Enzymatic Synthesis of Both Enantiomers of 2-Methylene-4-(fluoromethyl)-4-butanolides

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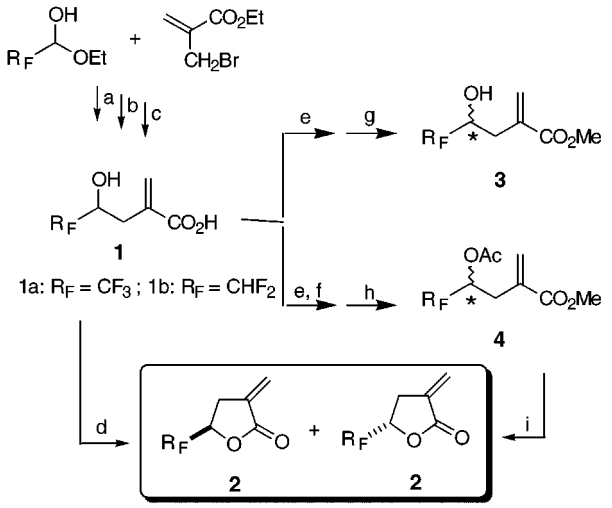
Since the discovery of the antitumor activity of uracil with a fluorine,[1] research for the modification of molecules with fluorine(s), which played a significant role on their biological activities or stabilities,[2−5] has been extensive. In particular, optically active fluorine-containing molecules have been recognized as quite an important class of materials because of their interesting characteristics and potential applicability to optical devices.[6] We have devoted our attention to the synthesis of functionalized chiral building blocks with a fluoroalkyl moiety for attaining ready access to these types of molecules in a highly efficient manner. As a continuation of our interest in the synthesis of materials modified with a fluoroalkyl group, which often exhibit unique bioogical properties,[7−9] we examined the enzymatic synthesis of chiral 3-methylene-5-(difluoromethyl)(or trifluoromethyl)-4-butanolide.

Enzymatic Lactonization.[10,11] The first synthetic strategy to obtain chiral 2-methylene-4-(fluoromethyl)-4-butanolides is the enzymatic synthetic route based on the use of the key intermediate 5,5,5-trifluoro(or 5,5-difluoro)-4-hydroxy-2-methylenepentanoic acid (**1**), as shown in Scheme 1.

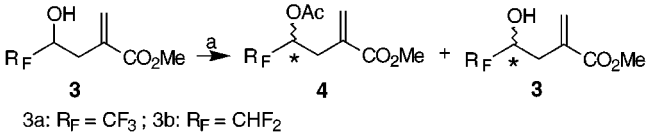
In the asymmetric lactonization of *rac*-**1** with Novozym 435 (*Candida antarctica*, Novo Nordisk Co. Ltd.) in diisopropyl ether, at 40% conversion from *rac*-**1a** (R_F = CF_3), 49% ee of (*S*)-**2a** was obtained, while 53% conversion of *rac*-**1b** (R_F = CHF_2) afforded (*S*)-**2b** in 22% ee. To obtain highly optically pure 2-methylene-4-(fluoromethyl)-4-butanolides (**2a** and **2b**) by lactonization with the enzymatic method, we examined the kinetic resolution of methyl esters (**3a** and **3b**, Scheme 2) with a wide variety of lipases and vinyl acetate in organic media.[12]

Scheme 1[a]



[a] Key: (a) Zn, THF; (b) HCl; (c) NaOH, THF; (d) Novozym 435, diisopropyl ether, molecular sieve; (e) MeI, $NaHCO_3$; (f) AcCl, pyr; (g) lipase, vinyl acetate, organic solvent; (h) lipase, H_2O; (i) Novozym 435.

Scheme 2[a]



[a] Key: (a) lipase, vinyl acetate, hexane.

On the basis of these results (see Table 1), in the system consisting of an enzyme (lipase) and vinyl acetate, by controlling the extent of esterification conversion, either product or unreacted substrate would be obtained with high enantioselectivity. The asymmetric esterification of the carbinol *rac*-**3b** with lipase PS (*Pseudomonas cepacia*, Amano Pharmaceutical Co., Japan) produces the corresponding (*S*)-**4b** (93% ee) at 36% conversion, while 62% conversion of *rac*-**3b** afforded (*R*)-**3b** in 97% ee as shown in Scheme 3. The obtained corresponding (*S*)-**4b** (93% ee) and (*R*)-**3b** (97% ee) would be useful precursors for the preparation of highly optically pure 2-methylene-4-(difluoromethyl)-4-butanolide. In the lactonization with Novozym 435, at 93% conversion from (*R*)-**3b** (97% ee), 97% ee of (*R*)-**2b** ($[\alpha]^{20}_D$ −23.10 (*c* 0.93, MeOH)) was obtained, while (*S*)-**4b** (93% ee) afforded (*S*)-**2b** ($[\alpha]^{20}_D$ +21.36 (*c* 0.99, MeOH)) in 98% ee by a one-pot reaction (sequential synthesis with deacylation and lactonization) in 87% conversion. However, in the case of **3a** (R_F = CF_3), there are numerous disadvantages associated with the above approach; e.g., the yield is not high, the reaction period is too long, and highly enriched products must be prepared at low conversion so that unreacted substrate may be obtained in low optical purity. Further, in the enzymatic reaction of fluorinated materials, it is important to choose a lipase that produces highly optically pure materials at reasonable conversion.[13]

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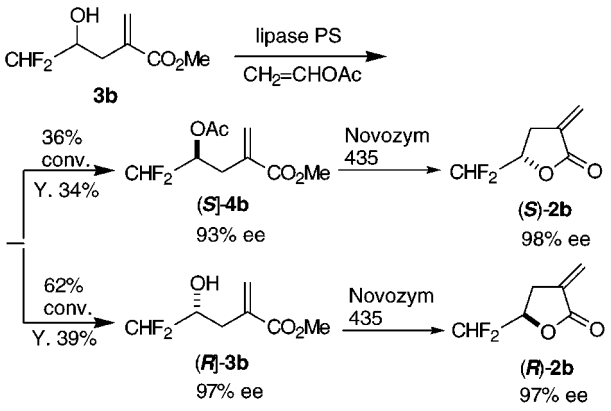
Table 1. Enzymatic Acetylation of Compounds 3a and 3b

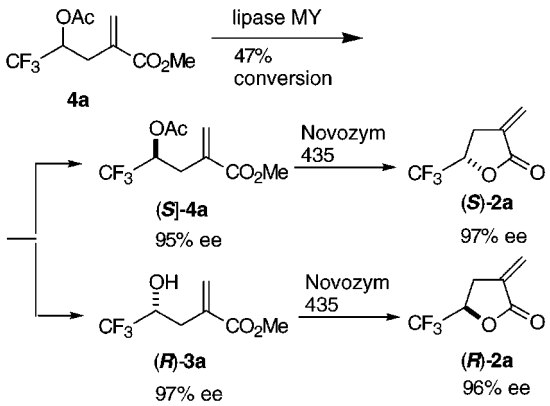
R_F	lipase[a]	time (h)	conversion (%)	optical purity (% ee) 4	optical purity (% ee) 3 (recovered)
CF_3	lipase PS	72	23	95 (*S*)	24 (*R*)
	lipase MY	72	15	96 (*R*)	17 (*S*)
CHF_2	lipase PS	10	27	93 (*S*)	46 (*R*)
	lipase PS	18	50	87 (*S*)	85 (*R*)
	lipase MY	12	4	51 (*R*)	23 (*S*)

[a] (a) Lipase PS (*Pseudomonas cepacia*, Amano Pharmaceutical Co. Ltd.), lipase MY (*Candida rugosa*, Meito Sangyo Co. Ltd.).

Scheme 3



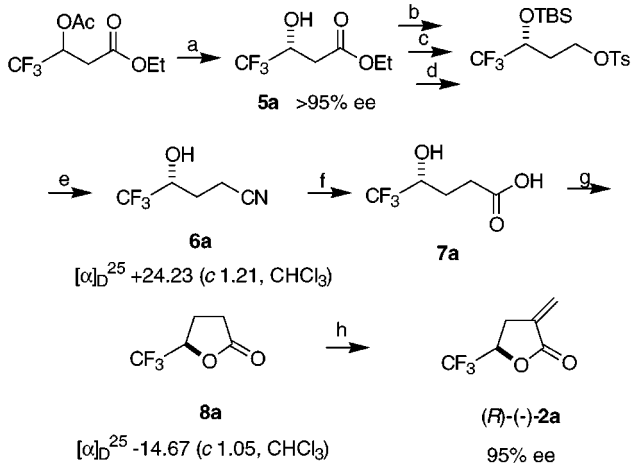
Scheme 4



To obviate the above disadvantages, we have developed a second route based upon the kinetic resolution of acetate derivative **4a** as shown in Scheme 4. The asymmetric hydrolysis of the acetate with lipase MY (*C. rugosa*; Meito Sangyo Co., Japan) produced the corresponding (*R*)-**3a** at 47% conversion, and the acetate derivative (*S*)-**4a** of the enantiomer with 95% ee was recovered. Further, the enzymatic lactonization of (*R*)-**3a** with Novozym 435 produced (*R*)-**2a** ($[\alpha]^{25}_D$ −20.9 (*c* 0.73, $CHCl_3$), 96% ee), while the one-pot reaction (deacylation and lactonization) of (*S*)-**4a** afforded (*S*)-**2a** ($[\alpha]^{25}_D$ +19.6 (*c* 0.67, MeOH), 97% ee).

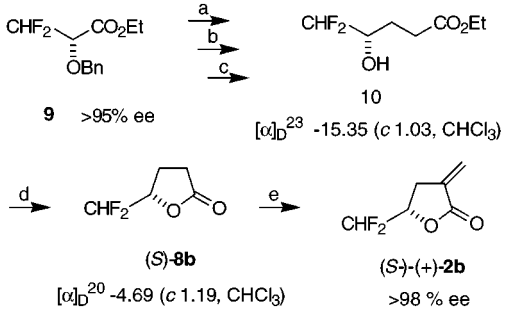
Determination of Absolute Configuration. The synthetic strategy to determine the absolute configuration of chiral 2-methylene-4-(fluoromethyl)-4-butanolides is the chemicoenzymatic method that is the use of chiral building block derived from the asymmetric resolution. In Scheme 5, derived from the asymmetric hydrolysis of the corresponding acetate derivative, lipase MY (*C. rugosa*, Meito Sangyo Co., Ltd.) was used as a starting material. Conversion of (*R*)-ethyl 3-hydroxy-4,4,4-trifluorobutyrate (*R*)-**5a**[14] to (*R*)-(−)-3-methylene-5-(trifluoromethyl)-4-butanolide was achieved by the following procedures. The (*R*)-(+)-**5a** was selectively reduced with diisobutyl alminum hydride to give in good yield the optically pure alcohol. The protected alcohol was then reacted with KCN in the presence of 18-crown-6 to give the compound (*R*)-**6a** (>95% ee). Lactonization was achieved by refluxing in the presence of *p*-toluenesulfonic acid (TsOH) in benzene. Finally, the methylene group was introduced into the lactone ring by treatment with the $CH_2N^+Me_2I^-$−MeI−lithium diisopropyl amide (LDA) system, affording (*R*)-(−)-2-methylene-4-(trifluoromethyl)-4-butanolide, ((*R*)-(−)-**2a**,[15] 95% ee by GLC). For the conversion given in Scheme 6, the synthetic starting material was the optically pure (*S*)-(+)-ethyl 2-(benzyloxy)-3,3-difluoropropionate **9** (>95% ee).[16] Treatment of propionate (*S*)-(+)-**9** with diisobutylaluminum hydride gave the corresponding aldehyde in situ, and then the reaction of aldehyde with Horner−Wittig reagent ($(EtO)_2P(O)CH_2CO_2Et$ and NaH) in Et_2O gave the α,β-unsaturated-γ-(benzyloxy)-γ-difluoromethyl ester. The hydro-

Scheme 5[a]



[a] Key: (a) lipase MY (*Candida rugosa*, Meito Sangyo Co. Ltd.), H_2O; hydrolysis conversion 31%; (b) TBA-Cl, CH_2Cl_2, pyr; yield 97%; (c) DIBALH, Et_2O; (d) TsCl, CH_2Cl_2, pyr; (e) KCN, 18-crown-6, H_2O; (f) KOH, EtOH; (g) TsOH, benzene; (h) LDA, CH_2NMe_2I; MeI, THF; $NaHCO_3$ (aq).

Scheme 6[a]



[a] Key: (a) DIBAL-H, Et_2O; (b) Et_2O, NaH, $(EtO)_2P(O)CH_2CO_2Et$; (c) H_2, Pd−C; (d) pyridium *p*-toluenesulfonate (PPTS), H_2O; (e) LDA, CH_2NMe_2I; MeI, THF; $NaHCO_3$ (aq).

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genolysis of the corresponding ester with $Pd-C/H_2$ produced the synthetic intermediate (*S*)-(−)-**10** (>95% ee), and then the lactonization was achieved by pyridinium *p*-toluenesulfonate. Finally, the methylene group was introduced into the lactone ring, giving (*S*)-(+)-3-methylene-5-(difluoromethyl)propionate ((*S*)-(+)-**2b**, >98% ee by GLC).

Experimental Section

General Methods. All commercially available reagents were used without further purification. Chemical shift of ^1H (500 MHz) and ^{13}C NMR spectra were recorded in ppm (δ) downfield from the following internal standards (Me_4Si, δ 0.00, or $CHCl_3$, δ 7.24). The ^{19}F (470 MHz) NMR spectra were recorded in ppm downfield from external C_6F_6 in $CDCl_3$ using a VXR 500 instrument. Gas−liquid chromatography (GLC) was performed using silicone GE ULBON HR-20M on Chromosorb W, 30 m × 3 mm. The optical purities of the materials were determined by GLC.

4-Hydroxy-2-methylene-5,5,5-trifluoropentanoic Acid (1a). To a stirred solution of ethyl trifluoroacetate (0.35 mL, 9.0 mmol) and zinc powder (0.705 g, 10.8 mmol) in diethyl ether (12 mL) at −78 °C was added $LiAlH_4$ (1.0 M solution in THF, 9.0 mL, 9.0 mmol) for 10 min under an argon. The mixture was stirred for 2 h at −30 °C, and then methyl (bromomethyl)acrylate (1.19 mL, 9.9 mmol) in THF (10 mL) was added dropwise to the above solution at 0 °C. The mixture was stirred at 60 °C for 30 min and then allowed to cool to room temperature over 8 h, and the mixture was quenched with 15 mL of 1 N HCl. The organic layer was separated and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. After the solvent was removed, THF (10 mL) was added to the residue. To this mixture solution at 0 °C were successively added 2.0 N NaOH (4.0 mL) and EtOH (4.0 mL). The mixture was stirred at room temperature for 4 h. The mixture was diluted with water and was then acidified with 6.0 N HCl. The mixture was extracted with CH_2Cl_2 and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with hexane/ether (1:1 to 0:1) to give 1.20 g (72%) of 4-hydroxy-2-methylene-5,5,5-trifluoropentanoic acid (**1a**): ^1H NMR ($CDCl_3$) δ 2.61 (1 H, ddd, J = 0.7, 9.8, 14.4 Hz), 2.80 (1 H, ddd, J = 0.7, 3.2, 14.4 Hz),4.19 (1 H, ddq, J = 3.2, 9.8, 6.6 Hz), 6.53 (1 H, d, J = 0.7 Hz), 5.95 (1 H, d, J =0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 32.72, 69.37 (q, J = 31.1 Hz), 124.91 (q, J = 281.8 Hz), 132,53, 134.11, 172.32; ^{19}F NMR ($CDCl_3$) δ −80.9 (d, J = 6.1 Hz); IR (neat) ν 1634, 1699, 3450 cm^{-1}.

4-Hydroxy-2-methylene-5,5-difluoropentanoic acid (1b): ^1H NMR ($CDCl_3$) δ 2.54 (1 H, dd, J = 9.3, 14.4 Hz), 2.73 (1 H, dd, J = 3.4, 14.7 Hz), 3.94−4.02 (1 H, m), 5.71 (1 H, dt, J = 3.7, 55.9 Hz), 5.91 (1 H, d, J = 1.0 Hz), 6.49 (1 H, d, J = 1.0 Hz); ^{19}F NMR ($CDCl_3$) δ −131.0 (1 F, ddd, J = 10.7, 54.9, 286.9 Hz), −132.3 (1 F, ddd, J =10.2, 56.5, 286.9 Hz); IR (neat) ν 1630, 1698, 2980 cm^{-1}.

Asymmetric Esterification. A mixture solution of methyl 5,5-difluoro-4-hydroxy-2-methylenepentanoate (**3b**) (1.10 g, 6.10 mmol), lipase PS (1.62 g; *P. cepacia*, Amano Pharmaceutical Co., Ltd. 8000 unit/mol), and vinyl acetate (5.62 mL, 61 mmol) in hexane (61 mL) was stirred at 30 °C. The progress of the reaction was readily followed by gas chromatography. The acetylation stopped at a conversion of 36%, and the mixture was diluted with diethyl ether. After the solid materials were filtered, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel, eluting with a mixture solution of hexane−diethyl ether (3:1−1:1) to give (*S*)-**4b** ($[\alpha]^{20}_D$ +8.68 (*c* 0.78, $CHCl_3$), 93% ee) (34% yield) and (*R*)-**3b** (46% ee, 64% yield). (*S*)-Methyl 5,5-difluoro-4-acetoxy-2-methylenepentanoate (*S*)-**4b**: ^1H NMR ($CDCl_3$) δ 2.07 (3 H, s), 2.55 (1 H, dd, J = 9.5, 14.4 Hz), 2.86 (1 H, ddd, J = 0.7, 3.7, 14.4 Hz), 3.79 (3 H, s), 5.24−5.33 (1 H, m), 5.68 (1 H, dd, J = 1.2, 2.2 Hz), 5.80 (1 H, ddd, J = 2.9, 54.4, 55.4 Hz), 6.27 (1 H, d, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 20.57, 30.71 (t, J =4.2 Hz), 52.18, 69.68 (t, J = 24.6 Hz), 113.77 (t, J = 254.0 Hz), 120.78, 134.75, 166.63, 169.82; ^{19}F NMR ($CDCl_3$) δ −129.5 (1 F, ddd, J = 10.9, 54.9, 289.2 Hz), −132.0 (1 F, ddd, J = 13.7, 56.4, 289.9 Hz). Anal. Calcd for $C_9H_{12}F_2O_4$: C, 48.65; H, 5.44. Found: C, 48.69; H, 5.51.

(*R*)-Methyl 5,5-difluoro-4-hydroxy-2-methylenepentanoate ((*R*)-3b): ^1H NMR ($CDCl_3$) δ 2.54 (1 H, dd, J = 9.0, 14.4 Hz), 2.72 (1 H, dd, J = 3.4, 14.4 Hz), 2.98 (1 H, d, J = 5.1 Hz), 3.81 (3 H, s), 3.89−3.99 (1 H, m), 5.70 (1 H, dt, J = 3.7, 55.7 Hz), 5.80 (1 H, dd, J = 1.0, 2.2 Hz), 6.36 (1H, d, J = 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 33.14 (t, J = 3.8 Hz), 52.40, 70.00 (t, J = 23.7 Hz), 115.95 (t, J = 244.2 Hz), 129.31, 135.46, 168.25; ^{19}F NMR ($CDCl_3$) δ −131.0 (1 F, ddd, J = 10.7, 54.9, 285.3 Hz), −136.8 (1 F, ddd, J = 10.7, 54.9, 285.3 Hz). Anal. Calcd for $C_7H_{10}F_2O_3$: C, 46.67; H, 5.59. Found: C, 46.68; H, 5.59.

Asymmetric Hydrolysis. A solution of methyl 5,5,5-trifluoro-4-acetoxy-2-methylenepentanoate (**4a**) (0.85 g, 3.54 mmol) and lipase MY (0.95 g; *C. rugosa*, Meito Sangyo Co., Ltd. 8000 unit/mol) in 35 mL of phosphate buffer (0.01 M, pH 7) was stirred at 30 °C. The reaction was monitored by gas chromatography. The acetylation stopped at a conversion of 47%, and the mixture was diluted with diethyl ether. After the solid materials were filtered, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel, eluting with a mixture of hexane−diethyl ether (4:1−1:1) to give (*R*)-**3a** ($[\alpha]_D^{25}$ +26.2 (*c* 0.90, $CHCl_3$), 97% ee) (34% yield) and (*S*)-**4a** ($[\alpha]^{25}_D$ +18.1 (*c* 0.79, $CHCl_3$), 95% ee) (65% yield). (*S*)-Methyl 5,5,5-trifluoro-4-acetoxy-2-methylene-pentanoate ((*S*)-**4a**): ^1H NMR ($CDCl_3$) δ 2.09 (3 H, s), 2.94 (1 H, ddd, J = 0.8, 3.2, 14.2 Hz), 2.57 (1 H, ddd, J = 0.7, 10.5, 14.4 Hz), 3.80 (3 H, s), 5.56 (1 H, ddq, J = 3.2, 9.8, 6.6 Hz), 5.69 (1 H, d, J = 1.0 Hz), 6.28 (1 H, d, J = 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 20.34, 31.62 (q, J = 3.6 Hz), 52.27, 68.04 (q, J = 24.5 Hz), 123.66 (q, J = 244.6 Hz), 129.30, 134.05, 166.34, 169.17; ^{19}F NMR ($CDCl_3$) δ −78.3 (d, J = 7.6 Hz). Anal. Calcd for $C_9H_{11}F_3O_4$: C, 45.01; H, 4.62. Found: C, 45.28; H, 4.84.

(*R*)-Methyl 5,5,5-trifluoro-4-hydroxy-2-methylenepentanoate ((*R*)-3a): ^1H NMR ($CDCl_3$) δ 2.62 (1 H, dd, J = 9.5, 14.4 Hz), 2.78 (1 H, ddd, J = 1.0, 2.9, 14.4 Hz), 3.37 (1 H, d, J =5.86 Hz), 3.82 (3 H, s), 4.10−4.18 (1 H, m), 5.83 (1 H, d, J = 0.7 Hz), 6.36 (1 H, d, J = 0.5 Hz); ^{13}C NMR ($CDCl_3$) δ 33.26, 52.52, 69.46 (q, J = 31.1 Hz), 124.97 (q, J = 282.2 Hz), 130.01, 134.75, 168.30; ^{19}F NMR ($CDCl_3$) δ −80.9 (d, J = 6.1 Hz). Anal. Calcd for $C_7H_9F_3O_3$: C, 42.43; H, 4.58. Found: C, 42.02; H, 4.69.

Asymmetric Lactonization: (a) Preparation of (*R*)-2a. A mixture of (*R*)-methyl 5,5,5-trifluoro-4-hydroxy-2-methylenepentanoate ((*R*)-**3a**) (0.28 g, 1.41 mmol, 97% ee) and Novozym 435 (1.61 g, 8000 unit/mol; *C. antarctica*, Novo Nordisk Co., Ltd.) in hexane (15 mL) was stirred at 30 °C overnight. The mixture was diluted with diethyl ether. After the solid materials were filtered, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel, eluting with a mixture solution of hexane−diethyl ether (2:1) to give (*R*)-2-methylene-4-(trifluoromethyl)-4-butanolide ((*R*)-**2a**) ($[\alpha]^{25}_D$ −20.9 (*c* 0.73, $CHCl_3$), 96% ee): ^1H NMR ($CDCl_3$) δ 3.05 (1 H, ddt, J = 4.4, 17.8, 2.7 Hz), 3.19 (1 H, ddt, J = 9.0, 17.8, 2.9 Hz), 4.81 (1 H, ddq, J = 4.4, 6.1, 9.0 Hz), 5.81 (1 H, t, J = 2.7 Hz) 6.38 (1 H, t, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$) δ 27.61 (q, J = 2.0 Hz), 72.61 (q, J = 34.8 Hz), 123.82 (q, J = 280.0 Hz), 125.25, 130.86 168.85; ^{19}F NMR ($CDCl_3$) δ −81.2 (d, J = 6.0 Hz); IR (neat) ν 1665, 1724 cm^{-1}.

(b) Preparation of (*S*)-2a. In the above reaction, (*S*)-methyl 5,5,5-trifluoro-4-acetoxy-2-methylenepentanoate (*S*)-**4a** (95% ee) was used, and worked up similarly, giving 2-methylene-4-(trifluoromethyl)-4-butanolide (*S*)-**2a** ($[\alpha]^{25}_D$ +19.6 (*c* 0.67, MeOH), 97% ee).

(*R*)-2-Methylene-4-(difluoromethyl)-4-butanolide ((*R*)-2b): $[\alpha]^{20}_D$ −23.10 (*c* 0.93, MeOH), 97% ee; ^1H NMR ($CDCl_3$): δ 3.05−3.09 (2 H, m), 4.69 (1 H, dddt, J = 2.7, 5.6, 7.8, 17.1 Hz), 5.77 (1 H, t, J = 2.4 Hz), 5.92 (1 H, ddd, J = 2.7, 54.0, 56.1 Hz), 6.34 (1 H, t, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$) δ 25.95 (dd, J = 2.7, 7.1 Hz), 73.37 (dd, J = 25.6, 30.2 Hz), 113.18 (dd, J = 243.4, 246.2 Hz), 123.88, 131.57, 168.80; ^{19}F NMR ($CDCl_3$) δ −131.0 (1 F, ddd, J = 6.1, 53.4, 296.0 Hz), −136.8 (1 F, ddd, J =16.8, 56.5, 296.0 Hz); IR (neat) ν 1668, 1772 cm^{-1}.

(*S*)-2-Methylene-4-(difluoromethyl)-4-butanolide ((*S*)-2b): $[\alpha]^{20}_D$ +21.36 (*c* 0.99, MeOH), 98% ee.

Preparation of (*R*)-(−)-2-Methylene-4-(trifluoromethyl)-4-butanolide (2a). (a) (*R*)-(+)-4-Hydroxy-5,5,5-trifluoropentanitirile (6a). To a solution of (*R*)-ethyl 3-(*tert*-butyldim-

ethylsiloxy)-4,4,4-trifluorobutyrate (3.0 g, 10.0 mmol) and diethyl ether (20 mL) was added a solution of DIBALH (1.0 M solution in hexane, 24 mL, 24 mmol) dropwise at 0 °C under argon atmosphere. After the consumption of the starting material was checked, the reaction was quenched by the sequential addition of saturated aqueous Na_2SO_4. After being stirred vigorously, the slurry was filtered though Celite, and then the precipitates were washed thoroughly with diethyl ether. After the solution was concentrated, the residue was purified by column chromatography on silica gel, eluting with a mixture of hexanes−ethyl acetate (6:1) to give 1.42 g (61%) of (*R*)-3-(*tert*-butyldimethylsiloxy)-4,4,4-trifluoro-1-butanol. To a solution of (*R*)-3-(*tert*-butyldimethylsiloxy)-4,4,4-trifluoro-1-butanol (1.15 g, 5.0 mmol) and *p*-toluenesulfonyl chloride (1.14 g, 6.0 mmol) in CH_2Cl_2 (10 mL) was added pyridine (5.0 mL) at 0 °C. After being stirred of 2 h at room temperature, the mixture was diluted with hexane and then passed through a pad of Celite. The filtrate was concentrated in vacuo. To a solution of the residue (crude tosylate) in DMSO (10 mL) were successively added KCN (332 mg, 5.1 mmol), 18-crown-6 (224 mg, 0.85 mmol), and water (1.0 mL) at 25 °C. The mixture was heated at 110 °C for 8 h, and then the whole was poured into water. Oily materials were extracted with diethyl ether, and the extracts was washed with brine before being dried over $MgSO_4$. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with a mixture of hexanes−ethyl acetate (2:1) to give (*R*)-(+)-**6a** (445 mg) in 35% yield: $[\alpha]^{25}_D$ +24.23 (*c* 1.21, $CHCl_3$), >95% ee. **(b) (*R*)-(−)-4-(Trifluoromethyl)-4-butanolide (8a).** A solution of (*R*)-(+)-**6a** (0.612 g, 4.0 mmol), EtOH (8 mL), water (3 mL), and KOH (1.34 g, 24 mmol) was refluxed for 48 h. The cooled mixture was diluted with water, and then the whole was acidified with 6 N HCl. Oily materials were extracted with CH_2Cl_2 and concentrated in vacuo. The residue was dissolved in benzene (10 mL) containing a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was refluxed for 36 h with Dean−Stark trap, and then the mixture was allowed to cool to room temperature. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with a solution of hexane−diethyl ether (2:1), to give (*R*)-(−)-**8a** (454 mg) in 73% yield: $[\alpha]^{19}_D$ −14.67 (*c* 1.05, $CHCl_3$), >95% ee. **(c) Preparation of (*R*)-(−)-2-Methylene-4-(trifluoromethyl)-4-butanolide (2a).** To a solution of *i*-Pr_2NH (0.35 mL, 2.53 mmol) in THF (2.5 mL) was added *n*-BuLi (1.56 mL, 2.53 mmol) over 20 min at −78 °C under a nitrogen atmosphere. After a solution of (*R*)-(−)-**8a** (0.354 g, 2.3 mmol) in THF (1.5 mL) was added to the above solution, the whole was stirred for 45 min at −78 °C, and then *N*,*N*-(dimethylmethylene)ammonium iodide (1.06 g, 5.75 mmol) was added to the mixture. The mixture was stirred for 1 h at 0 °C and then for 6 h at room temperature. On removal of the solvent, the residue was taken up in MeOH (5.0 mL, 0 °C) before the addition of MeI (1.15 mL, 18.4 mmol). The mixture was stirred for 8 h at room temperature, and then the solvent was removed in vacuo. The resultant red solid was dissolved in CH_2Cl_2 (5.0 mL), and then the solution was stirred with 10% $NaHCO_3$ (aq) for 48 h at room temperature. Oily materials were extracted with CH_2Cl_2. The extract was washed with brine before being dried over $MgSO_4$. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with a mixture of pentane−diethyl ether (2:1) to give compound (*R*)-(−)-**2a** (178 mg), 95% ee by GLC in 47% yield.

Preparation of (*S*)-(−)-2-Methylene-4-(difluoromethyl)-4-butanolide (2b). (a) (*S*)-(−)-Ethyl 4-Hydroxy-5,5-difluoropentanate (10). A suspension of NaH (0.720 g, 30 mmol) in THF (30 mL) was added to a solution of triethyl phosphonoacetate (6.55 mL, 33 mmol) in THF (30 mL) at 0 °C under argon atmosphere. In another flask, DIBALH (1.0 M hexane, 25 mL) was added dropwise to a solution of (*S*)-(+)-**9** (6.12 g, 25 mmol, >95% ee) in diethyl ether (25 mL) at −78 °C under an argon atmosphere. After being stirred for 2 h at −78 °C, the cold anion solution (Horner−Wittig reagent) was added dropwise via syringe to the pregenerated aldehyde. After the whole was stirred at −78 °C for 1 h, the mixture was allowed to warm to room temperature over 6 h and then quenched with 15 mL of 3 N HCl. The organic layer was separated, washed with brine, and dried over $MgSO_4$. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with a mixture of hexanes−ethyl acetate (20:1), to give the γ-(benzyloxy)-α,β-unsaturated ester (5.50 g) in 81% yield.

To a solution of the γ-(benzyloxy)-α,β-unsaturated ester and 5% Pd−C (1.40 g) in EtOH (20 mL) was added one drop of 1 N HCl. The mixture was stirred under a hydrogen atmosphere for 12 h at room temperature, and the catalyst was removed by filtration. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with a solution of hexanes−ethyl acetate (4:1), to give (*S*)-(−)-ethyl 4-hydroxy-5,5-difluoropentanate (**10**) (3.66 g) in 80% yield ($[\alpha]^{23}_D$ −15.35 (*c* 1.03, $CHCl_3$), >95% ee). The optical purity was determined by ^{19}F NMR integral intensity after conversion to MTPA-ester. **(b) (*S*)-(−)-4-(Difluoromethyl)-4-butanolide (8b).** (*S*)-(−)-Ethyl 4-hydroxy-5,5-difluoropentanate (**10**) (456 mg, 2.50 mmol, >95% ee) was added to a solution of pyridinium *p*-toluenesulfonate (catalytic amount) in benzene (10 mL). The mixture was refluxed for 36 h with a Dean−Stark trap, and then the whole was allowed to cool to room temperature. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with a solution of hexane−diethyl ether (1:1) to give (*S*)-(−)-4-(difluoromethyl)-4-butanolide **8b** (291 mg) in 86% yield ($[\alpha]^{20}_D$ −4.69 (*c* 1.19, $CHCl_3$)), >95% ee by GLC. **(c) (*S*)-(−)-2-Methylene-4-(difluoromethyl)-4-butanolide (2b).** In the same procedure as for the preparation of **2a** from (*R*)-(−)-**8a**, (*S*)-(−)-**8b** (313 mg, 2.3 mmol) was used and worked up similarly, giving (*S*)-(−)-2-methylene-4-(difluoromethyl)-4-butanolide **2b** in >98% ee with GLC in 35% yield.

Supporting Information Available: Copies of proton NMR spectra (10 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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