Highly Enantioselective Synthesis of Both Enantiomers of γ-Substituted Butenolides by Bakers' Yeast Reduction and Lipase-Catalyzed Hydrolysis. Total Synthesis of (3A*S*,6a*S*)-Ethisolide, Whisky Lactone, and (−)-Avenaciolide

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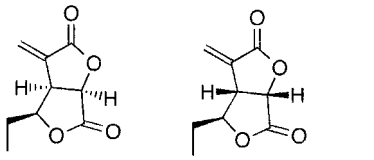
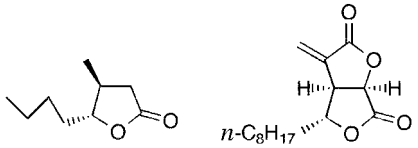
Reduction of 3-chloro-4-oxoalkanoates **5** with bakers' yeast gave (4*S*)-3-chloro-4-hydroxyalkanoates, which were hydrolyzed and dehydrochlorinated to give (γ*S*)-alkylbutenolides with >96% ee. Reduction of **5** with $NaBH_4$ gave *syn*-3-chloro-4-hydroxyalkanoate **6**. Asymmetric hydrolysis of *syn*-4-chloro-3-hydroxyalkanoate (±)-**10** with lipase afforded (3*R*,4*R*)-**6** and (3*S*,4*S*)-**10** with high optical purities. Hydrolysis and dehydrochlorination of (3*R*,4*R*)-**6** gave (γ*R*)-alkylbutenolides with >85% ee. Total syntheses of (3a*S*,6a*S*)-ethisolide, whisky lactone, and (−)-avenaciolide from these butenolides are described.

An optically active butenolide is an important and versatile compound for the synthesis of naturally occurring compounds containing a γ-butyrolactone ring. Many papers on the syntheses of optically active butenolides have been reported. For example, γ-methylbutenolide (β-angelicalactone) has been synthesized via the reduction of sulfur compounds with bakers' yeast[1,2] and also via several steps from D-ribonolactone[3,4] and (+)-L-tartaric acid.[5] Syntheses by the use of microbes and pig liver esterase are also reported.[6] In this paper, we wish to report a convenient and highly enantioselective synthesis of both enantiomers of optically active γ-substituted butenolides by using bakers' yeast reduction and lipase-catalyzed hydrolysis.[7] Furthermore, syntheses of some natural products such as (3a*S*,6a*S*)-ethisolide (**2**) (a diastereoisomer of ethisolide (**1**)),[8] whisky lactone (**3**),[9] and (−)-avenaciolide (**4**)[10] have been established from optically active butenolides obtained by the present reactions.



ethisolide **1** (3*aS*,6*aS*)-ethisolide **2**



whisky lactone **3** (-)-avenaciolide **4**

Although there are many methods for the preparation of chiral building blocks, practical and convenient methods are quite restricted. Among them, the asymmetric reduction with bakers' yeast (*Saccharomyces cerevisiae*) is quite practical and experimentally simple and often provides chiral compounds with high optical purity.[11] For a decade, we have been studying the asymmetric reduction of ketones and olefins with bakers' yeast.[12] Recently,

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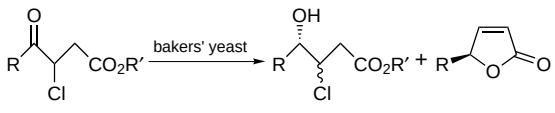
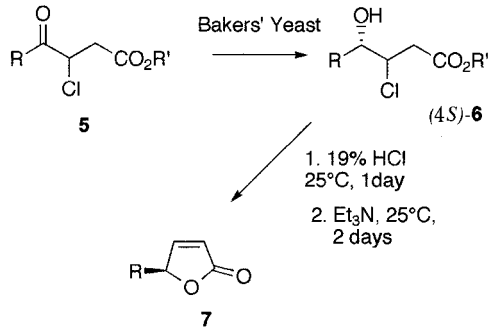
Table 1. Reduction of Chloro Ketone 5 with Bakers' Yeast



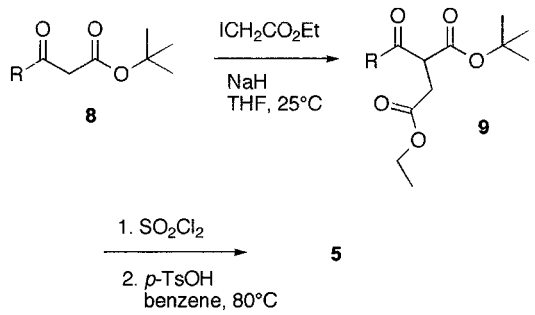
5 (4*S*)-**6** **7**

	5		reaction	(4*S*)-6		7
entry	R	R′	time (day)	yield (%)	$[\alpha]_D$ ($CHCl_3$)	yield (%)
a	CH_3	C_2H_5	2	75	+10.1	0
b	C_2H_5	CH_3	4	41	+11.1	10
c	C_2H_5	C_2H_5	3	41	+10.4	0
			4	53	+8.71	0
d	*n*-C_4H_9	C_2H_5	7	22	+5.78	4
e	*n*-C_8H_{17}	CH_3	15	0		11

we reported asymmetric reduction of α-chlorinated ketones with bakers' yeast.[7a,13] The present paper describes the synthesis of optically active butenolides **7** starting from the reduction of 3-chloro-4-oxoalkanoates **5** with bakers' yeast. Compound **5** was prepared via 3 steps from *tert*-butyl 3-oxoalkanoate (**8**) as shown below. The



reaction of **8** with iodoacetate in the presence of sodium hydride gave diester **9** in 77−99% yields. Chlorination of **9** with sulfuryl chloride and the subsequent decarboxylation by heating the chlorinated product at the reflux temperature of benzene in the presence of *p*-toluenesulfonic acid afforded **5** in 78−99% yields.



Reduction of **5** with industrial bakers' yeast was carried out in tap water at 35 °C for 2−7 days, giving (4*S*)-3-chloro-4-hydroxyalkanoates **6** in 22−75% yields. These results are tabulated in Table 1.

Alkanoates substituted with small alkyl groups were reduced to afford chiral alcohols in good yields. On the other hand, alkanoates (**5d** and **5e**) bearing longer chains such as butyl and octyl groups gave the reduced products

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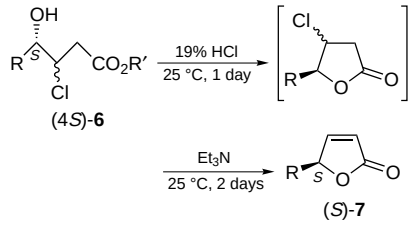
Table 2. Synthesis of (γ*S*)-Butenolides 7



			(*S*-7		
entry	R	R′	yield (two steps, %)	$[\alpha]_D$ ($CHCl_3$)	ee[a] (%)
a	Me	Et	56	+110.6 (*c* 1.23)	99[b]
b	Et	Me	66	+95.3 (*c* 3.61)	>96
c	Et	Et	69	+103 (*c* 2.71)	>96
d	*n*-C_4H_9	Et	73	+92.3 (*c* 3.39)	>96
[**e**	*n*-C_8H_{17}	Me	11	+40.7 (*c* 1.18)	>59][c]

[a] Optical purity was determined by ^1H NMR analysis of CCl_4−$CDCl_3$ (3/1) solution in the presence of $Eu(hfc)_3$, unless otherwise noticed. [b] Determined by GC fitted with chiral column. [c] These are data of the sample obtained in Table 1.

in low yields accompanied with (γ*S*)-alkylbutenolides, which were simultaneously produced via hydrolysis, lactonization, and dehydrochlorination reactions.

Hydrolysis of (4*S*)-**6** with 19% hydrochloric acid at 25 °C for 24 h and the subsequent dehydrochlorination with an excess amount of triethylamine gave optically pure (γ*S*)-alkylbutenolides (**7**) in good yields, as shown in Table 2.

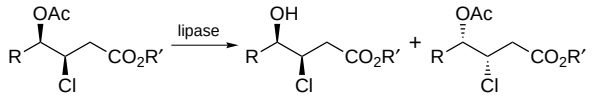
Enantiomeric excess was determined by ^1H NMR analysis of CCl_4−$CDCl_3$ (3/1) solution in the presence of $Eu(hfc)_3$. Irradiation of the signal of the γ-proton of (*S*)-**7d** showed a single doublet due to the α-proton in contrast to the spectrum of (±)-**7d** exhibiting a pair of two doublets at the same irradiation level. The enantiomeric purity of (γ*S*)-octylbutenolide (**7e**) was unsatisfactory.

The low yields on the bakers' yeast reduction of longer alkyl chain molecules such as **5d** and **5e** were improved by using lipase-catalyzed hydrolysis of acetates. The racemic acetates of 3-chloro-4-hydroxyalkanoate (±)-**6**, which is easily obtainable by $NaBH_4$ reduction of ketone **5**, were prepared and treated with lipase "Amano P" in 1/10 M phosphorus buffer solution. The reaction mixture was checked by TLC, and the reaction was stopped when the spots of the starting material **10** and optically active hydroxyl ester (3*R*,4*R*)-**6** became almost equal in their largeness. The products were purified with column chromatography and analyzed by ^1H NMR spectra. These results are tabulated in Table 3. Most of the optical purities were determined in the next step.

Optically active hydroxyester (3*R*,4*R*)-**6** was converted to butenolides (*R*)-**7** by the same method as shown in the preparation of (*S*)-**7**, and these results are shown in Table 4. Optical purities were determined by comparison of $[\alpha]_D$ with those of authentic samples. All of the butenolides were obtained in more than 85% enantiomeric excess.

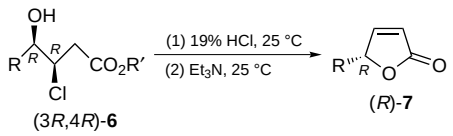
Some of the optically active natural products possessing a γ-lactone ring were prepared by the conjugate addition to the butenolide. Bis-γ-lactone **2**, the diastereomer of ethisolide **1**, was prepared via Michael addition to α,β-unsaturated esters **7**, as shown in Scheme 1. Michael addition of *tert*-butyl α-substituted propionates

Table 3. Asymmetric Hydrolysis of (±)-10 with Lipase



			reaction		(3*R*,4*R*)-**6**		(3*S*,4*S*)-**10**	
entry	R	R′	*T* (°C)	time (h)	yield (%)	$[\alpha]_D$	yield (%)	$[\alpha]_D$
a	CH_3	C_2H_5	25	12	29	+11.9	30	−33.6
b	C_2H_5	CH_3	25	7.5	29	+21.4	43	−18.3
c	C_2H_5	C_2H_5	25	10.5	29	+22.1	22	−23.9
d	*n*-C_4H_9	C_2H_5	25	40	35	+19.5	18	+5.58
e	*n*-C_8H_{17}	CH_3	25	42	26	+10.6	31	+15.7
f	*n*-C_8H_{17}	C_2H_5	25	40	31	+12.3	22	+8.16

Table 4. Synthesis of (γ*R*)-Butenolides 7

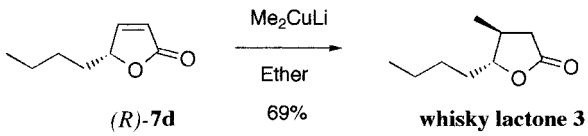


			(*R*)-**7**		
entry	R	R′	yield (%)	$[\alpha]_D$ ($CHCl_3$)	ee (%)
a	CH_3	C_2H_5	45	−100 (*c* 0.13)	>99[b]
b	C_2H_5	CH_3	34	−106.5 (*c* 0.92)	96[b]
c	C_2H_5	C_2H_5	39	−99.6 (*c* 1.35)	86[b]
d	*n*-C_4H_9	C_2H_5	74	−99.0 (*c* 1.38)	98[c]
e	*n*-C_8H_{17}	CH_3	31	−59.0 (*c* 0.80)[a]	87[c]
f	*n*-C_8H_{17}	C_2H_5	58	−64.9 (*c* 2.46)[a]	94[c]

[a] Measured in 1,4-dioxane. [b] Determined by GC fitted with chiral column. [c] Determined by comparison of the optical rotation.

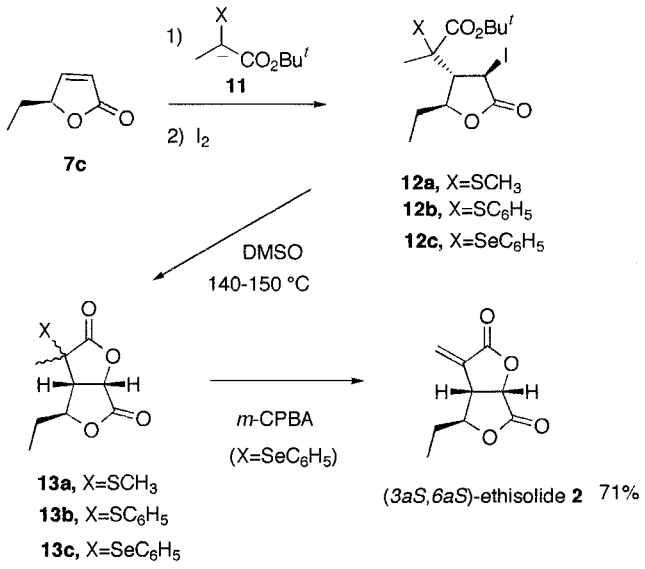
[CH_3CHXCO_2Bu-*t*] (**11a**, X = SCH_3; **11b**, X = SC_6H_5; **11c**, X = SeC_6H_5) to the butenolide **7c** followed by the subsequent addition of iodine proceeded smoothly to give all *trans*-substituted γ-lactones **12** in good yields. Thermal treatment of **12** in DMSO at 140−150 °C gave bis-γ-lactone **13** in 47−91% yields. Oxidation of **13a** and **13b** with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the corresponding sulfoxides in 45 and 91% yields, respectively. Thermal desulfonylation of these sulfoxides, however, resulted in the recovery of the starting materials. On the other hand, oxidation of the phenylseleno lactone **13c** with peracetic acid led to spontaneous deselenation, giving *exo*-methylene lactone **2** in 71% yield.

Michael addition of Me_2CuLi to (*R*)-**7d** stereospecifically afforded the trans-addition product, whisky lactone **3**, in 69% yield, of which physical data were identical with those of the literature.[14]



Furthermore, butenolide (γ*R*)-**7e**, which has been prepared via the lipase-catalyzed kinetic resolution as shown in Tables 3 and 4, was used for the total synthesis of (−)-avenaciolide.[7b] Avenaciolide (**4**) is an antifungal agent first isolated from *Aspergillus avenaceaus*[10] and attracts the attention of organic chemists because of the unique bis-γ-lactone structure. Total synthesis of optically active avenaciolide has been reported by many groups.[15,16] The synthetic method reported by Schlessinger[15b] was modified and applied for the present synthesis. Here, we describe the total synthesis of **4** starting from (*R*)-**7e**, as shown in Scheme 2. Michael addition of lithiated **11c** to (*R*)-**7e** followed by the addition of iodine gave all-trans-substituted tetrahydro-2-furanone **12e** in 89% yield exclusively. Treatment of **12e** in DMSO at 140−150 °C gave γ-bislactone **13e** in 47% yield. Mild oxidation of the selenide **13e** with peracetic acid at 0−25 °C proceeded via the elimination of phenylselenol to give (−)-avenaciolide **4** with 91% ee. This total synthesis consists of completely stereocontrolled reactions that afforded only the desired products without any stereoisomers.

Scheme 1



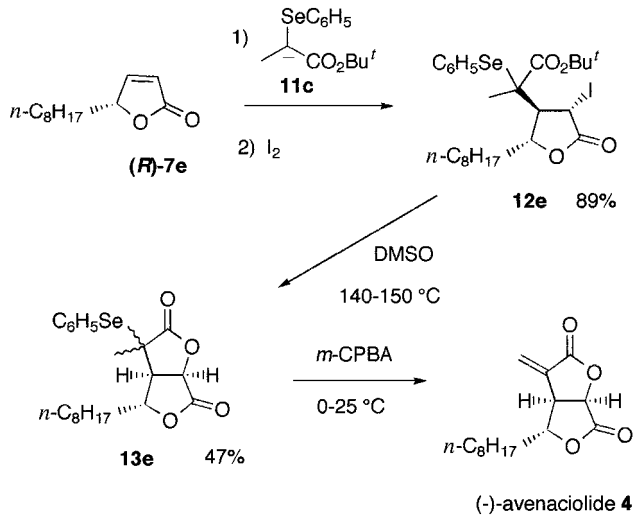
Although the chirality of carbon-3 of **5** bearing the chlorine atom is no consideration for the synthesis of optically active butenolides, the chlorine atom activates the carbonyl group for the reduction of ketone **5** with bakers' yeast because 4-oxoalkanoates bearing no chlo-

(14) Masuda, M.; Nishimura, K. *Chem. Lett.* **1981**, 1333.

(15) Syntheses of (±)-avenaciolide: (a) Parker, W. L.; Johnson, F.. *J. Org. Chem.* **1973**, *38*, 2489. (b) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544. (c) See ref 8d. (d) Sakai, T.; Horikawa, H.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 2039. (e) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1985**, *50*, 1128.

(16) Syntheses of optically active avenaciolide: (a) Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 3870. (b) Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1975**, 3657. (c) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 6237. (d) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron* **1988**, *44*, 4061.

Scheme 2



rine atom are scarcely reduced by bakers' yeast. The chlorine atom also plays an important role in the formation of the C=C bond. The present method is experimentally simple, practical, and useful for the syntheses of optically active butenolides and their derivatives.

Experimental Section

IR spectra were measured as films for oils or by the KBr method for solids. ^{1}H NMR spectra were determined at 60, 100, 200, and 500 MHz and ^{13}C NMR spectra at 50 MHz. ^{1}H NMR spectra were obtained at 60 MHz unless otherwise described. Enantiomeric excess was determined with an HPLC apparatus fitted with Daicel Chiralcel OB-H (4.6 mm ∅ × 250 mm) or with a GC apparatus fitted with a chiral column (Chirasil-DEX CB, 0.25 mm × 25 m) or by comparison of the optical rotation with that of an authentic sample. TLC was performed on glass plates coated with silica gel (Merk silica gel 60 plate, 0.25 mm in thickness).

Fermentation was carried out in boiled tap water in a thermostated bath at 35 ± 2 °C by using industrial pressed bakers' yeast purchased from oriental Yeast Co., Ltd. All glassware was sterilized with boiling water before use.

The synthesis of 3-chloro-4-oxoalkanoate **5** was carried out via three steps from *tert*-butyl 3-oxoalkanoate **8**. Some representative examples are shown.

Ethyl 3-Chloro-4-oxopentanoate (5a). To a mixture of 880 mg (22.0 mmol) of 60% NaH in oil and 60 mL of dry benzene was added 3.48 mL (21.0 mmol) of *tert*-butyl 3-oxobutanoate, and then 0.2 g of trioctylmethylammonium chloride was added. After 20 min, 2.48 g (21.0 mmol) of ethyl iodoacetate was added, and then the mixture was stirred for 36 h at room temperature. It was poured into water and acidified with 10% HCl, and then the organic layer was extracted with ether. The combined extract was washed with water and dried over anhydrous $MgSO_4$. Removal of the solvent gave 7.47 g of an oil, which was purified with column chromatography [silica gel (100 g), hexane/ethyl acetate = 40/1−3/1] to give 5.15 g (100%) of ethyl *tert*-butyl 2-acetylsuccinate (**5a′**).

To a solution of **5a′** (3.08 g, 12.6 mmol) in CH_2Cl_2 (2 mL) was added dropwise a solution of sulfryl chloride (1.39 mL, 15.7 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 3 h at room temperature and then for 40 min at reflux temperature. After removal of the volatile materials under reduced pressure, the residue obtained was dissolved in benzene (10 mL), and *p*-toluensulfonic acid (0.1 g) was added. The mixture was heated at the reflux temperature, and then usual workup gave 2.51 g of crude **5a**, which was purified with column chromatography [silica gel (20 g), hexane/ethyl acetate = 10/1] to give 1.75 g (78%) of **5a**: IR (neat) 3000, 1740, 1730, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, J = 7.14 Hz, 3H), 2.40 (s, 3H), 2.79 (dd, J = 6.22, 17.0 Hz, 1H), 3.12 (dd, J = 7.44, 17.0 Hz, 1H), 4.16 (q, J = 7.16 Hz, 2H), 4.61 (dd, J = 7.54, 7.48 Hz, 1H). Anal. Calcd for $C_7H_{11}ClO_3$: C, 47.07; H, 6.28. Found: C, 46.77; H, 6.46.

Methyl 3-Chloro-4-oxohexanoate (5b). To a mixture of 2.3 g (57.5 mmol) of 60% NaH in an oil and anhydrous benzene (150 mL) was added *tert*-butyl 3-oxopentanoate (9.49 g, 55.2 mmol) and then trioctylmethylammonium chloride (0.5 g). After 30 min, methyl iodoacetate (11.0 g, 55.2 mmol) was added dropwise, and then the mixture was stirred for 19 h at room temperature. It was poured into water and acidified with 10% HCl, and then the organic layer was extracted with ether. The combined extract was washed with water and dried over anhydrous $MgSO_4$. Removal of the solvent gave an oil, which was purified with column chromatography [silica gel (100 g), hexane/ethyl acetate = 40/1−3/1] to give 10.4 g (77%) of methyl *tert*-butyl 2-propanoylsuccinate (**5b′**).

To a solution of **5b′** (1.12 g, 4.59 mmol) in CH_2Cl_2 (2 mL) was added dropwise a solution of sulfuryl chloride (0.505 mL, 5.71 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 2 h at room temperature and then for 2 h at the reflux temperature. After removal of volatile materials under reduced pressure, the residue obtained was dissolved in benzene (5 mL), and *p*-toluensulfonic acid (0.2 g) was added. The mixture was heated at the reflux temperature for 12 h, and then usual workup gave the crude **5b**, which was purified with column chromatography [silica gel (20 g), hexane/ethyl acetate = 10/1] to give 810 mg (99%) of **5b**: IR (neat) 3000, 2950, 1740, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (t, J = 7 Hz, 3H), 2.8 (m, 4H), 3.62 (s, 3H), 4.48 (dd, J = 7, 9 Hz, 1H), 4.47 (dd, J = 7, 9 Hz, 1H). Anal. Calcd for $C_7H_{11}O_5Cl$: C, 47.07; H, 6.21. Found: C, 47.12; H, 6.00.

Ethyl 3-chloro-4-oxohexanoate (5c) was prepared by the decarboxylation of the corresponding succinate, which was obtained in 99% yield from *tert*-butyl 3-oxopentanoate, as described above: 98% yield; R_f 0.53 (hexane/ethyl acetate = 2/1).

Ethyl 3-chloro-4-oxooctanoate (5d) was prepared by the decarboxylation of the corresponding succinate, which was obtained in 79% yield from *tert*-butyl 3-oxoheptanoate, as described above: 86% yield; R_f 0.49 (hexane/ethyl acetate = 4/1).

Methyl 3-chloro-4-oxododecanoate (5e) was prepared by the decarboxylation of the corresponding succinate, which was ohtained in 91% yield from *tert*-butyl 3-oxoundecanoate, as described above: 88% yield; R_f 0.48 (hexane/ethyl acetate = 4/1).

Synthesis of ethyl (4*S*)-3-chloro-4-hydroxypentanoate (6a) is reported in the previous paper.[13a]

Methyl (4*S*)-3-Chloro-4-hydroxyhexanoate (6b). To a mixture of KH_2PO_4 (0.4 g), $NH_4H_2PO_4$ (0.4 g), $MgSO_4$ (0.2 g), $CaCO_3$ (1.2 g), glucose (12 g), and boiling water (200 mL) was added 12 g of bakers' yeast at 35 °C. After bubbles formed (ca. 30 min), 1.42 g (7.96 mmol) of **5b** was added, and then the mixture was stirred at 35 °C. After 4 and 12 h, respectively, 12 g of glucose was added. After 50 h, 6 g of bakers' yeast was added. After 4 days, the organic materials were extracted with ether, washed with water, dried over $MgSO_4$, and concentrated. The residual oil (1.11 g) was chromatographed on silica gel (40 g) [hexane/ethyl acetate (20/1−1/1)] to give 591 mg (43%) of (4*S*)-**6b**: R_f 0.35 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ +11.1 (*c* 3.11, $CHCl_3$); IR (neat) 3500, 3000, 1745 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.98 (t, J = 7 Hz, 3H), 1.50 (m, 2H), 2.75 (m, 2H), 3.20 (broad s, 1H), 3.60 (m, 1H), 3.65 (s, 3H), 4.15 (m, 1H).

Anal. Calcd for $C_7H_{13}ClO_3$: C, 46.55; H, 7.25. Found: C, 46.76; H, 7.31.

The second fraction gave 108 mg (10%) of (*S*)-**7b**.

Ethyl (4*S*)-3-Chloro-4-hydroxyhexanoate (6c). To a mixture of KH_2PO_4 (2.4 g), $NH_4H_2PO_4$ (2.4 g), $MgSO_4$ (1.2 g), $CaCO_3$ (7.2 g), glucose (70 g), and boiling water (1.2 l) was added 70 g of bakers' yeast at 35 °C. After bubbles formed (ca. 30 min), 7.94 g (41.2 mmol) of **5c** was added, and then the mixture was stirred at 35 °C. After 5, 12, and 68 h,

respectively, 70 g of glucose was added. After 34 h, 70 g of bakers' yeast was added. After 3 days, the organic materials were extracted with ether, washed with water, dried over $MgSO_4$, and concentrated. The residual oil (6.16 g) was chromatographed on silica gel [hexane/ethyl acetate (20/1−1/1)] to give 0.856 g (11%) of the starting material **5c** as a first fraction: R_f 0.43 (hexane/ethyl acetate = 4/1). Second fraction gave 3.4 g (42%) of (4*S*)-**6c**: R_f 0.23 (hexane/ethyl acetate = 4/1); $[\alpha]^{22}_D$ +10.4 (*c* 3.22, $CHCl_3$).

Ethyl (4*S*)-3-Chloro-4-hydroxyoctanoate (6d). Compound **5d** (1.90 g, 8.62 mmol) was treated with 27 g (total) of bakers' yeast and 63 g (total) of glucose for 7 days, as shown in the preparation of (4*S*)-**6c**. The crude oil (1.94 g) was chromatographed on silica gel [hexane/ethyl acetate (30/1−1/1)] to give 421 mg (22%) of the starting material **5d**: R_f 0.67 (hexane/ethyl acetate = 2/1). The second fraction gave 417 mg (22%) of **6d**: R_f 0.56 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ +5.78 (*c* 3.0, $CHCl_3$). The third fraction gave 52 mg (4%) of **7d**: R_f 0.31 (hexane/ethyl acetate = 2/1).

(*S*)-5-Octyl-2(5*H*)-furanone (7e). Compound **5e** (2.77 g, 8.45 mmol) was treated with 48 g (total) of bakers' yeast and 96 g (total) of glucose at 30−31 °C for 8 days, as shown in the preparation of (4*S*)-**6c**. The crude oil (2.97 g) was chromatographed on silica gel [hexane/ethyl acetate (10/1−1/1)] to give 182 mg (11%) of (*S*)-**7e**: R_f 0.26 (hexane/ethyl acetate = 4/1); $[\alpha]^{23}_D$ +40.7 (*c* 1.18, dioxane) [lit.[17] $[\alpha]^{25}_D$ +69.2 (*c* 2.10, dioxane)]; 59% ee by ^{1}H NMR (100 Mz, $CCl_4/CHCl_3$ (3/1)) in the presence of Eu(hfc)$_3$.

Synthesis of (5*S*)-5-methyl-2(5*H*)-furanone (7a) is reported in the previous paper.[13a]

(*S*)-5-Ethyl-2(5*H*)-furanone (7c). A mixture of 3.40 g (17.5 mmol) of **6c**, concentrated HCl (15 mL), and water (15 mL) was stirred for 1 day at room temperature. The organic materials were extracted with methylene chloride, washed with water, dried over $MgSO_4$, and concentrated. The residual oil (2.35 g) was dissolved in dry ether (30 mL), and triethylamine (6 mL) was added. The mixture was stirred for 2 days at room temperature and then acidified. The organic materials were extracted with ether, washed with water, and dried. Concentration of the solvent gave the crude product (1.39 g), which was chromatographed on silica gel (hexane/ethyl acetate = 20/1−1/1) to give 1.35 g (69%) of (*S*)-**7c**: R_f 0.38 (hexane/ethyl acetae = 1/1); $[\alpha]^{22}_D$ +103 (*c* 2.71, $CHCl_3$) (lit.[17] $[\alpha]^{23}_D$ −95 (liquid)); >96% ee by ^{1}H NMR (100 MHz, $CCl_4/CHCl_3$ (3/1)) in the presence of Eu(hfc)$_3$.

(*S*)-5-Butyl-2(5*H*)-furanone (7d). A mixture of 400 mg (1.80 mmol) of **6d**, concd HCl (2 mL), and water (2 mL) was stirred for 1 day at room temperature and then worked up as described above. The product was dissolved in dry ether (5 mL), and triethylamine (1 mL) was added. The mixture was stirred for 2 days at room temperature and then worked up as described above. The crude product (227 mg) was chromatographed on silica gel (hexane/ethyl acetate = 10/1−2/1) to give 184 mg (73%) of (*S*)-**7d**: R_f 0.31 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ +92.3 (*c* 3.39, $CHCl_3$) (lit.[6b] $[\alpha]_D$ −101 ($CHCl_3$)); >96% ee by ^{1}H NMR (100 MHz, $CCl_4/CHCl_3$ (3/1)) in the presence of Eu(hfc)$_3$.

(±)-*syn*-Ethyl 3-Chloro-4-hydroxydodecanoate (6f). To a solution of 1.00 g (5.60 mmol) of **5f** in ethanol (10 mL) was added $NaBH_4$ (71 mg, 1.87 mmol) at 0 °C. The mixture was stirred for 10 min and then acidified with 10% HCl. The organic materials were extracted with ether, washed with water, and dried over $MgSO_4$. Removal of the solvent gave 1.48 g of the crude product, which was chromatographed on silica gel (hexane/ethyl acetate = 10/1−1/1) to give 717 mg (71%) of (±)-*syn*-**6f**: R_f 0.35 (hexane/ethyl acetate = 2/1); IR (neat) 3500, 2970, 1745, 1380 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.88 (broad t, J = 6 Hz, 3H), 1.26 (t, J = 7 Hz, 3H), 1.27 (broad s, 14H), 2.77 (m, 2H), 3.60 (broad s, 1H), 4.11 (t, J = 7 Hz, 2H), 4.20 (m, 2H). Anal. Calcd for $C_{14}H_{27}ClO_3$: C, 60.31; H, 9.76. Found: C, 60.69; H, 10.08.

(17) Vigneron, J. P.; Blanchard, J. M. *Tetrahedron Lett.* **1980**, *21*, 1739.

(±)-*syn*-Ethyl 3-Chloro-4-hydroxypentanoate (6a). To a solution of 709 mg (3.97 mmol) of **5a** in ethanol (7 mL) was added $NaBH_4$ (50 mg, 1.32 mmol) at 0 °C. The mixture was stirred for 10 min and worked up as described above. The crude product was purified with column chromatography on silica gel (hexane/ethyl acetate = 2/1), giving 597 mg (83%) of **6a**: syn/anti = 78/22 by GC analysis of the acetate **10a**; R_f 0.30 (hexane/ethyl acetate = 2/1); IR (neat) 3470, 3000, 1740, 1380 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.23 (d, J = 6 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 2.25 (broad s, 1H), 2.70 (m, 2H), 3.6−4.2 (m, 2H), 4.08 (q, J = 7 Hz, 2H).

(±)-*syn*-Ethyl 3-Chloro-4-hydroxyhexanoate (6c). To a solution of 340 mg (1.77 mmol) of **5c** in ethanol (4 mL) was added $NaBH_4$ (22 mg, 0.59 mmol) at 0 °C. The mixture was stirred for 10 min and then worked up as described above. The crude product was purified with column chromatography on silica gel (hexane/ether = 5/1−3/1), giving 165 mg (48%) of (±)-*syn*-**6c**: R_f 0.40 (hexane/ethyl acetate = 2/1).

(±)-*syn*-Ethyl 3-Chloro-4-hydroxyoctanoate (6d). To a solution of 2.00 g (9.07 mmol) of **5d** in ethanol (20 mL) was added $NaBH_4$ (90 mg, 2.37 mmol) at 0 °C. The mixture was stirred for 15 min and then worked up as described above. Column chromatography (silica gel, hexane/ethyl acetate = 20/1−1/1) of the crude product gave 1.47 g (73%) of (±)-*syn*-**6d**: R_f 0.3 (hexane/ethyl acetate = 4/1).

(±)-*syn*-Methyl 3-Chloro-4-hydroxydodecanoate (6e). To a solution of 4.30 g (16.4 mmol) of **5e** in ethanol (50 mL) was added $NaBH_4$ (207 mg, 5.46 mmol) at 0 °C. The mixture was stirred for 20 min and then worked up as described above. Column chromatography (silica gel, hexane/ethyl acetate = 4/1) of the crude product gave 3.74 g (86%) of (±)-*syn*-**6e**: syn/anti = 98/2 by ^{13}C NMR of the acetate **10e**; R_f 0.25 (hexane/ethyl acetate = 4/1).

(±)-*syn*-Ethyl 4-Acetoxy-3-chlorododecanoate (10f). A mixture of (±)-*syn*-**6f** (1.27 g, 4.56 mmol), acetic anhydride (1 mL), and pyridine (3 mL) was stirred for 24 h at room temperature and then acidified with 10% HCl. The organic materials were extracted with methylene chloride, washed with water, dried over $MgSO_4$, and concentrated. The residual oil was chromatographed on silica gel (hexane/ethyl acetate = 20/1−1/1) to give 1.49 g (100%) of (±)-*syn*-**10f**: R_f 0.6 (hexane/ethyl acetate = 4/1); IR (neat) 2950, 1740, 1370 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.89 (broad t, J = 6 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 1.29 (broad s, 12H), 1.60 (m, 2H), 2.05 (s, 3H), 2.63 (d, J = 7 Hz, 2H), 4.13 (q, J = 7 Hz, 2H), 4.31 (m, 1H), 5.06 (m, 1H). Anal. Calcd for $C_{16}H_{29}ClO_4$: C, 59.89; H, 9.11. Found: C, 59.86; H, 9.48.

Other acetates **10** were prepared as described in the preparation of **10f**.

(±)-*syn*-Ethyl 4-Acetoxy-3-chloropentanoate (10a): 92% yield; R_f 0.6 (hexane/ethyl acetate = 2/1); syn/anti = 78/22 by GC analysis.

(±)-*syn*-Methyl 4-Acetoxy-3-chlorohexanoate (10b): 74% yield; R_f 0.55 (hexane/ethyl acetate = 2/1); syn/anti = 77/23 by ^{1}H NMR (200 MHz, $CDCl_3$) analysis.

(±)-*syn*-Ethyl 4-Acetoxy-3-chlorohexanoate (10c): 89% yield; R_f 0.4 (hexane/ethyl acetate = 4/1).

(±)-*syn*-Ethyl 4-Acetoxy-3-chlorooctanoate (10d): 100% yield; R_f 0.6 (hexane/ethyl acetate = 4/1).

(±)-*syn*-Methyl 4-Acetoxy-3-chlorododecanoate (10e): 76% yield; R_f 0.66 (hexane/ethyl acetate = 2/1); syn/anti = >98/2 by ^{13}C NMR.

(3*R*,4*R*)-Ethyl 3-Chloro-4-hydroxydodecanoate (6f) and (3*S*,4*S*)-Ethyl 4-Acetoxy-3-chlorododecanoate (10f). A mixture of (±)-**10f** (750 mg, 2.34 mmol), 1/10 M phosphoric acid buffer solution (pH 7.2, 80 mL), and lipase P (400 mg) was stirred for 40 h at 25 °C. The organic materials were extracted with ether, and the combined extract was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was chromatographed on silica gel (hexane/ethyl acetate = 30/1−4/1) to give 166 mg (22%) of (3*S*,4*S*)-**10f** as a first fraction: R_f 0.60 (hexane/ethyl acetate = 4/1); $[\alpha]^{26}_D$ +8.16 (*c* 2.99, $CHCl_3$). Anal. Calcd for $C_{16}H_{29}ClO_4$: C, 59.89; H, 9.11. Found: C, 59.86; H, 9.48.

The second fraction gave 201 mg (31%) of (3*R*,4*R*)-**6f**: R_f 0.50 (hexane/ethyl acetate = 4/1); $[\alpha]^{26}_D$ +12.3 (*c* 2.60, $CHCl_3$). Spectral data were identical with those of the racemate. Anal. Calcd for $C_{14}H_{27}ClO_3$: C, 60.31; H, 9.76. Found: C, 60.69; H, 10.08.

(3*R*,4*R*)-Ethyl 3-Chloro-4-hydroxypentanoate (6a) and (3*S*,4*S*)-4-Acetoxy-3-chloropentanoate (10a). A mixture of (±)-**10a** (1.80 g, 8.09 mmol), 0.1 M phosphate buffer solution (pH 7.2, 100 mL), and lipase PS (0.90 g) was stirred for 12 h at 25 °C. The organic materials were extracted with ethyl acetate, and the combined extract was washed with water, dried over $MgSO_4$, and concentrated. The residual oil (1.55 g) was chromatographed on silica gel (hexane/ethyl acetate = 50/1−2/1) to give 435 mg (29.9%) of (3*S*,4*S*)-**10a** as a first fraction: R_f 0.50 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ −33.6 (*c* 1.90, $CHCl_3$). The second fraction gave 518 mg (28.8%) of (3*R*,4*R*)-**6a**: R_f 0.28 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ +11.9 (*c* 1.04, $CHCl_3$). The spectral data were identical with those of the racemate.

(3*R*,4*R*)-Methyl 3-Chloro-4-hydroxyhexanoate (6b) and (3*S*,4*S*)-4-Acetoxy-3-chlorohexanoate (10b). A mixture of (±)-**10b** (750 mg, 3.37 mmol), 0.1 M phosphate buffer solution (pH 7.2, 80 mL), and lipase PS (400 mg) was stirred for 7.5 h at 25 °C. The organic materials were extracted with ethyl acetate, and the combined extract was washed with water, dried over $MgSO_4$, and concentrated. The residual oil (512 mg) was chromatographed on silica gel (hexane/ethyl acetate = 30/1−2/1) to give 322 mg (42.9%) of (3*S*,4*S*)-**10b** as a first fraction [R_f 0.53 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ −18.3 (*c* 1.90, $CHCl_3$)] and to give 91 mg (28.8%) of (3*R*,4*R*)-**6b** as a second fraction: R_f 0.33 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ +21.4 (*c* 1.04, $CHCl_3$). The spectral data were identical with those of the racemate.

(3*R*,4*R*)-Ethyl 3-Chloro-4-hydroxyhexanoate (6c) and (3*S*,4*S*)-4-Acetoxy-3-chlorohexanoate (10c). A mixture of (±)-**10c** (1.75 g, 7.40 mmol), 0.1 M phosphate buffer solution (pH 7.2, 100 mL), and lipase PS (0.90 g) was stirred for 10.5 h at 25 °C. The organic materials were extracted with ethyl acetate, and the combined extract was washed with water, dried over $MgSO_4$, and concentrated. The residual oil (1.47 g) was chromatographed on silica gel (hexane/ethyl acetate = 30/1−3/1) to give 389 mg (22.4%) of (3*S*,4*S*)-**10c** as a first fraction: R_f 0.55 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ −23.9 (*c* 1.59, $CHCl_3$). The second fraction gave 435 mg (29.4%) of (3*R*,4*R*)-**6c**: R_f 0.35 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ +22.1 (*c* 2.02, $CHCl_3$). The spectral data were identical with those of the racemate.

(3*R*,4*R*)-Ethyl 3-Chloro-4-hydroxyoctanoate (6d) and (3*S*,4*S*)-4-Acetoxy-3-chlorooctanoate (10d). A mixture of (±)-**10d** (400 mg, 1.51 mmol), 0.1 M phosphate buffer solution (20 mL), and lipase P (200 mg) was stirred for 40 h at 25 °C and then worked up as described above. The crude product (329 mg) was purified by column chromatography (silica gel, hexane/ethyl acetate = 10/1), giving 70 mg (18%) of (3*S*,4*S*)-**10d** as a first fraction [R_f 0.55 (hexane/ethyl acetate = 4/1); $[\alpha]^{26}_D$ +5.58 (*c* 2.33, $CHCl_3$)] and 117 mg (35%) of (3*R*,4*R*)-**6d** as a second fraction: R_f 0.30 (hexane/ethyl acetate = 4/1); $[\alpha]^{26}_D$ +19.5 (*c* 1.96, $CHCl_3$). The spectral data were identical with those of the racemate.

(3*R*,4*R*)-3-Chloro-4-hydroxydodecanoate (6e) and (3*S*,-4*S*)-4-Acetoxy-3-chlorododecanoate (10e). A mixture of 200 mg (0.653 mmol) of (±)-**10e**, 0.1 M phosphate buffer solution (pH 7.2, 10 mL), and lipase P (100 mg) was stirred at 25 °C for 42 h and then worked up as described above. The crude product (234 mg) was purified by column chromatography (silica gel, hexane/ethyl acetate = 10/1), giving 62 mg (31%) of (3*S*,4*S*)-**10e** as a first fraction: R_f 0.50 (hexane/ethyl acetate = 2/1); $[\alpha]^{27}_D$ +15.7 (*c* 2.72, $CHCl_3$); 87% ee by ^1H NMR in the presence of Eu(hfc)$_3$. The second fraction gave 45 mg (26%) of (3*R*,4*R*)-**6e**: R_f 0.40 (hexane/ethyl acetate = 2/1); $[\alpha]^{26}_D$ +10.6 (*c* 1.94, $CHCl_3$).

(*R*)-5-Methyl-2(5*H*)-furanone (7a). A mixture of (3*R*,-4*R*)-**6** (280 mg, 1.60 mmol) and 19% HCl (3 mL) was stirred for 2 days at room temperature and then for 1 day at 40 °C. The organic materials were extracted with ethyl acetate, and the combined extract was washed with water, dried over $MgSO_4$, and concentrated. A mixture of the residual oil (239 mg), triethylamine (1.5 mL, mmol), and dry ether (9 mL) was stirred for 3 days at room temperature and poured into ice−water. The organic materials were extracted with ethyl acetate and dried over $MgSO_4$. Concentration of the solvent gave the crude product (107 mg), which was chromatographed on silica gel (hexane/ethyl acetate = 50/1−5/1) to afford 71 mg (45.3%) of **7e**: R_f 0.20 (hexane/ethyl acetate = 2/1); $[\alpha]^{19}_D$ −96.4 (*c* 1.40, $CHCl_3$) (lit.[3] $[\alpha]_D$ −107.0 (*c* 0.92, $CHCl_3$)); >99% ee by GC analysis fitted with chiral column. The spectral data were identical with those of the authentic sample.[13a]

(*R*)-5-Ethyl-2(5*H*)-furanone (7b). Ester (3*R*,4*R*)-**6b** (108 mg, 0.598 mmol) was hydrolyzed with 19% HCl and then treated with triethylamine, as described in the preparation of (*R*)-**7a**. The crude product was chromatographed on silica gel (hexane/ethyl acetate =50/1−10/1) to give 23 mg (34%) of **7b**: R_f 0.29 (hexane/ethyl acetate); $[\alpha]^{22}_D$ −106.5 (*c* 0.92, $CHCl_3$) (lit.[17] $[\alpha]_D$ −95.0 (liquid)); 96% ee by GC analysis fitted with chiral column. The spectral data were identical with those of (*S*)-**7b**.

(*R*)-5-Butyl-2(5*H*)-furanone (7d). Ester (3*R*,4*R*)-**6d** (54 mg, 0.24 mmol) was hydrolyzed with 19% HCl and then treated with triethylamine, as described in the preparation of (*R*)-**7a**. The crude product was purified with column chromatography (silica gel, hexane/ethyl acetate = 10/1−3/1) to give 25 mg (74%) of **7d**: R_f 0.35 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ −99.0 (*c* 1.38, $CHCl_3$) (lit.[9h] $[\alpha]_D$ −101 ($CHCl_3$)); 98% ee by comparison of the optical rotation. The spectral data were identical with those of the authentic sample.[9h]

(*R*)-Octyl-2(5*H*)-furanone (7e). Ester (3*R*,4*R*)-**6e** (527 mg, 1.72 mmol) was hydrolyzed with 19% HCl and treated with triethylamine, as described in the preparation of (*R*)-**7a**. The crude product was chromatographed on silica gel (hexane/ethyl acetate = 20/1) to give 232 mg (69%) of (*R*)-**7e**: R_f 0.30 (hexane/ethyl acetate = 4/1); $[\alpha]^{22}_D$ −66.7 (*c* 2.37, $CHCl_3$) (lit.[17] $[\alpha]_D$ −69.2 (*c* 2.0, dioxane); 87% ee by comparison of the optical rotation. Spectral data were identical with those of (*S*)-**7e**.

Synthesis of (*R*)-7f from (3*R*,4*R*)-6f. Ester (3*R*,4*R*)-**6f** (180 mg, 0.646 mmol) was hydrolyzed with 19% HCl and then treated with triethylamine, as described in the preparation of (*R*)-**7a**. The crude product was chromatographed on silica gel (hexane/ethyl acetate = 20/1) to give 92 mg (73%) of (*R*)-**7f**: R_f 0.25 (hexane/ethyl acetae = 4/1); $[\alpha]^{25}_D$ −64.9 (*c* 2.56, dioxane) (lit.[17] $[\alpha]_D$ −69.2 (*c* 2.0, dioxane)); 94% ee by comparison of the optical rotation. Spectral data were identical with those of (*S*)-**7e**.

(3*R*,4*R*,5*S*)-4-[1-(*tert*-Butoxycarbonyl)-1-(phenylseleno-)ethyl]-5-ethyl-3-iodotetrahydro-2-furanone (12c). To a solution of diisopropylamine (0.134 mL, 1.0 mmol) in dry THF (1 mL) was added dropwise butyllithium (1.6 M, 0.63 mL, 1.0 mmol) at −20 °C. The mixture was stirred for 30 min, and then a solution of *tert*-butyl 2-(phenylseleno)propanoate (230 mg, 0.80 mmol) in 1 mL of dry THF was added at −78 °C. After 30 min, (*R*)-**7c** (111 mg, 1.0 mmol) was slowly added. After 3 h, a solution of iodine (253 mg, 1.0 mmol) in dry THF (0.5 mL) was added. The mixture was stirred for 30 min and then quenched with 10% HCl. The organic materials were extracted with ether, and the combined extract was washed with aqueous sodium thiosulfate and water and dried over $MgSO_4$. Concentration of the solvent gave a crude product (510 mg), which was chromatographed on silica gel (hexane/ethyl acetate = 2/1 to ethyl acetate) to give 384 mg (92%) of **12c**: R_f 0.75 (hexane/ethyl acetate = 1.1); IR (neat) 3000, 1780, 1720, 1570 cm^{-1}; ^1H NMR (CCl_4) δ 1.22 (t, J = 7 Hz, 3H), 1.44 (s, 9H), 1.47 (s, 3H), 1.70 (m, 2H), 2.93 (m, 1H), 4.0−4.5 (m, 1H), 4.64 (m, 1H), 7.2−7.7 (m, 5H). Anal. Calcd for $C_{19}H_{25}IO_4Se$: C, 43.61; H, 4.82. Found: C, 43.35; H, 4.64.

Bislactonization of 12c to 13c. A solution of **12c** (384 mg, 0.734 mmol) in DMSO (0.5 mL) was stirred for 20 min at 150 °C and then quenched with water. The organic materials were extracted with methylene chloride, and the combined extract was washed with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (hexane/ethyl acetate = 3/1 to ethyl acetate) to give 98 mg

(40%) of **13c**: ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7 Hz, 3H), 1.2−2.0 (m, 2H), 1.60 (s, 3H), 2.93 (t, J = 7 Hz, 1H), 4.30 (m, 1H), 4.60 (d, J = 7 Hz, 1H), 7.0−7.8 (m, 5H).

(3a*S*,6a*S*)-Ethisolide (2). To a mixture of **13c** (71 mg, 0.21 mmol), acetic acid (0.037 mL), and THF (1 mL) was added 35% H_2O_2 (0.21 mL, 2.2 mmol) at 0 °C. The ice bath was removed, and the mixture was stirred for 1 h. The organic materials were extracted with ether, and the combined extract was washed with water, dried over $MgSO_4$, and concentrated. The crude product (35 mg) was purified with preparative TLC (hexane/ethyl acetate = 1/2) to give 27 mg (71%) of **2**: R_f 0.3−0.5 (hexane/ethyl acetate = 1/2); $[\alpha]^{24}_D$ +75 (*c* 0.34, EtOH); IR (neat) 2950, 1780, 1770, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, J = 7 Hz, 3H), 1.85 (m, 2H), 3.55 (m, 1H), 4.38 (m, 1H), 5.03 (d, J = 8.5 Hz, 1H), 5.86 (d, J = 2.0 Hz, 1H), 6.47 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.09, 29.1, 43.7, 74.3, 86.2, 126.3, 134.6, 167.4, 169.7. These data were identical with those of the literature data.[8d]

(5*R*,4*S*)-5-Butyl-4-methyltetrahydro-2-furanone (Whisky Lactone) (3). To a mixture of CuI (162 mg, 0.85 mmol) and ether (1 mL) was added dropwise methyllithium (1.19 M, 1.4 mL (1.7 mmol)) at −25 °C. After 30 min, a solution of (*R*)-**7d** (22 mg, 0.157 mmol) in ether (0.5 mL) was added dropwise, and the mixture was stirred for 1 h at −25 °C and quenched with saturated NH_4Cl solution (1 mL). The organic materials were extracted with ether, and the combined extact was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was chromatographed on silica gel (hexane/ether = 3/1), giving 17 mg (69%) of **3**: R_f 0.50 (hexane/ethyl acetate = 2/1); $[\alpha]^{24}_D$ +79.3 (*c* 1.08, MeOH) (lit.[14] $[\alpha]_D$ +79 (*c* 1.04, MeOH)).

(3*R*,4*R*)-Ethyl 3-Chloro-4-hydroxyhexanoate (6c). A mixture of (±)-**10c** (1.75 g, 7.40 mmol), 1/10 M phosphoric acid buffer solution (pH 7.2, 100 mL), and lipase PS (0.90 g) was stirred for 10.5 h at 25 °C. The organic materials were extracted with ethyl acetate, and the combined extract was washed with water, dried over $MgSO_4$, and concentrated. The residual oil (1.47 g) was chromatographed on silica gel (hexane/ethyl acetate = 30/1−3/1) to give 389 mg (22.4%) of (3*S*,4*S*)-**10c** as a first fraction [R_f 0.55 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ −23.9 (*c* 1.59, $CHCl_3$)] and 435 mg (29.4%) of (3*R*,4*R*)-**6c** as a second fraction: R_f 0.35 (hexane/ethyl acetate = 2/1); $[\alpha]^{22}_D$ +22.1 (*c* 2.02, $CHCl_3$). The spectral data were identical with those of the racemate.

(3*S*,4*S*,5*R*)-4-[1-(*tert*-Butoxycarbonyl)-1-(phenylseleno-)ethyl]-3-iodo-5-octyltetrahydro-2-furanone (12e). To a 10 mL two-necked flask were charged diisopropylamine (0.06 mL, 0.45 mmol) and dry THF (0.5 mL), and the solution was cooled to −20 °C. Butyllithium (1.57 M, 0.29 mL, 0.45 mmol) was added dropwise, and the mixture was stirred for 30 min and cooled to −78 °C. A solution of *tert*-butyl 2-(phenylseleno)propionate (110 mg, 0.38 mmol) in dry THF (0.5 mL) was added. After 1 h, a solution of **7e** (75 mg, 0.38 mmol) in THF (0.5 mL) was added, and the mixture was stirred for 3 h. A mixture of iodine (100 mg, 0.40 mmol) and THF (0.5 mL) was added, and the mixture was stirred for 1 h and quenched with 10% HCl. The organic materials were extracted with ether, and the etherial solution was washed with an aqueous solution of sodium thiosulfate and water and dried over $MgSO_4$. Concentration of the solvent gave 316 mg of the crude product, which was chromatographed (hexane/ethyl acetate (50/1 = 5/1) on silica gel to give 206 mg (89%) of **12e**: R_f 0.55 (hexane/ethyl acetate = 4/1); $[\alpha]^{23}_D$ −15.2 (*c* 2.33, $CHCl_3$); IR (neat) 2950, 1775, 1720, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (broad t, J = 6 Hz, 3H), 1.28 (broad s, 14H), 1.42 (s, 9H), 1.47 (s, 3H), 2.9−3.1 (m, 1H), 4.0−4.4 (m, 1H), 5.6−5.8 (dd, 1H), 7.2−7.7 (m, 5H).

Bislactonization of 12e to 13e. A solution of **12e** (180 mg, 0.297 mmol) in dry DMSO (2 mL) was heated at 140−150 °C for 15 min under an atmosphere of nitrogen and then poured into water. The organic materials were extracted with methylene chloride, washed with water, dried over $MgSO_4$, and concentrated. The crude product was chromatographed on silica gel (hexane/ethyl acetate = 10/1−1/1) to give 59 mg (47%) of **13e**: R_f 0.55 (hexane/ethyl acetate = 2/1); IR (neat) 2950, 1785, 1580 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.89 (broad t, J = 6 Hz, 3H), 1.30 (broad s, 14H), 1.58 (s, 3H), 3.00 (m, 1H), 4.40 (m, 1H), 4.92 (d, J = 9 Hz, 1H), 7.2−7.8 (m, 5H).

(−)-Avenaciolide 4. To a solution of **13e** (31 mg, 0.073 mmol) and acetic acid (0.02 mL) in THF (0.4 mL) was added 35% H_2O_2 (0.76 mL, 0.78 mmol) at 0 °C. The ice bath was removed, and the mixture was stirred for 1 h and quenched with water. The organic materials were extracted with ether, washed with water, and dried over $MgSO_4$. Concentration of the solvent gave the crude product (18 mg), which was chromatographed on silica gel (hexane/ethyl acetate = 5/1) to give 6 mg (31%) of **4**: R_f 0.45 (hexane/ethyl acetate = 2/1); $[\alpha]^{24}_D$ −38 (*c* 1.0, EtOH) (lit.[16a] $[\alpha]^{20}_D$ −41.1 (*c* 0.27, EtOH); 91% ee; mp 49−51 °C (lit.[16a] mp 50−51 °C, lit.[16b] mp 54−56 °C); IR (neat) 2950, 2860, 1785, 1665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (broad t, J = 7 Hz, 3H), 1.2−1.6 (m, 12H), 1.78 (m, 2H), 3.50 (m, 1H), 4.42 (dt, J = 3.8 and 6.6 Hz, 1H), 5.03 (d, J = 8.6 Hz, 1H), 5.87 (d, J = 2.0 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H).

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Supporting Information Available: ^{1}H and ^{13}C spectra of compounds **5c**−**e**, **6c**,**d**, (*S*)-**7c**, (*S*)-**7d**, (*S*)-**7e**, (±)-*syn*-**6c**, (±)-*syn*-**6d**, (±)-*syn*-**6e**, (±)-*syn*-**10a**, (±)-*syn*-**10b**, (±)-*syn*-**10c**, (±)-*syn*-**10d**, and (±)-*syn*-**10e** and elemental analysis data of some of them (3 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.

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