Brown, E.; Daugan, A. *Tetrahedron Lett.* **1985**, *26*, 3997.

(2) Tennant, G. *Comprehensive Organic Chemistry*; Barton, D., Ollis. D., Eds.; Pergamon Press: New York, 1979; Vol. 2, p 385.

(3) Toshimitsu, A.; Fuji, H. *Chem. Lett.* **1992**, 2017.

(4) For recent review see; Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071. Chen, C. S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. Wang, Y. -F.; Wong, C. -H. *J. Org. Chem.* **1988**, *53*, 3129. Kirchner, G. Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 7072 and refs cited therein.

(5) Itoh, T.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1991**, *56*, 1521.

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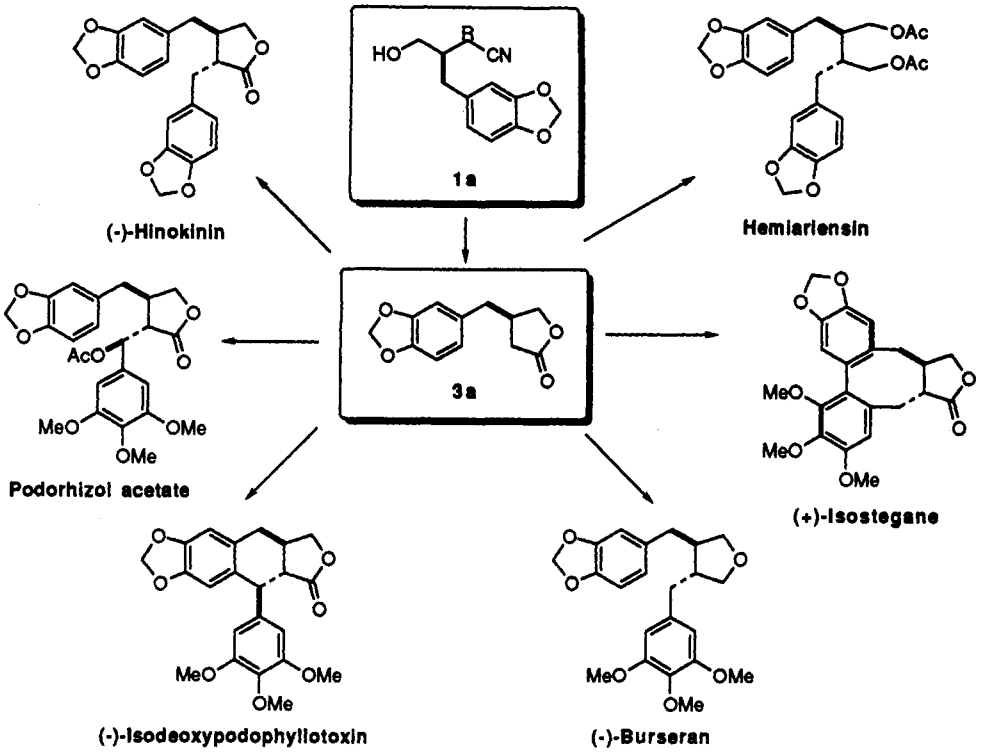
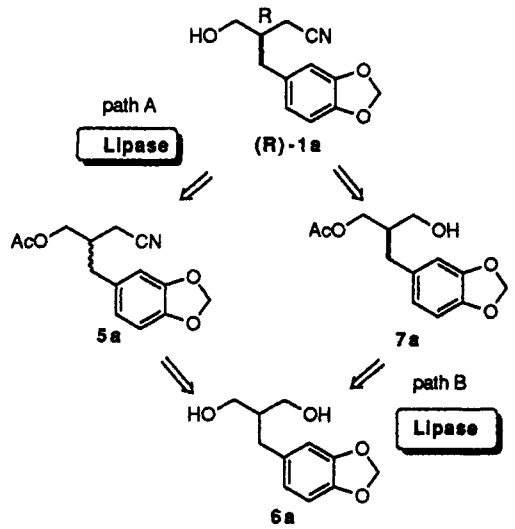
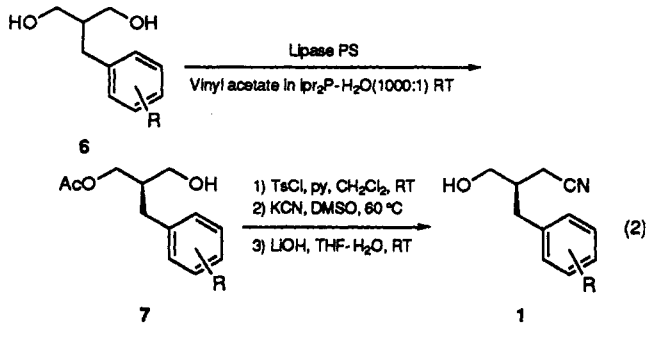


Figure 1.

Scheme I



The latter strategy, path B, was found to be a very successful means of preparing the desired hydroxy nitriles 1 in an optically pure state (eq 2). It was first demonstrated



by Achiwa et al.[6a] that 2-benzyl-1,3-propanediol (**6b**) was converted to optically pure monoacetate **7b** by lipase PS.

A functional group on the benzene ring did not affect the enantioselectivity of the lipase-catalyzed reaction. The desired enantiospecific monoacetylation of 2-[[3,4-(methylenedioxy)phenyl]methyl]-1,3-propanediol (**6a**) was accomplished by lipase PS. Optically pure acetate (*R*)-**7a** was obtained in 97% yield when **6a** was treated with 50 wt% of lipase PS in a mixed solvent of diisopropyl ether (iPr_2O) and water (1000:1) in the presence of vinyl acetate as an acyl donor. The optical purity was confirmed by ^{19}F NMR analysis of the corresponding (+)-α-methoxy-α-(trifluoromethyl)-α-phenylacetate (MTPA)[7] of **7a**. Correct selection of the solvent system was essential for achieving the monoacetylation. Both reaction rate and enantioselectivity were decreased when the reaction was carried out in hexane, tetrahydrofuran (THF), or vinyl acetate.[8] Addition of a trace amount of water in iPr_2O enhanced the rate drastically,[9] and the reaction was completed in several hours with stirring at room temperature, though it required 78 h in dry iPr_2O. This lipase-catalyzed monoacetylation of a prochiral diol was found to be applicable to a broad variety of types of diols **6**. Thus optically active monoacetates **7c–e**,were obtained by this reaction in excellent yield. These monoacetates **7** were then converted to hydroxy nitriles **1** in high yield using a three-step procedure. Tosylation of the hydroxyl group

(6) (a) Tsuji, K.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 6189. (b) Atsuumi, S.; Nakano, M; Koike, Y.; Tanak, S.; Ohkubo, M.; Yonezawa, T.; Funabashi, H.; Hashimoto, J.; Morishima, H. *Ibid.* **1990**, *31*, 1601. Grisenti, P.; Ferraboschi, P.; Manzocchi, A.; Santaniello, E. *Tetrahedron* **1992**, *48*, 3827.

(7) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(8) Reaction time, yield, and % ee of **6a** in various solvent systems: in THF (3 h, 72%, 75% ee); in hexane (24 h, 63%, 97% ee); in vinyl acetate (70 h, 70 %, 97% ee).

(9) (a) Zaks, A.; Klibanov, A. M. *J. Biol. Chem.* **1988**, *263*, 8017. (b) Kitaguchi, H.; Fitzpatrick, P. A.; Hunter, J. E.; Klibanov, A. M. *J. Am. Chem. Soc.* **1989**, *110*, 3094. (c) Sakurai, T.; Margolin, A. L.; Russell, A. J.; Klibanov, A. M. *Ibid.* **1988**, *110*, 7236. (d) Kitaguchi, H.; Itoh, H.; Ono, M. *Chem. Lett.* **1990**, 1203. (e) Gutman, A. L.; Shapira, M. *J. Chem. Soc. Chem. Commun.* **1991**, 1467.

Table I. Results of the Preparation of γ-Hydroxy Nitriles 1 *via* an Enzymatic Reaction

entry	substrate	time (h)	% ee of 7 (yield)	$[\alpha]_D$ of 7 in $CHCl_3$ (deg)	% ee of 1 (yield)	$[\alpha]_D$ of 1 in $CHCl_3$ (deg)
1	**6a**	1[a]–5	>98 (100)	+34.1 (*c* 0.76)	>98 (85)	−26.4 (*c* 1.0)
2	**6b**	6	>98 (92)[b]	+20.6 (*c* 1.0)	>98 (88)	−40.3 (*c* 0.96)
3	**6c**	2.5	>98 (97)	+23.8 (*c* 1.06)	>98 (74)	−43.8 (*c* 0.73)
4	**6d**	5	90 (83)	+22.5 (*c* 0.88)	>98 (90)[c]	−43.4 (*c* 1.04)
5	**6e**	2	>98 (100)	+34.0 (*c* 0.87)	>98 (76)	−46.4 (*c* 0.83)
6	**6f**	9	>98 (97)[d]	+40.8 (*c* 0.78)	>98 (76)	−85.4 (*c* 0.64)

[a] It was sometimes recorded that this reaction was completed after only 1 h of stirring at rt. [b] In lit.[6a] 97% ee; $[\alpha]_D$ +27.7°. [c] After recrystallization of the tosylate from hexane. [d] In lit.[6a] 90% ee.

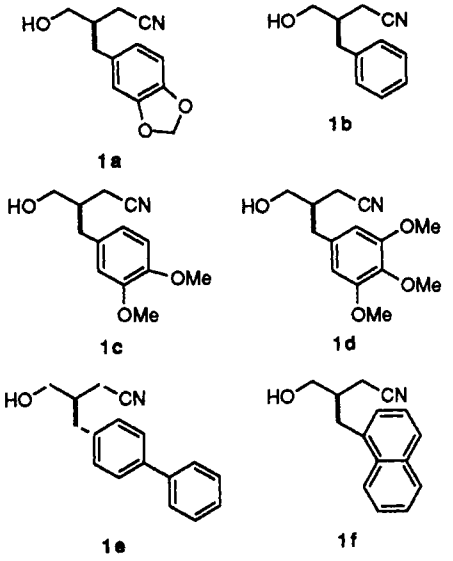


Figure 2.

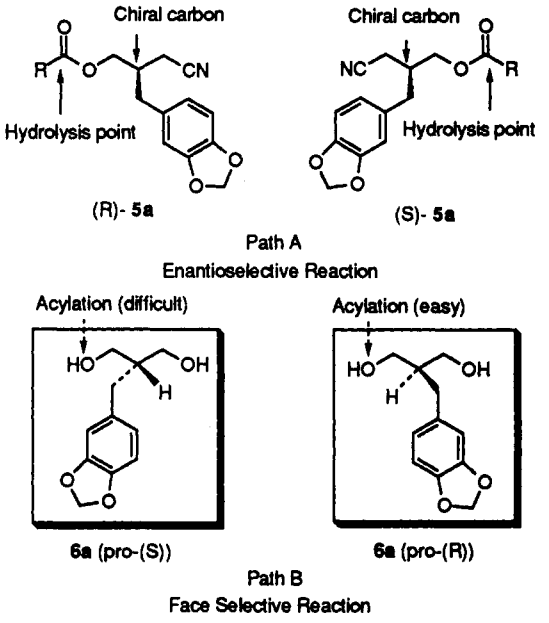


Figure 3.

of 7 followed by treatment with potassium cyanide in dimethyl sulfoxide (DMSO) at 80 °C gave the corresponding acetate 5. The acetoxy group of 5 was finally hydrolyzed by treatment with lithium hydroxide in a mixed solvent of THF–H_2O (3:1) at 0 °C to finish 1 in good overall yield from the starting monoacetates 7 (eq 2). Results of preparation of optically pure 4-hydroxyalkanenitriles 1 are summarized in Table I. Monoacetate **7d**, which was the only sample not obtained in an optically pure state (90% ee), could be optically enriched to >98% ee by recrystallization of the tosylate **4d** (entry 4). Therefore, six types of optically pure 4-hydroxyalkanenitriles, **1a–f**, were synthesized *via* the lipase-catalyzed reaction. Since the cyano group of 1 can be converted to various functional groups, these hydroxy nitriles are very useful building blocks for various natural compounds.

No hydrolysis of any racemic esters 5 by lipases was enantioselective, while the lipase-catalyzed monoacetylation of diols 6 proceeded with complete enantioselection. These observations are helpful in considering the strategy of how to use the lipase in preparing optically active compounds. In the former reaction, the enantioselectivity depends on the ease of discriminating two enantiomers of **5a** by the enzyme (Figure 3, upper). On the other hand, the enzyme reacts with diol **6a** at an easily accessible site and this fixes the enantioselectivity (Figure 3, lower). Therefore, path A is an enzyme-catalyzed enantioselective reaction toward a racemic substrate and path B is a face-selective one toward a prochiral substrate. It seems reasonable that the latter reaction is preferable if the substrate possesses a chiral carbon at a position apart from the reaction site. Enantioselective hydrolysis of broadly varied types of prochiral diacetates of 1,3-diols was demonstrated.[6,10] In the enzymatic hydrolysis of racemic esters, good enantioselection is limited for a specific substrate[11] when a chiral carbon is at a position which is separated from the hydrolysis point of the substrate. Therefore, it seems that reaction of a prochiral substrate is preferable to enantioselective hydrolysis of a racemic ester for the purpose of preparing a compound like 1 optically pure.[12]

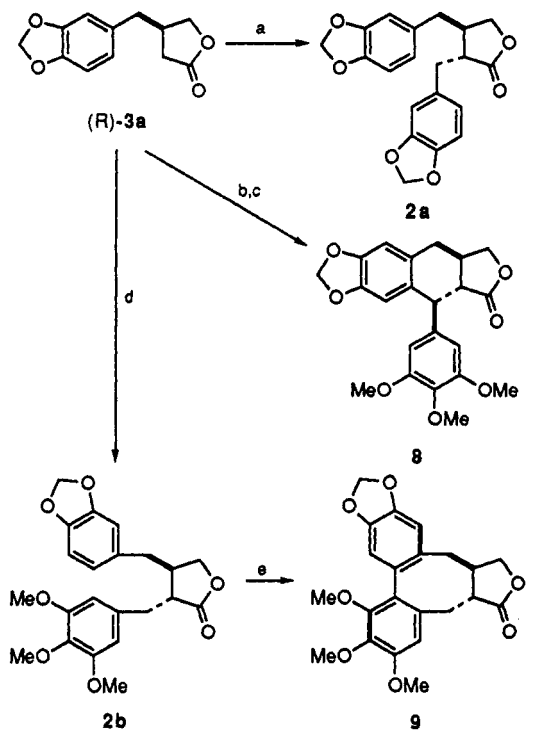
Enantioselective Total Synthesis of Antitumor Lignans. Optically pure lactone (*R*)-**3a** was conveniently synthesized from the nitrile (*R*)-**1a**. This hydroxy nitrile was treated with 2 M NaOH aqueous solution under reflux conditions for 2 h followed by acidification with 2 M HCl to afford optically pure lactone (*R*)-**3a**[1c] in 93% yield. An alkaline treatment was essential for the successful conversion of **1a** to lactone **3a** by the hydrolysis of the cyano group of **1a**, because partial racemization occured when **1a** was subjected to hydrolysis under strongly acidic

(10) (a) Guanti, G.; Banfi, L.; Narisano, E. *J. Org. Chem.* **1992**, *52*, 1540. (b) Wong, Y- F.; Wong, C-H. *J. Org. Chem.* **1988**, *53*, 3129. (c) Kerscher, V.; Kreiser, W. *Tetrahedron Lett.* **1987**, *28*, 531. (d) Ramos Tombo, G. M.; Schär, H. -P.; Busquets, X. F.; Ghisalba, O. *Ibid.* **1986**, *27*, 5707. Some examples of successful enantioslective hydrolysis of prochiral diacetate are also found in refs, see. (e) Smith, G. B.; Bhupathy, M.; Dezeny, G. C.; Douglas, A. W.; Lander, R. J. *J. Org. Chem.* **1992**, *57*, 4544. (f) Estermann, H.; Prasad, K.; Shapiro, M. J.; Bolsterli, J. J.; Walkinshaw. *Tetrahedron Lett.* **1990**, *31*, 445. (g) Nakada, M.; Kobayashi, S.; Ohno, M. *Ibid.* **1988**, *29*, 3951. (h) Roy, R.; Rey, A. W. *Ibid.* **1987**, *28*, 4935. (i) Hemmerle, H.; Gais, H.-J. *Ibid.* **1987**, *28*, 3471.

(11) For examples, see. (a) Rocco, V. P.; Danishefsky, S. J.; Schulte, G. K. *Tetrahedron Lett.* **1991**, *32*, 6671. (b) Wallace, J. S.; Reda, K. B.; Williams, M. E.; Morrow C. J. *J. Org. Chem.* **1990**, *55*, 3544, (c) Nakamura, K.; Ishihara, K.; Ohno, A.; Uemura, M.; Nishimura, H.; Hayashi, Y. *Tetrahedron Lett.* **1990**, *31*, 445.

(12) We are grateful to Professor Kaoru Nakamura of Kyoto University for helpful discussions about this idea.

Scheme II[a]



[a] (a) LDA, THF, −78 °C 2 h, then piperonyl bromide, THF–HMPA = 60:1, −50 °C to −20 °C 3 h, yield = 81%. (b) LDA, THF, −78 °C, 2 h, then 3,4,5-trimethoxybenzaldehyde, 1 h, yield = 85%. (c) TFA, CH_2Cl_2, rt, 1 h, yield = 85%. (d) LDA, THF, −50 °C 1 h, then 3,4,5-trimethoxybenzyl bromide, 3 h, yield = 81%. (e) $Fe(ClO_4)_3 \cdot nH_2O$, TFA–CH_2Cl_2 = 1:10, rt, 1 h, then benzene reflux 24 h, yield = 67%.

conditions. Thus, we succeeded in efficiently synthesizing the key intermediate (*R*)-**3a** for various chiral lignans. To the best of our knowledge, this is one of the best means found to date of synthesizing optically pure lactone (*R*)-**3a**.[13]

Enantioselective total synthesis of (−)-hinokinin (**2a**), (−)-isodeoxypodophyllotoxin (**8**), and (+)-isostegane (**9**) was accomplished from lactone (*R*)-**3a** as described in Scheme II. Treatment of (*R*)-**3a** with lithium diisopropylamide (LDA) and then piperonyl bromide in a mixed solvent of THF–HMPA (60:1) gave **2a** in 81% yield. This reaction proceeded with complete stereoselectivity and the desired *trans*-isomer was obtained as the sole product. Isodeoxypodophyllotoxin (**8**) was also derived from the same lithium enolate of (*R*)-**3a** by a two-step process involving reaction with 3,4,5-trimethoxybenzaldehyde at −78 °C and subsequent treatment with trifluoroacetic acid (TFA) at rt for 1 h to finish cyclization cleanly with 85% yield. Synthesis of (+)-isostegan was successfully accomplished from (*R*)-**3a** *via* an intramolecular oxidative coupling reaction of the two aromatic rings using iron(III) perchlorate ($Fe(ClO_4)_3$) as an oxidant according to Wakamatsu et al.[14] Thus, (*R*)-**3a** was converted to the 2,3-disubstituted-4-butanolide **2b**[1m] in 81% yield with complete stereoselection. The lactone **2b** was then oxidized by $Fe(ClO_4)_3$ in a TFA–CH_2Cl_2 mixed solution realizing intramolecular oxidative coupling reaction to give biphenylyl lactone. Although the coupling reaction proceeded with excellent regioselectivity, the resulting biphenyl lactone was found by ^1H NMR analysis to be a 6:1 mixture of the two diastereoisomers of the desired natural (+)-isostegane (**9**) and undesired (−)-stegane.[1n] Fortunately, undesired (−)-stegane was isomerized completely to the desired **9** by heating under reflux conditions in benzene for 24 h. Thus, optically pure **9** was obtained after recrystallization from methanol in 67% yield from **2b**. We have succeeded in the efficient total synthesis of three types of antitumor lignans from optically pure 4-hydroxyalkanenitrile **1a** that was obtained *via* an enzymatic reaction. Our present synthesis is so simple that we expect it to become one of the most promising methods for synthesizing antitumor lignans.

In conclusion, the present reaction offers one of the most simple and straightforward methods of synthesizing optically pure lignans. This enzymatic reaction is a facile means for enantioselective preparation of broadly varied types of 4-hydroxyalkanenitriles **1**. Since the starting diols **6** are readily prepared from diethyl malonate, the present procedure will significantly extend the scope of preparation of 4-hydroxyalkanenitriles and allow their broad synthetic application.

(13) The present method provided (*R*)-**3a** in six steps with 57% overall yield from cheap piperonylchloride. The earlier record is 35% and the procedure involves resolution of racemic methyl 2-piperonylhemisuccinate by (−)-ephedrine.[1p] Overall yields of other methods[1c,j,o] are not more than 25% from commercially available starting materials.

(14) Tanaka, M.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4161, and refs cited therin.

Experimental Section

General Procedures. Wako gel C-300 and Wako gel B5F were used for flash column chromatography and thin-layer chromatography (TLC), respectively. Melting points are uncorrected.

2-[[3,4-(Methylenedioxy)phenyl]methyl]propane-1,3-diol (6a). To a solution of sodium hydride (60% in mineral oil; 3.45 g; 86 mmol) in dimethylformamide (DMF; 16 mL) was added a THF (60 mL) solution of diethyl malonate (17.52 g, 109 mmol) at −10 °C and the mixture was stirred for 30 min at 0 °C. To the mixture was added a THF (12 mL) solution of piperonyl chloride (12.44 g, 72 mmol) at −10 °C over 7 h followed by stirring at rt for 12 h. The mixture was acidified by 2 M HCl and extracted with ether to give an oily product (28 g). Diethyl α-piperonylmalonate (15.33 g, 52 mmol) was obtained after distillation under reduced pressure (175 °C at 4 mmHg). To a THF (130 mL) solution of $LiAlH_4$ (3.95 g, 102 mmol) was added a THF (30 mL) solution of the malonate (15.33 g, 52 mmol) at 0 °C over 30 min, and then the mixture was stirred for 4 h at rt. The reaction was quenched by addition of methanol (4.1 mL), 15% NaOH aqueous solution (4.0 mL), water (16.4 mL), and 2 M HCl at 0 °C and was extracted by ether. Diol **6a** (10.9 g, 52 mmol) was obtained by recrystallization from $CHCl_3$ as white needles in quantitative yield (overall yield from piperonyl chloride is 72%). mp 97 °C; Rf 0.1, hexane/ethyl acetate (1:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 1.9–2.1 (1H, m), 2.41 (2H, brs, OH), 2.54 (2H, d, J = 7.6 Hz), 3.65 (2H, dd, J_1 = 3.9 Hz, J_2 = 10.6 Hz), 3.79 (2H, dd, J_1 = 3.9 Hz, J_2 = 10.7 Hz), 5.92 (2H, s), 6.62 (1H, d, J = 8.3 Hz), 6.68 (1H, s), 6.73 (1H, d, J = 7.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 34.0, 44.0, 65.4, 100.8, 108.16, 109.3, 121.8, 133.6, 145.9, 147.6 ppm; IR (neat) 3300, 2950, 2870, 1500, 1370, 1250, 1040, 930, 800, 740 cm-1. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.54; H, 6.72.

Using the same procedure, diols **6b**,[6] **6c**, **6d**, **6e**, and **6f**[6] were prepared.

2-Benzyl-1,3-propanediol (6b):[6] bp100 °C (2 mmHg) (Kugelrohr); R_f 0.1, hexane/ethyl acetate (1:1); ^1H NMR (100 MHz, δ, $CDCl_3$) 1.8–2.0 (1H, m), 2.5 (2H, d, J = 6.5 Hz), 3.4–3.7 (4H, brs), 4.1 (2H, brs, OH), 7.3 (5H, brs); IR (neat) 3350, 3050, 1460, 1040, 790, 700 cm^{-1}.

2-[(3,4-Dimethoxyphenyl)methyl]propane-1,3-diol (6c): bp 80 °C (7 mmHg) (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$) 2.06 (1H, m), 2.34 (2H, brs, OH), 2.56 (2H, d, J = 7.7 Hz), 3.61–3.81 (4H, m), 3.84 (6H, s), 6.69–6.81 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 33.9, 44.0, 55.8, 55.9, 65.6, 111.3, 112.2, 120.9, 132.4, 147.4, and 148.9; IR (neat) 3400, 2900, 1580, 1450, 1030, 760, 730 cm^{-1}.

2-[(3,4,5-Trimethoxyphenyl)methyl]propane-1,3-diol (6d): mp 58 °C; ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.0–2.1 (1H, m), 2.55 (2H, d, J = 7.3 Hz), 2.6 (2H, brs, OH), 3.61–3.69 (2H, m), 3.80 (3H, s), 3.82 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 34.6, 43.8, 56.0, 60.8, 65.4, 105.8, 135.7, 136.2, 153.0 ppm; IR (neat) 3450, 2900, 1590, 1330, 800, 780 cm^{-1}.

2-[(4-Phenylphenyl)methyl]propane-1,3-diol (6e): mp 87 °C; ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.97(2H, brs, OH), 2.06–2.20 (1H, m), 2.70 (2H, d, J = 7.6 Hz), 3.73 (2H, dd, J_1 = 6.7 Hz, J_2 = 10.6 Hz), 3.88 (2H, dd, J_1 = 4.0 Hz, J_2 = 10.6 Hz), 7.26–7.62 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 33.9, 43.9, 127.0, 127.1, 127.2, 128.7, 129.4, 139.0, 139.1, 140.9 ppm; IR (neat) 3300, 2900, 1480, 1040, 840, 760 cm^{-1}.

2-(1-Naphthylmethyl)propane-1,3-diol (6f):[6] mp 65 °C; R_f 0.1, hexane/ethyl acetate (1:1); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.1–2.3 (1H, m), 2.63 (2H, brs, OH), 3.1 (2H, d, J = 7.4 Hz), 3.75 (2H, dd, J_1 = 10.7 Hz, J_2 = 6.5 Hz), 3.85 (2H, dd, J_1 = 10.7 Hz, J_2 = 4.0 Hz), 7.3–8.1 (7H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 31.2, 42.9, 65.5, 123.8, 125.3, 125.5, 125.9, 127.0, 127.2, 128.8, 131.9, 134.0, 136.0 ppm; IR (neat) 3300, 2900, 1590, 1450, 1350, 1100, 980, 790 cm^{-1}.

Lipase-Catalyzed Acylation of Diol 6. (*R*)-3-Hydroxy-2-[[3,4-(methylenedioxy)phenyl]methyl]propyl Acetate (7a). A suspension of **6a** (5.33 g, 25.3 mmol), Lipase PS (2.67 g), vinyl acetate (3.51 mL, 38 mmol), 2,6-di-*tert*-butyl-4-methylphenol (111 mg, 0.50 mmol, antioxidant), and water (0.13 mL) in *i*-Pr_2O (126 mL) was stirred at rt. After being stirred for 5 h, the mixture was filtered through a sintered glass filter with a Celite pad. The filtrate was evaporated and chromatographed on a SiO_2 flash column, hexane/ethyl acetate (7:1), to give **7a** (6.21 g, 24.5 mmol) in 97% yield as a colorless oil: bp 175 °C (6 mmHg) (Kugelrohr); R_f 0.7, hexane/ethyl acetate (1:1); $[\alpha]^{22}_D$ +34.1° (c 0.76, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.9–2.1 (1H, m), 2.0 (3H, s), 2.5 (2H, dd, J_1 = 7.5 Hz, J_2 = 5.4 Hz), 3.5 (2H, ddd, J_1 = 20.1 Hz, J_2 = 12.1 Hz, J_3 = 5.4 Hz), 4.1 (2H, ddd, J_1 = 24.4 Hz, J_2 = 11.2 Hz, J_3 = 6.4 Hz), 5.8 (2H, s), 6.7 (3H, d, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 20.8, 33.9, 42.5, 61.8, 63.8, 100.8, 108.1, 109.3, 121.8, 133.0, 145.9, 147.6, 171.6 ppm; IR (neat) 3450, 2950, 1730 (CO), 1500, 1440, 1370, 1250, 1190, 1100, 1040, 930, 810, 770 cm^{-1}; ^{19}F NMR(188 MHz, $CDCl_3$) of (+)-MTPA ester of **7a**, 90.4 ppm (C_6F_6 as internal reference), >98% ee. Using the same procedure, monoacetates **7b**,[6] **7c**, **7d**, **7e**, and **7f**[6] were prepared.

(*R*)-2-Benzyl-3-hydroxypropyl acetate (7b):[6] 92% yield (6 h at rt); bp 120 °C (2.5 mmHg) (Kugelrohr); R_f 0.7, hexane/ethyl acetate (1:3); $[\alpha]^{23}_D$ +20.6° (c 1.0, $CHCl_3$), lit.[6a] +27.7° (97% ee), +28.6° (>94% ee);[6b] ^{1}H NMR (100 MHz, δ, $CDCl_3$) 2.0 (3H, s), 1.9–2.1 (1H, m), 2.6 (2H, d, J = 9.7 Hz), 3.5–3.6 (2H, m), 3.9 (1H, brs, OH), 4.0–4.1 (2H, m), 7.0–7.2 (5H, m); IR (neat) 3450, 2950, 1720 (CO), 1500, 1370, 1040, 750, 710 cm^{-1}; ^{19}F NMR(188 MHz, $CDCl_3$, C_6F_6) of (+)-MTPA ester of **7b**, 90.6 ppm, >98% ee.

(*R*)-2-[(3,4-Dimethoxyphenyl)methyl]-3-hydroxypropyl acetate (7c): 97% yield (2.5 h); bp 175 °C (9 mmHg) (Kugelrohr); R_f 0.2, hexane/ethyl acetate (1:1); $[\alpha]^{15}_D$ +23.8° (c 1.06, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.9 (1H, brs, OH), 2.09 (3H, s), 2.30 (2H, dd, J_1 = 12.2 Hz, J_2 = 7.5 Hz), 3.51 (1H, dd, J_1 = 11.2 Hz, J_2 = 6.0 Hz), 3.61 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.7 Hz), 3.85 (3H, s), 3.86 (3H, s), 4.08 (1H, dd, J_1 = 11.3 Hz, J_2 = 6.5 Hz), 4.19 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.6 Hz), 6.7–6.9 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 20.9, 33.9, 42.5, 55.8, 55.90, 62.1, 64.0, 111.3, 112.2, 121.0, 131.8, 147.5, 148.8, 171.3 ppm; IR (neat) 3450, 2920, 1720(CO), 1580, 1240, 1140, 760, 730 cm^{-1}; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) of (+)-MTPA ester of **7c**, 90.5 ppm, >98% ee.

(*R*)-3-Hydroxy-2-[(3,4,5-trimethoxyphenyl)methyl]propyl acetate(7d): 83% yield (5 h); bp 190 °C (3 mmHg) (Kugelrohr); R_f 0.2, hexane/ethyl acetate (1:1); $[\alpha]^{19}_D$ +22.5° (c 0.875, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.08 (3H, s), 2.15 (2H, m), 2.5–2.7 (2H, m), 4.52 (1H, dd, J_1 = 11.3 Hz, J_2 = 5.9 Hz), 3.61 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.8 Hz), 4.09 (1H, dd, J_1 = 11.3 Hz, J_2 = 6.4 Hz), 4.19 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.7 Hz), 6.39 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 20.9, 34.7, 42.4, 56.0, 60.8, 62.0, 64.0, 105.9, 135.1, 153.1, 171.6 ppm; IR (neat) 3450, 2950, 1720 (CO), 1590, 1460, 1120, 820, 780 cm^{-1}; ^{19}F NMR(188 MHz, $CDCl_3$, C_6F_6) of **7d**, 90.3 ppm/90.4 ppm (95:5), 90% ee.

(*R*)-3-Hydroxy-2-(4-phenylbenzyl)propyl acetate (7e): 100% yield (2 h); mp 51 °C; R_f 0.4, hexane/ethyl acetate (1:1); $[\alpha]^{17}_D$ +34.0° (c 0.87, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.15 (3H, s), 2.2–2.3 (1H, m), 2.76 (2H, dd, J_1 = 7.5 Hz, J_2 = 4.8 Hz), 3.59 (1H, dd, J_1 = 12.5 Hz, J_2 = 5.7 Hz), 3.69 (1H, dd, J_1 = 10.7 Hz, J_2 = 4.3 Hz), 4.17 (1H, dd, J_1 = 11.2 Hz, J_2 = 6.4 Hz), 4.28 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.7 Hz), 7.3–7.66 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 20.9, 33.9, 42.4, 62.0, 64.0, 126.9, 127.1, 127.2, 128.7, 129.4, 138.4, 139.2, 140.8, 171.7 ppm; IR (neat) 3500, 2950, 1710 (CO) 1440, 1040, 960, 760 cm^{-1}; ^{19}F NMR(188 MHz, $CDCl_3$, C_6F_6) of **7e**, 90.5 ppm, >98% ee.

(*R*)-3-Hydroxy-2-(1-naphthylmethyl)propyl acetate (7f):[6] 97% yield (9 h); bp 160 °C (5 mmHg) (Kugelrohr); R_f 0.42, hexane/ethyl acetate (1:1); $[\alpha]^{17}_D$ +40.8° (c 0.78, $CHCl_3$), lit.[6b] +35.7° (86% ee); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.1 (3H,s), 2.2 (1H, brs, OH), 2.3 (1H, m), 3.06 (1H, dd, J_1 = 13.7 Hz, J_2 = 7.3 Hz), 3.18 (1H, dd, J_1 = 13.8 Hz, J_2 = 7.2 Hz), 3.59 (1H, dd, J_1 = 11.7 Hz, J_2 = 6.3 Hz), 3.67 (1H, dd, J_1 = 11.6 Hz, J_2 = 4.7 Hz), 4.16 (1H, dd, J_1 = 11.2 Hz, J_2 = 6.0 Hz), 4.24 (1H, dd, J_1 = 11.4 Hz, J_2 = 5.4 Hz), 7.5–8.2 (7H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 20.9, 31.3, 41.5, 62.2, 64.2, 123.7, 125.4, 125.6, 126.0, 127.2, 127.4, 128.9, 131.9, 134.0, 135.4 ppm; IR (neat) 3450, 2950, 1730 (CO), 1030, 780 cm^{-1}; ^{19}F NMR(188 MHz, $CDCl_3$, C_6F_6) of **7f**, 90.6 ppm, >98% ee.

(*R*)-4-Hydroxy-3-[[3,4-(methylenedioxy)phenyl]methyl]butanenitrile (1a). To a CH_2Cl_2 (40 mL) solution of **7a** (6.20 g, 25 mmol) and pyridine (12 mL) was added a CH_2Cl_2 (5 mL) solution of *p*-TsCl (7.03 g, 37 mmol) at 0 °C under argon. The reaction mixture was stirred for 21 h at rt, quenched by addition of crushed ice, and extracted with CH_2Cl_2. The combined organic layers were dried, evaporated, and chromatographed on a SiO_2 flash column, hexane/ethyl acetate (7:1), to give *p*-toluenesulfonate **4a** (9.61 g, 24 mmol) in 96% yield as a colorless oil. To a 17.0-mL DMSO solution of KCN (1.78 g, 26 mmol) was added dropwise a DMSO (30 mL) solution of **4a** (9.61 g, 24 mmol) at 90 °C, and then the mixture was stirred at the same temperature for 24 h. After being cooled to rt, the reaction mixture was extracted with a mixed solvent (ether/ethyl acetate (1:1)). The organic layer was dried, evaporated, and chromatographed on a SiO_2 flash column, (hexane/ethyl acetate (5:1 to 2:1), giving (*R*)-**5a** (5.43 g, 21 mmol) in 88% yield: $[\alpha]^{22}_D$ −8.02° (c 2.25, $CHCl_3$). (*R*)-**5a** (5.43 g, 21 mmol) was treated with LiOH·H_2O (961 mg, 22.9 mmol) in 80 mL of THF–H_2O (3:1) at rt for 17 h, extracted with ether, evaporated, and chromatographed on a SiO_2 flash column giving **1a** (4.39 g, 21 mmol) as a coloress oil in quantitative yield: bp 160 °C (3 mmHg) (Kugelrohr); R_f 0.3, hexane/ethyl acetate (1:1); $[\alpha]^{25}_D$ −26.4° (c 1.04, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.0 (1H, brs, OH), 2.1–2.2 (1H, m), 2.42 (2H, t, J = 6.1 Hz), 2.58 (1H, dd, J_1 = 13.9 Hz, J_2 = 8.0 Hz), 2.72 (1H, dd, J_1 = 13.9 Hz, J_2 = 6.9 Hz), 3.59 (1H, dd, J_1 = 10.5 Hz, J_2 = 7.1 Hz), 3.73 (1H, dd, J_1 = 10.7 Hz, J_2 = 4.5 Hz), 5.93 (2H, s), 6.6–6.8 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 18.4, 36.0, 39.8, 63.2, 100.9, 108.4, 109.1, 118.6, 121.9, 131.9, 146.2, 147.8 ppm; IR (neat) 3450, 2930, 2270, 1620, 1500, 1440, 1250, 1200, 1040, 940, 870, 820, 780 cm^{-1}; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) of (+)-MTPA ester of **1a**, 91.0 ppm, >98% ee. Anal. Calcd for $C_{12}H_{13}NO_3$: C65.74; H, 5.98; N, 6.39. Found: C, 66.24; H, 6.17; N, 7.08.

Using the same procedure, hydroxy nitriles **1b–f**, were synthesized from the corresponding monoacetates **7** in the yields listed on Table 1.

(*R*)-3-Benzyl-4-hydroxybutanenitrile (1b): bp 130 °C (4 mmHg) (Kugelrohr); R_f 0.5, hexane/ethyl acetae (1:1); $[\alpha]^{17}_D$ −40.3° (c 0.958, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.70–1.90 (1H, brs, OH), 2.10–2.30 (1H, m), 2.37 (1H, dd, J_1 = 16.82 Hz, J_2 = 6.46 Hz), 2.49 (1H, dd, J_1 = 16.88 Hz, J_2 = 5.92 Hz), 2.67 (1H, dd, J_1 = 13.78 Hz, J_2 = 7.98 Hz), 2.81 (1H, dd, J_1 = 13.76 Hz, J_2 = 6.92 Hz), 3.64 (1H, dd, J_1 = 10.75 Hz, J_2 = 6.84 Hz), 3.75 (1H, dd, J_1 = 10.77 Hz, J_2 = 4.75 Hz), 7.17–7.36 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 18.41, 36.31, 39.63, 63.30, 118.58, 126.63, 128.66, 128.92, 138.23 ppm; IR (neat); 3400, 3050, 2920, 2250 (CN) 1600, 1420, 950 740 cm^{-1}; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) of (+)-MTPA ester of **1b**, 90.3 ppm, >98% ee. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.65; H, 7.52; N, 7.92.

(*R*)-3-[(3,4-Dimethoxyphenyl)methyl]-4-hydroxybutanenitrile (1c): bp 190 °C (3 mmHg) (Kugelrohr); R_f 0.22, hexane/ethyl acetate (1:1); $[\alpha]^{16}_D$ −43.8° (c 0.73, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.8(1H, brs, OH), 2.1–2.2 (1H, m), 2.35 (1H, dd, J_1 = 7.6 Hz, J_2 = 5.8 Hz), 2.53 (1H, dd, J_1 = 13.9 Hz, J_2 = 8.1 Hz),

2.69 (1H, dd, J_1 = 13.8 Hz, J_2 = 6.9 Hz), 3.54 (1H, dd, J_1 = 10.6 Hz, J_2 = 6.8 Hz), 3.67 (1H, dd, J_1 = 10.7 Hz, J_2 = 4.8 Hz), 3.78 (3H, s), 3.79 (3H, s), 6.6–6.8 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 18.4, 35.9, 39.8, 63.4, 55.9, 111.4, 112.0, 118.6, 121.0, 130.7, 147.8, 149.0 ppm; IR (neat); 3500, 2950, 2250 (CN) 1590, 1450, 940, 760 cm^{-1}; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) of (+)-MTPA ester of **1c**, 90.5 ppm, >98% ee. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.37; H, 7.28; N, 5.95. Found: C, 66.58; H, 7.11; N, 6.08.

(*R*)-3-[(3,4,5-Trimethoxyphenyl)methyl]-4-hydroxybutanenitrile (1d): mp 44 °C; R_f 0.2, hexane/ethyl acetae (1:1); $[\alpha]^{16}_D$ −43.3° (*c* 1.04, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.98 (1H, brs, OH), 2.1–2.2 (1H, m), 2.43 (1H, dd, J_1 = 8.7 Hz, J_2 = 5.8 Hz), 2.58 (1H, dd, J_1 = 13.8 Hz, J_2 = 8.2 Hz), 2.75 (1H, dd, J_1 = 13.8 Hz, J_2 = 8.2 Hz), 3.61 (1H, dd, J_1 = 10.6 Hz, J_2 = 6.9 Hz), 3.71 (1H, dd, J_1 = 10.7 Hz, J_2 = 4.7 Hz), 3.81 (3H, s), 3.83 (6H, s), 6.39 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 18.5, 36.7, 39.7, 56.1, 60.8, 63.4, 105.8, 118.5, 134.0, and 153.3 ppm; IR (neat) 3450, 2900, 2250 (CN) 1580, 1450, 1000, 780 cm^{-1}; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) of (+)-MTPA ester of **1d**, 90.5 ppm, >98% ee. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.99; H, 7.20; N, 5.40

(*R*)-3-[(4-Phenylbenzyl)-4-hydroxybutanenitrile (1e): mp 74 °C; R_f 0.45, hexane/ethyl acetae (1:1); $[\alpha]^{19}_D$ −46.4° (*c* 0.83, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.73 (1H, brs, OH), 2.2–2.3 (1H, m), 2.43–2.6 (2H, m), 2.73 (1H, dd, J_1 = 13.9 Hz, J_2 = 7.9 Hz), 2.86 (1H, dd, J_1 = 13.8 Hz, J_2 = 6.9 Hz), 2.66 (1H, dd, J_1 = 10.5 Hz, J_2 = 7.0 Hz), 3.79 (1H, dd, J_1 = 10.6 Hz, J_2 = 4.6 Hz) 7.3–7.6 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 18.6, 36.0, 39.7, 63.5, 118.5, 127.0, 127.3, 127.4, 128.8, 129.4, 137.3, 139.7, 140.7 ppm; IR (neat) 3450, 2900, 2250 (CN) 1600, 1480, 1030, 760 cm^{-1}; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) of (+)-MTPA ester of **1e**, 90.5 ppm, >98% ee. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.18; H, 6.88; N, 5.70

(R)-3-(1-Naphthylmethyl)-4-hydroxybutanenitrile (1f): bp 170 °C (4.5 mmHg) (Kugelrohr); R_f 0.52, hexane/ethyl acetate (1:1); $[\alpha]^{21}_D$ −85.4° (*c* 0.64, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.90 (1H, brs, OH), 2.4–2.5 (3H, m), 3.09 (1H, dd, J_1 = 14.0 Hz, J_2 = 7.4 Hz), 3.32 (1H, dd, J_1 = 13.8 Hz, J_2 = 6.3 Hz), 3.69 (1H, dd, J_1 = 10.7 Hz, J_2 = 5.9 Hz), 3.79 (1H, dd, J_1 = 10.6 Hz, J_2 = 4.2 Hz), 7.3–8.0 (7H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 18.9, 35.6, 38.6, 63.6, 118.6, 123.4, 125.4, 125.8, 126.3, 127.4, 127.6, 129.0, 131.7, 134.0, 134.4 ppm; IR (neat) 3450, 2900, 2250 (CN) 1590, 1460, 1080, 790 cm^{-1}; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) of (+)-MTPA ester of **1f**, 90.5 ppm, >98% ee. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.00; H, 6.80; N, 6.55.

(*S*)-2-[[3,4-(Methylenedioxy)phenyl]methyl]-3-[(*p*-tolylsulfonyl)oxy]propylacetate (4a): R_f 0.6, hexane/ethyl acetate (1:1); $[\alpha]^{25}_D$ +7.10° (*c* 1.38, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.9 (3H, s), 2.1–2.3 (2H, m), 2.4 (3H, s), 2.5 (2H, d, *J* = 7.3 Hz), 3.8–4.0 (4H, m), 5.9 (2H, s), 6.5 (2H, d, *J* = 9.0 Hz), 6.6 (1H, d, *J* = 7.8 Hz), 7.3 (2H, d, *J* = 8.3 Hz), 7.7 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 20.6, 21.6, 33.5, 39.6, 62.9, 68.8, 100.9, 108.2, 109.1, 121.9, 127.9, 129.8, 131.5, 132.6, 144.9, 146.1, 147.7, 170.6 ppm; IR (neat) 2950, 2900, 1740 (CO), 1600, 1500, 1360, 1250, 1040, 970, 940, 670 cm^{-1}.

(*S*)-2-Benzyl-3-[(*p*-tolylsulfonyl)oxy]propyl acetate (4b): mp 38 °C; R_f 0.3 hexane/ethyl acetate (4:1); $[\alpha]^{20}_D$ +7.38° (c1.03, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.99 (3H, s), 2.2–2.4 (1H, m), 2.49 (3H, s), 2.67 (2H, d, *J* = 6.8 Hz), 3.9–4.2 (4H, m), 7.0–7.1 (2H, m), 7.2–7.3 (3H, m), 7.37 (2H, d, *J* = 8.0 Hz), 7.80 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 20.6, 21.6, 33.8, 39.4, 62.9, 68.8, 126.5, 127.9, 128.5, 128.8, 129.8, 132.6, 137.9, 144.8, 170.5 ppm; IR (neat) 2950, 2900, 1730 (CO), 1600, 1500, 1450, 1350, 1240, 1170, 1100, 1040, 970, 810, 740, 700 cm^{-1}.

(*S*)-2-[(3,4-Dimethoxyphenyl)methyl]-3-[(*p*-tolylsulfonyl)oxy]propyl acetate (4c): 190 °C dec (10 mmHg) (Kugelrohr); R_f 0.48 hexane/ethyl acetate (1:1); $[\alpha]^{20}_D$ +11.1° (*c* 0.715, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.95 (3H, s), 2.2–2.3 (1H, m), 2.45 (3H, s), 2.58–2.62 (2H, m), 3.84 (6H, s), 3.93–4.08 (4H, m), 6.57–6.76 (3H, m), 7.30 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 20.7, 21.6, 33.4, 39.6, 55.9, 63.1, 68.9, 108.1, 111.3, 112.1, 121.0, 127.9, 129.8, 130.4, 144.9, 149.0, 170.6 ppm; IR (neat) 2950, 1730 (CO), 1590, 1360, 030, 950, 820 cm^{-1}.

(*S*)-3-[(*p*-Tolylsulfonyloxy]-2-[(3,4,5-trimethoxyphenyl-)methyl]propyl acetate (4d): mp 56 °C (recrystallized from hexane); R_f 0.4 hexane/ethyl acetate (1:1); $[\alpha]^{18}_D$ +12.8° (*c* 1.15, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.95 (3H, s), 2.2–2.3 (1H, m), 2.44 (3H, s), 2.60 (2H, dd, J_1 = 7.6 Hz, J_2 = 2.3 Hz), 3.81 (9H, s), 3.9–4.0 (4H, m), 6.33 (2H, s), 7.33 (2H, d, *J* = 8.1 Hz), 7.76 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 20.6, 21.6, 34.2, 39.5, 56.1, 60.8, 63.1, 68.8, 106.0, 127.9, 129.8, 133.6, 144.9, 153.3, 170.5 ppm; IR (neat) 2950, 1730 (CO), 1580, 1460, 1030, 950, 810 cm^{-1}.

(*S*)-2-[(4-Phenylphenyl)methyl]-3-[(*p*-tolylsulfonyl)-oxy]propyl acetate (4e): mp 110 °C; R_f 0.5 hexane/ethyl acetate (1:1); $[\alpha]^{19}_D$ +10.2° (*c* 1.06, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.98 (3H, s), 2.2–2.4 (1H, m), 2.44 (3H, s), 2.69 (2H, d, *J* = 7.3 Hz), 3.9–4.1 (4H, m), 7.1–7.8 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 20.7, 21.6, 33.5, 39.5, 63.1, 68.9, 126.9, 127.2, 127.3, 128.0, 128.7, 129.3, 129.8, 132.7, 137.0, 139.5, 140.7, 144.9, 170.6 ppm; IR (neat) 2950, 1730 (CO), 1050, 820 cm^{-1}.

(*S*)-2-(1-Naphthylmethyl)-3-[(*p*-tolylsulfonyl)oxy]propyl acetate(4f): 210 °C dec (5 mmHg); R_f 0.6 hexane/ethyl acetate (1:1); $[\alpha]^{23}_D$ +5.2° (*c* 1.35, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.99 (3H, s), 2.3–2.5 (1H, m), 2.44 (3H, s), 3.10 (2H, d, *J* = 7.3 Hz), 3.9–4.15 (4H, m), 7.15–7.40 (4H, m), 7.45–7.95 (7H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 20.7, 21.6, 31.0, 38.4, 63.3, 69.1, 123.3, 125.3, 125.7, 126.2, 127.4, 127.5, 127.9, 129.0, 129.8, 131.6, 132.6, 134.0, 144.9, 170.6 ppm; IR (neat) 3050, 2950, 1740 (CO), 1600, 1360, 1040, 960, 800 cm^{-1}.

(*R*)-3-Cyano-[[3,4-(Methylenedioxy)phenyl]methyl]propyl acetate(5a): bp 175 °C (6 mmHg) (Kugelrohr); R_f 0.7 (hexane/ethyl acetate (1:1); $[\alpha]^{26}_D$ −7.88° (*c* 0.80, $CHCl_3$); ^{1}H NMR (100 MHz, δ, CCl_4) 2.0 (3H, s), 2.0–2.1 (1H, m), 2.2–2.4 (2H, m), 2.5–2.8 (2H, m), 3.9–4.1 (2H, m), 5.9 (2H, s), 6.5–6.7 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 19.0, 20.7, 36.2, 37.0, 65.0, 101.0, 108.5, 109.1, 117.8, 122.0, 131.0, 146.5, 147.9, 170.6 ppm; IR (neat) 2870, 2230 (CN), 1730 (CO), 1480, 1030, 800, 770 cm^{-1}.

(*R*)-2-Benzyl-3-cyanopropyl acetate(5b): bp 110 °C (2 mmHg) (Kugelrohr); R_f 0.7, hexane/ethyl acetate(1:1); $[\alpha]^{18}_D$ −6.75° (*c* 0.80, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.01 (3H, s), 2.2–2.4 (1H, m), 2.3–2.4 (2H, m), 2.5–2.8 (2H, m), 3.92 (1H, dd, J_1 = 11. Hz, J_2 = 6.9 Hz) 4.13 (1H, dd, J_1 = 11.5 Hz, J_2 = 4.6 Hz), 7.1–7.3 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 19.0, 20.7, 36.8, 65.1, 117.8, 126.9, 127.9, 128.8, 128.9, 137.4, 170.6 ppm; IR (neat) 2900, 2220 (CN) 1749 (CO), 1040, 700 cm^{-1}.

(*R*)-3-Cyano-2-[(3,4-dimethoxyphenyl)methyl]propyl acetate (5c): bp 180 °C (7 mmHg) (Kugelrohr); R_f 0.4, hexane/ethyl acetate (1:1); $[\alpha]^{16}_D$ −15.2° (*c* 0.69, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.10 (3H, s), 2.3–2.5 (3H, m), 2.65 (1H, dd, J_1 = 13.6 Hz, J_2 = 7.8 Hz), 2.77 (1H, dd, J_1 = 13.8 Hz, J_2 = 6.5 Hz), 3.83 (3H, s), 3.87 (3H, s), 4.0 (1H, dd, J_1 = 11.4 Hz, J_2 = 7.0 Hz), 5.22 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.5 Hz), 6.7–6.8 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 19.0, 20.8, 36.1, 36.9, 55.9, 65.1, 111.4, 112.0, 117.8, 121.0, 129.9, 148.0, 149.1, 170.6 ppm; IR (neat) 2950, 2250 (CN) 1740 (CO), 1370, 1030, 740 cm^{-1}.

(*R*)-3-Cyano-2-[(3,4,5-trimethoxyphenyl)methyl]propyl acetate (5d): bp 180 °C (3 mmHg) (Kugelrohr); R_f 0.4, hexane/ethyl acetate (1:1); $[\alpha]^{16}_D$ −15.5° (*c* 0.84, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.10 (3H, s), 2.3–2.4 (3H, m), 2.64 (1H, dd, J_1 = 12.7 Hz, J_2 = 7.4 Hz), 2.76 (1H, dd, J_1 = 14.5 Hz, J_2 = 5.8 Hz), 3.82 (3H, s), 3.84 (6H, s), 4.0 (1H, dd, J_1 = 9.9 Hz, J_2 = 7.2 Hz), 4.23 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.2 Hz), 6.38 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 19.0, 20.7, 36.8, 36.8, 56.1, 60.8, 65.1, 105.8, 117.8, 133.0, 153.4, 170.6 ppm; IR (neat) 2950, 2230 (CN) 1730 (CO), 1360, 1230, 1040, 780 cm^{-1}.

(*R*)-3-Cyano-2-[(4-phenylphenyl)methyl]propyl acetate(5e): mp 82 °C; R_f 0.5 hexane/ethyl acetate (1:1); $[\alpha]^{19}_D$ −11.0° (*c* 0.76, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.11(3H, s) 2.3–2.4(3H, m) 2.7–2.9(2H, m) 4.04(1H, dd, J_1= 11.5 Hz, J_2 = 6.8 Hz), 4.85 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.2 Hz), 7.2–7.6 (9H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 19.1, 20.8, 36.2, 65.1, 117.8, 127.0, 127.3, 127.5, 128.8, 129.4, 136.4, 139.9, 140.6, 170.6 ppm; IR (neat) 2950, 2230 (CN), 1720 (CO), 1360, 890, 760, 680 cm^{-1}.

(*R*)-3-Cyano-2-(1-naphthylmethyl)propyl acetate(5f): bp 180 °C (5 mmHg) (Kugelrohr); R_f 0.5, hexane/ethyl acetate (1:1); $[\alpha]^{21}_D$ −26.4° (*c* 0.89, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.12 (3H, s), 2.43 (2H, dd, J_1 = 7.6 Hz, J_2 = 5.6 Hz), 2.5–2.7 (1H, m), 3.15 (1H, dd, J_1 = 14.1 Hz, J_2 = 7.9 Hz), 3.31 (1H, dd, J_1 = 14.0 Hz, J_2 = 6.7 Hz), 4.10 (1H, dd, J_1 = 11.4 Hz, J_2 = 6.9 Hz), 4.27 (1H, dd, J_1 = 11.5 Hz, J_2 = 4.6 Hz), 7.3–8.0 (7H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 19.4, 20.8, 33.8, 35.8, 65.3, 117.8, 123.1, 125.4,

125.8, 126.4, 127.5, 127.9, 129.0, 131.5, 133.5, 134.1, 170.6 ppm; IR (neat) 3050, 2950, 2250 (CN). 1740 (CO), 1600, 1040, 800, 740 cm^{-1}. Substrates (±)-**5bb** to (±)-**5be** for the lipase-catalyzed hydrolysis were prepared from corresponding racemic hydroxy nitriles 1.

(±)-2-Benzyl-3-cyanopropyl 2-(methylthio)acetate (5bb): bp 150 °C (4 mmHg) (Kugelrohr); R_f 0.4, hexane/ethyl acetate (3:1); ^1H NMR (100 MHz, δ, CCl_4) 2.2 (3H, s), 2.2–2.4 (1H, m), 2.4 (2H, d, J = 14.3 Hz), 2.7–2.9 (2H, m), 3.2 (2H, s), 4.0–4.3 (2H, m), 7.2–7.5 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 16.38, 19.16, 24.35, 35.55, 66.46, 116.05, 169.42 ppm; IR (neat) 3050, 2950, 2250 (CN), 1740 (CO), 1020, 970, 700 cm^{-1}.

(±)-2-Benzyl-3-cyanopropyl 2-(phenylthio)acetate (5bc): bp 200 °C (3 mmHg) (Kugelrohr); R_f 0.6, hexane/ethyl acetate (3:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 2.2–2.4 (3H, m), 2.7 (2H, dd, J_1 = 4.9 Hz, J_2 = 2.0 Hz), 3.7 (2H, s), 4.0 (1H, dd, J_1 = 11.4 Hz, J_2 = 6.7 Hz), 4.7 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.3 Hz), 7.1–7.4 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 18.8, 363, 36.8, 65.7, 117.7, 126.9, 127.2, 128.8, 128.9, 129.2, 129.8, 134.6, 137.2, 169.3 ppm; IR (neat) 3060, 2920, 2240 (CN), 1730 (CO), 1580, 1000, 740 cm^{-1}.

(±)-2-Benzyl-3-cyanopropyl 2-methoxyacetate (5bd): bp 125 °C (2.5 mmHg) (Kugelrohr); R_f 0.4, hexane/ethyl acetate (3:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 2.3–2.5 (3H, m), 2.7–2.9 (2H, m), 3.5 (3H, s), 4.0–4.4 (4H, m), 7.2–7.4 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 19.1, 36.5, 36.8, 59.4, 65.4, 69.6, 117.7, 127.0, 128.9, 128.9, 137.2, 169.9 ppm; IR (neat) 2900, 2240 (CN), 1750 (CO), 1450, 920, 740, 700 cm^{-1}.

(±)-2-Benzyl-3-cyanopropyl 2-phenoxyacetate (5be): bp 170 °C (2 mmHg) (Kugelrohr); R_f 0.5, hexane/ethyl acetate (3:1); ^1H NMR (200 MHz, δ, CDl_3) 2.2–2.4 (3H, m), 2.7 (2H, t, J = 6.8 Hz), 4.1 (1H, dd, J_1 = 11.4 Hz, J_2 = 6.8 Hz), 4.3 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.4 Hz), 4.7 (2H, s), 6.9–7.4 (10H, m); ^{13}C NMR (50 MHz, CDCl3) 18.8, 26.8, 36.4, 65.0, 65.6, 114.4, 117.6, 121.9, 127.0, 128.8, 128.9, 129.7, 137.2, 157.6, 168.7 ppm; IR (neat) 3050, 3020, 2240 (CN), 1750 (CO), 1490, 1080, 750 cm^{-1}.

(±)-3-Cyano-2-[[3,4-(methylenedioxy)phenyl]methyl]propyl acetate (5a): bp 175 °C (6 mmHg) (Kugelrohr); R_f 0.7, hexane/ethyl acetate (1:1); ^1H NMR (100 MHz, δ, CCl_4) 2.0 (3H, s), 2.0–2.1 (1H, m), 2.2–2.4 (2H, m), 2.5–2.8 (2H, m), 3.9–4.1 (2H, m), 5.9 (2H, s), 6.5–6.7 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 19.0, 20.7, 36.2, 37.0, 65.0, 101.0, 108.5, 109.1, 117.8, 122.0, 131.0, 146.5, 147.9, 170.6 ppm; IR (neat) 2870, 2230 (CN), 1730 (CO), 1480, 1360, 1030, 800, 770 cm^{-1}.

Lipase-Catalyzed Hydrolysis. Ester (±)-**5a** (60 mg, 0.23 mmol) in 0.1 M phosphate buffer (pH 7.2, 2.0 mL) and acetone (0.2 mL) was treated with lipase PS (30 mg) at rt for 3 h stirring. The mixture was extracted with ethyl acetate and separated by silica gel TLC. The optical purity of the produced alcohol **1a** was determind by the ^1H NMR analysis of the corresponding (+)-MTPA ester (13% ee). As described in the text, neither any enzyme nor acyl group was found that hydrolyzed **5** with good enantioselectivity.

(*R*)-3-[[3,4-(Methylenedioxy)phenyl]methyl]-4,5-dihydrofuran-2(3*H*)-one (3a): [1c,j,o] A suspension of (*R*)-**1a** (3.79 g, 17.2 mmol) in 86 mL of 2 M NaOH was heated at reflux for 2 h. After being cooled to rt, the mixture was acidified by 2 M HCl and extracted with ether. SiO_2 flash column chromatography, hexane/ethyl acetate (10:1 to 2:1), gave **3a** (3.52 g, 16.0 mmol) in 93% yield: $[\alpha]^{25}_D$ +5.24° (*c* 1.03, $CHCl_3$), lit.[1c] +5.02° (*R*); bp 150 °C (6 mmHg) (Kugelrohr); R_f 0.6 hexane/ethyl acetate (1:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 2.26 (1H, dd, J_1 = 17.3 Hz, J_2 = 6.7 Hz), 2.59 (1H, dd, J_1 = 17.3 Hz, J_2 = 7.8 Hz), 2.70 (2H, t, J = 5.69 Hz), 2.7–2.9 (1H, m), 4.01 (1H, dd, J_1 = 9.2 Hz, J_2 = 5.8 Hz), 5.94 (2H, s), 6.55–6.76 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 34.1, 37.3, 38.6, 72.5, 101.0, 108.4, 108.8, 121.6, 131.9, 146.4, 147.9, 176.8 ppm; IR (neat) 2930, 1760 (CO), 1600, 1440, 1360, 1020, 770 cm^{-1}.

(−)-Hinokinin (2a): [1b-h] (*R*)-**3a** (127.5 mg, 0.579 mmol) was treated with LDA (0.69 mmol) in THF (4 mL) at −70 °C with stirring for 1 h to afford the corresponding enolate. To this enolate solution was added a THF (2 mL) solution of piperonyl bromide (172 mg, 0.87 mmol) and 0.1 mL of hexamethylphosphoric triamide (HMPA) at −50 °C. After being stirred for 2 h and warmed to −20 °C, the mixture was added to aqueous NH_4Cl and extracted with ethyl acetate. SiO_2 flash column chromatography, hexane/ethyl acetate (50:1 to 1:1), giving **2a** (166.8 mg, 0.47 mmol) in 81% yield: $[\alpha]^{20}_D$ −34.2° (*c* 1.00, $CHCl_3$) lit.[1b,c] −35°. IR and NMR spectra identical to reported spectra.[2b,d,e]

(−)-Isodeoxypodophyllotoxin (8): [1i-k] Prepared from (*R*)-**3a** according to the reference[2i] in 72% yield: mp 250°C; Rf 0.4 hexane/ethyl acetate (1:1); $[\alpha]^{25}_D$ −81.2° (*c* 1.0, $CHCl_3$), after recrystallization from CH_2Cl_2–ether, lit. −84.6°,[1k] −80.3°,[1i] −80.5°;[1j] ^{13}C NMR (50 MHz, $CDCl_3$) 33.0, 40.1, 46.7, 48.7, 56.2, 60.8, 70.9, 101.1, 106.5, 108.4, 110.0, 127.8, 132.3, 136.9, 138.7, 146.4, 146.6, 153.1, 175.3 ppm; IR and ^{1}NMR spectra identical to reported spectra.[1i]

(+)-Isostegane (9): [1d,l,n] (*R*)-**3a** was converted to lithium enolate and then treated with 3,4,5-trimethoxybenzaldehyde (626 mg, 2.4 mmol) at −78 °C and warmed to −50 °C for 2 h with stirring. The reaction was quenched by addition of aqueous NH_4Cl, acidified by 2 M HCl and extracted with ether. The combined organic layers were dried, evaporated, and chromatographed on a SiO_2 flash column to give deoxypodophizone (**2b**) (651mg, 1.62 mmmol) in 81% yield: $[\alpha]^{22}_D$ −22.0° (*c* 1.03, $CHCl_3$), lit.[1l] −21.6°. To a solution of trifluoroacetic acid (1.5 mL), CH_2Cl_2 (3.0 mL), and iron(III) perchlorate (304 mg, 0.6 mmol, monohydrate) was added 12 mL of a CH_2Cl_2 solution of **2c** (100 mg, 0.25 mmol) dropwise at rt over 30 min and then it was stirred for an additional 30 min at the same temperature.[13] The reaction mixture was neutralized by addition of saturated aqueous sodium bicarbonate solution and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to give coupling product (72 mg, $[\alpha]^{24}_D$ +96° (*c* 0.81, $CHCl_3$)) as an oily residue. ^1H NMR analysis of revealed that this product was a mixture of diastereomers because two signals of the methylene proton of the methylenedioxy group was observed at 5.88 and 5.98 ppm (1:6), respectively. The residue was diluted with benzene (7 mL) and heated for 24 h under reflux conditions. After being cooled to rt, the solvent was evaporated, chromatographed on a SiO_2 column, hexane/ethyl acetate (5:1), and finally recrystallized from methanol giving **9** (66 mg, 0.168 mmol) as colorless needles in 67% yield: mp 202 °C; R_f 0.3 after triple development, hexane/ethyl acetate (3:1); $[\alpha]^{19}_D$ +162° (*c* 0.77, $CHCl_3$), lit.[1n] +154°; ^{13}C NMR (50 MHz, $CDCl_3$) 32.3, 34.1, 47.0, 50.0, 56.0, 60.8, 60.9, 70.0, 101.2, 107.5, 108.7, 111.7, 126.4, 128.3, 132.3, 136.0, 140.9, 145.9, 147.6, 151.9, 153.3, 176.5 ppm; IR and ^{1}NMR identical to reported spectra.[1n]

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of compounds **6c,d**, **7a**, **7c–e**, **5a–5be**, and **4a–f** (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.