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Synthesis of Chiral Difluorinated [6]-Gingerol

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Abstract: Total synthesis of chiral difluorinated [6]-gingerol using key intermediates (*R*)-(+)- and (*S*)-(-)-ethyl 2,2-difluoro-3-hydroxyoctanoates, obtained *via* enzymatic resolution with olipase/4S (*Rhizopus japonicus*) is described.

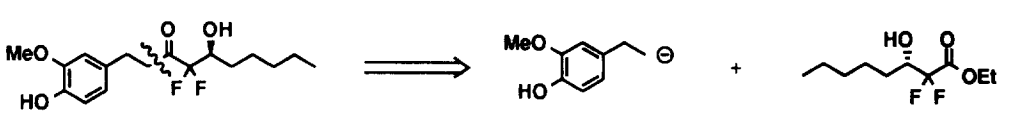
Introduction

The β-hydroxycarbonyl structure is frequently found in natural products, and this framework is widely used as a key intermediate in organic synthesis to afford highly functionalized compounds. For example, [6]-gingerol[1] derived from natural ginger, known as the potent inhibitor of prostaglandin biosynthesis,[2] has acidic methylene protons and tends to undergo ready dehydration. Substitution of the two geminal hydrogens attached to this methylene by fluorines would inhibit such reactions because of the difficulty to generate a fluorocation species, and would exert a pronounced influence on its chemical property with no significant effect on its geometry, which has possibility to show unexpected biological properties.[3] Furthermore, β-hydroxycarbonyl compounds possessing fluorine(s) at the α-position are paid much attention due to the remarkable ability of these compounds to function as biologically active materials, or optical devises such as ferroelectric liquid crystals.[4,5] Clearly, selective introduction of the difluoromethylene functionality at a specific position of the target molecule remains an important synthetic challenge.

We have devoted our attention on the synthesis of functionalized chiral building blocks with α,α-difluoro-β-hydroxycarbonyl moiety for attaining the ready access to these types of molecules in a highly efficient manner. In this paper, as a part of our studies on biochemical preparation of optically active fluorine-containing molecules, we would like to report the facile synthesis of optically active ethyl 2,2-difluoro-3-hydroxyoctanoate with enzymatic resolution and total synthesis of optically active fluorinated [6]-Gingerol derivatives.

Results and Discussion

Based on the recent impressive progress made on total synthesis of gingerol,[6] we designed our starting chiral building block (*R*)-(+)- or (*S*)-(-)-ethyl 2,2-difluoro-3-hydroxyoctanoate (**1**) as a key intermediate.



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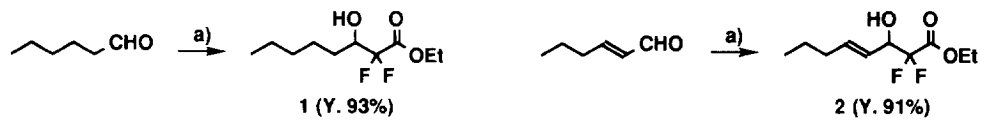
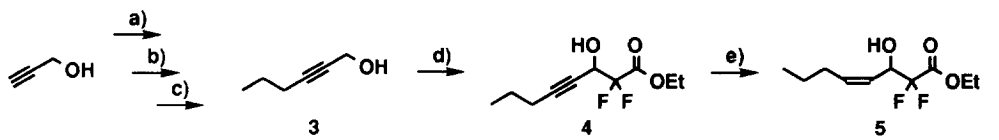
Recently, Mochizuki *et. al.*[7] have reported synthesis of optically active methyl 2,2-difluoro-3-hydroxy-tetradecanoate using bottom-fermentation yeast, *Saccharomyces cerevisiae* IFO 0565. However, no reports on chiral alkyl 2,2-difluoro-3-hydroxyoctanoate have been made in literature. On the other hand, Sugai *et al.*[8] have

revealed that lipase-catalyzed transesterification of 2,2-difluoro-3-hydroxytetradecanoic acid in tetrahydrofuran to obtain the chiral material did not proceed. Furthermore, asymmetric Reformatsky-Type reaction using (-)-cinconidine,[9] and asymmetric reduction with baker's yeast[10] of the corresponding α,α-difluoro-β-keto ester have been examined. Unfortunately, the above both reactions were unsuccessful. Therefore, we examined the enzymatic resolution to search for a practical route to chiral ethyl 2,2-difluoro-3-hydroxyoctanate (**1**) with high *E* value. For this purpose, we examined two methods: (1) the search of the additive to enhance the enantioselectivity of asymmetric hydrolysis by lipases, and (2) the modification of ethyl 2,2-difluoro-3-hydroxyoctanate (**1**). α,α-Difluoro-β-hydroxyesters (**1**), (**2**), (**4**), (**5**) for the enzymatic transformation were prepared by synthetic strategies shown in Schemes 1 and 2.

At first, kinetic resolutions of ethyl 2,2-difluoro-3-hydroxyoctanate (**1**), with a wide range of lipases were examined under the different reaction conditions: (a) enzymatic resolution in water, (b) addition of 1 *N* NaOH to water medium for neutralization, and (c) medium in KH_2PO_4-NaOH, pH 7.0 buffer. Since *E* value was found to be insufficient for practical resolutions (Table 1, except entry 1), we examined various additives to increase enantioselectivity of biocatalytic resolution. Recently, effective additives to enhance the enantioselectivity of lipase-catalyzed hydrolysis have been reported by several research groups.[11] In the above procedure, several additives, such as LiCl, quinidine, 18-crown-6, 12-crown-4, were examined. Unfortunately, additives were not effective in enhancing the *E* value. To improve the scope and limitation of lipase-catalyzed asymmetric hydrolysis the modification of material was examined.



Scheme1: a) Zn, $BrCF_2CO_2Et$ / THF, rt



Scheme2: a) DHP, TsOH / CH_2Cl_2, rt b) *n*-BuLi, HMPA, $CH_3CH_2CH_2I$ / THF, -78 °C ~ rt c) TsOH / EtOH, reflux d) MnO_2 / THF ; Zn, $BrCF_2CO_2Et$ / THF, rt, Y. 39% e) Lindlar / hexane, Y. 97%

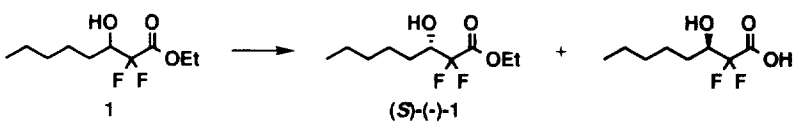


Table 1 Asymmetric hydrolysis of ethyl α,α-difluoro-β-hydroxyester (**1**)

Entry	Enzyme[a]	Method[b]	Time (hr)	Compound[c] (%)	Optical purity (% ee) [d]	*E* value
1	olipase/4S	A	11.0	40	55	18.0
2	olipase/4S	B	4.0	81	79	3.0
3	lipase AK	A	8.0	19	20	15.3
4	lipase AK	B	1.7	70	73	3.8
5	lipase AK	C	1.0	38	34	4.8

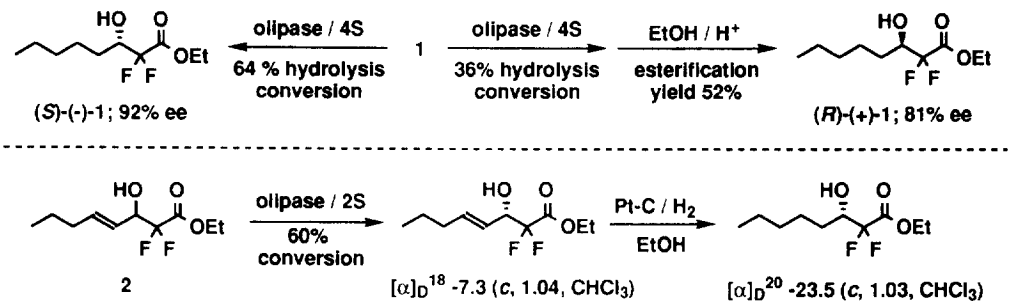
a) olipase/4S (*Rhizopus japonicus*), lipaseAK (*Pseudomonas fluorescens*) b) Method A: 0.1 *M* H_2O, 6000 unit / mmol, 30 °C; Method B: 0.1 *M* H_2O, 6000 unit / mmol, 30 °C, added 1 *N* NaOH to neutralize acid; Method C: 0.1 *M* KH_2PO_4-NaOH, pH 7.0 buffer, 6000unit / mmol, 30 °C c) Determined by ^{19}F NMR integral intensity. d) Optical purity determined by the diastereomeric excess of PPPA ester.

Table 2 Asymmetric hydrolysis of ethyl α,α-difluoro-β-hydroxyesters

Entry	Enzyme	Compound no	Time (hr)	Conversion (%)	Optical purity (% ee) a)	*E* value
1	lipase AK	**2**	0.5	39	21	2.3
2	lipase AK	**5**	2.0	54	12	1.4
3	lipase AK	**4**	1.0	61	61	4.0
4	olipase/2S	**2**	1.0	44	62	24.0
5	olipase/2S	**5**	14.0	13	8	3.6
6	olipase/2S	**4**	43.0	39	33	4.3

a) Enantiomeric excess (% ee) of recovered ethyl α,α-difluoro-β-hydroxyester

The results shown in Table 1 and 2 support that the entry 1 (Table 1) and 4 (Table 2) appear to be useful for preparing of enantiomerically enriched ethyl 2,2-difluoro-3-hydroxyoctanate (**1**). As shown in Figure 1, by controlling the extent of hydrolysis conversion, either product or unreacted substrate would be obtained with high enantioselectivity. Thus highly enantiomerically enriched ethyl 2,2-difluoro-3-hydroxyoctanate can be prepared by extension of the conversions, while reacted 2,2-difluoro-3-hydroxyoctanoic acid is obtained with high ee values by stopping the reactions at low conversions. Thus, enzymatic hydrolysis of ethyl 2,2-difluoro-3-hydroxyoctanate (**1**) (64% conversion) afforded (*S*)-(-)-(**1**) in 92% ee, while enzymatic hydrolysis of (**1**) (36% conversion) and the following recrystalization from diethyl ether-ethyl acetate afforded (*R*)-(+)-(**1**) in 81% ee. [12]



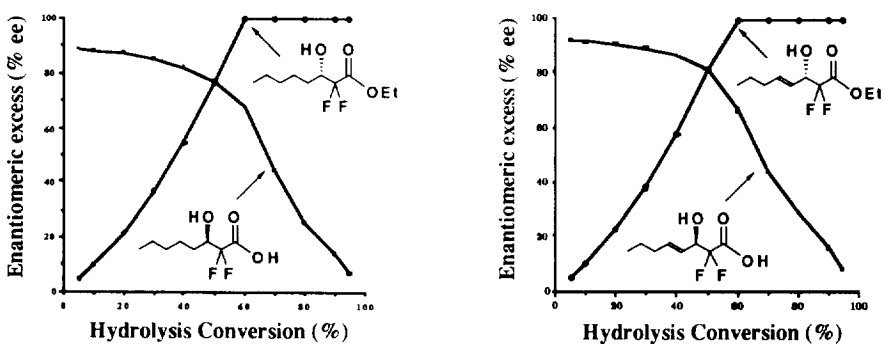
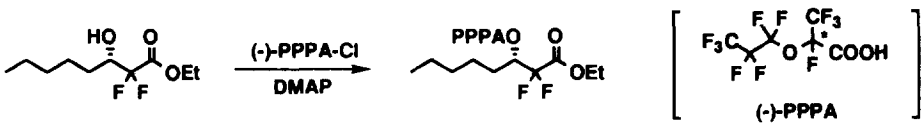


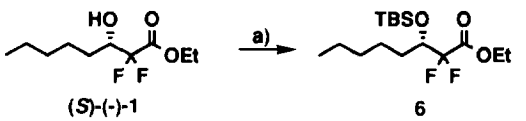
Figure 1 Dependence of enantiomeric excess on the hydrolysis conversion

The diastereomeric purity was determined by gas chromatography after conversion of the (*R*)-(+)- and (*S*)-(-)-ethyl 2,2-difluoro-3-hydroxyoctanate (**1**) to their diastereomeric ester by optically active PPPA (perfluoropropoxypropionic acid).[13]

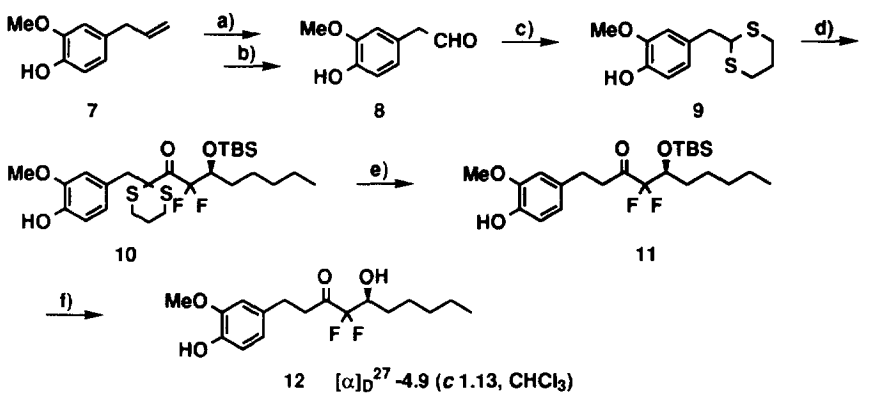


Total synthesis of difluorinated [6]-gingerol

Finally we developed the synthesis of optically active difluorogingerol starting with (*S*)-(-)-ethyl 2,2-difluoro-3-hydroxyoctanoate (**1**, 92% ee) and (*R*)-(+)-ethyl 2,2-difluoro-3-hydroxyoctanoate (**1**, 81% ee) (Scheme 3). Both enantiomers of ethyl 2,2-difluoro-3-hydroxyoctanoate were first protected with chloro *t*-butyldimethylsilyl and imidazole, giving silyl ether. On the other hand, unprotected eugenol was converted into the corresponding aldehyde by ozonolysis in MeOH-CH_2Cl_2 solution followed by reductive treatment with Me_2S. Thioacetal compound was derived from the aldehyde with 1,3-propyldithiol and borane trifluoride diethyl ether complex.[14] Gingerol skeleton was obtained by coupling of lithium thioacetal and silyl ether. Finally [6]-2,2-difluorogingerol was synthesized from coupling compound by carrying out reductive desulfidation with raney nickel followed by desilylation with tetrabutylammonium fluoride.



a) TBSCl, imidazole / DMF, rt; yield 95%



Scheme 3 ; a) O_3 / MeOH-CH_2Cl_2 (2 : 1), -78 °C b) Me_2S, rt; yield 86% (86%) c) $HS(CH_2)_3SH$, BF_3-OEt_2 / THF, 0 °C; yield 81% (81%) d) *n*-BuLi, 6 / THF, -78 °C; yield 65% (49%) e) Raney Ni / EtOH, reflux; yield 95% (49%) f) $Bu_4N^+F^-$ / THF, rt; yield 81% (80%) ; yield in parentheses is a case of enantiomer 12, $[\alpha]_D^{24}$ +4.4 (*c* 1.54, $CHCl_3$)

Experimental Section

General. Commercially available reagents were used without further purification. The zinc for Reformatsky-Type reaction was activated by washing with 3 *N* HCl, dist. water, dried ethanol and dried ether. NMR spectra were recorded at 200 MHz or 500 MHz for ^1H NMR (internal Me_4Si) and at 470 MHz for ^{19}F NMR {ppm from the internal C_6F_6 (-162.9 ppm)} at 50 MHz for ^{13}C NMR in $CDCl_3$. Yields were those of isolated products.

Ethyl 2,2-difluoro-3-hydroxyoctanoate (1). To a solution of caproaldehyde (2.40 mL, 20 mmol) and zinc (1.96 g) in freshly dried tetrahydrofuran (100 mL), ethyl bromodifluoroacetate (30 mmol) was added at room temperature. After 1 hr of stirring at that temperature, the mixture was quenched with 1 *N* HCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were

dried over $MgSO_4$, and the solvent was removed. The residual oil was purified by bulb-to-bulb distillation (5 mmHg, oil bath; 120 ℃) to give ethyl 2,2-difluoro-3-hydroxyoctanoate (**1**) (4.14 g, 18.5 mmol) in 93% yield; bp 103-106 ℃ (3 mmHg); ^{1}H NMR ($CDCl_3$): δ 0.90 (3 H, t, J = 7.08 Hz), 1.28-1.73 (11H, m), 1.37 (3H, t, J = 7.08 Hz), 2.01 (1H, br s), 3.97-4.08 (1H, m), 4.36 (2H, q, J = 7.08 Hz); ^{13}C NMR ($CDCl_3$): δ 13.93, 13.99, 22.52, 24.94, 29.17 (dd, J = 2.94, 1.72 Hz), 31.54, 63.11, 71.77 (dd, J = 27.09, 24.77 Hz), 114.85 (dd, J = 254.85, 252.40 Hz), 163.96 (dd J = 32.75, 30.80 Hz); ^{19}F NMR ($CDCl_3$): δ -123.55, -116.16 (ABX, J_{F-F} = 263.98, J_{F-H} = 15.26, J_{F-H} = 7.63 Hz); IR (neat): ν 3448 (OH), 1763 (C=O) cm^{-1} ; R_f = 0.28 (20% AcOEt-Hexane).

(*E*)-Ethyl 2,2-difluoro-3-hydroxyoctenoate (2). In the above reaction, (*E*)-2-hexenal and ethyl bromodifluoroacetate were used and worked-up similarly, giving (*E*)-ethyl 2,2-difluoro-3-hydroxyoctenoate (**2**); ^{1}H NMR ($CDCl_3$): δ 0.91 (3H, t, J = 7.32 Hz), 1.36 (3H, t, J = 7.08Hz), 1.43 (2H, sept, J = 7.33Hz), 2.08 (2H, q, J = 7.08Hz), 4.35 (2H, q, J = 7.08Hz), 4.47-4.56 (1H, m), 5.53 (1H, dd, J = 15.38, 7.08 Hz), 5.93 (1H, dtd, J = 15.38, 6.38, 0.97 Hz); ^{13}C NMR ($CDCl_3$): δ 13.33, 13.69, 21.72, 34.22, 62.92, 72.71 (dd, J = 27.30, 24.77 Hz), 113.99 (dd, J = 255.6, 252.9 Hz), 122.63 (dd, J = 3.75, 1.9 Hz), 138.26, 163.55 (dd, J = 32.35, 31.0 Hz); ^{19}F NMR ($CDCl_3$): δ -122.03, -116.52 (ABX, J_{F-F} = 262.5, J_{F-H} = 13.74, J_{F-H} = 7.63 Hz); IR (neat): ν 3457 (OH), 1757 (C=O) cm^{-1} ; R_f = 0.28 (20% AcOEt-Hexane).

Ethyl 2,2-difluoro-3-hydroxy-4-octynoate (4). To a solution of MnO_2 (60 g) in freshly dried tetrahydrofuran (100 mL), 2-hexynol (**3**) (105 mmol) was added at room temperature. After 4 hr of stirring, the reaction solution was filterated under argon atmosphere. On the other hand, to a solution of zinc (9.15 g) in freshly dried tetrahydrofuran (100 mL), ethyl bromodifluoroacetate (105 mmol) was added at room temperature. After 10 min. of stirring at that temperature and was added with the filtrate. After 30 min. of stirring, the mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 20% AcOEt-Hexane) to give Ethyl 2,2-difluoro-3-hydroxy-4-octynoate (**4**) (6.00 g, 27.3 mmol) in 39% yield; ^{1}H NMR ($CDCl_3$): δ 0.98 (3H, t, J = 7.54Hz), 1.37 (3H, t, J = 7.08Hz), 1.55 (2H, sept, J = 7.08Hz) , 2.22 (2H, td, J = 7.08, 1.95 Hz), 2.43 (1H, br s), 4.37 (2H, q, J = 7.08Hz), 4.75-4.82 (1H, m); ^{13}C NMR ($CDCl_3$): δ 13.35, 13.94, 20.62, 21.64, 63.31, 63.69 (t, J = 28.81Hz), 72.98 (dd, J = 4.45, 2.28 Hz), 89.84, 112.52 (dd, J = 257.05, 254.10 Hz), 162.78 (t, J = 30.75 Hz); ^{19}F NMR ($CDCl_3$): δ -120.12, -116.71 (ABX, J_{F-F} = 261.0, J_{F-H} = 12.23, J_{F-H} = 7.99 Hz); IR (neat): ν 3483 (OH), 1766 (C=O) cm^{-1} ; R_f = 0.26 (20% AcOEt-Hexane).

(*Z*)-Ethyl 2,2-difluoro-3-hydroxy-4-octenoate (5). To a solution of ethyl 2,2-difluoro-3-hydroxy-4-octynoate (**4**) (1.41 g, 6.41mmol) and Lindlar catalyst (64 mg) in hexane (80 mL) was added, and the whole was stirred for 30 min. at room temperature under hydrogen. The precipitate was filtrated and then the solvent was removed. The residual oil was purified by column chromatography (silica gel, 20% AcOEt-Hexane) to give (Z)-ethyl 2,2-difluoro-3-hydroxy-4-octenoate (**5**) (1.38 g, 6.21 mmol) in 97% yield; ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t,J = 7.33 Hz), 1.37 (3H, t,J = 7.08 Hz), 1.43 (2H, sept.d, J = 7.56,1.46Hz), 2.03-2.20 (3H, m), 4.36 (2H, q, J = 7.08Hz), 4.82-4.92 (1H, m), 5.45-5.51 (1H, m), 5.82-5.89 (1H, m); ^{13}C NMR ($CDCl_3$): δ 13.70, 13.84, 22.46, 30.03, 63.14, 67.83 (dd, J = 28.11, 24.72 Hz), 114.21 (dd, J = 255.7, 253 Hz), 122.06 (dd, J = 4.05, 1.75 Hz), 139.01, 163.61 (dd, J = 32.3, 30.8 Hz); ^{19}F NMR ($CDCl_3$): δ -122.44, -116.52 (ABX. J_{F-F} = 262.5, J_{F-H} = 13.73, J_{F-H} = 9.15 Hz); IR (neat): ν 3452 (-OH), 1759 (C=O) cm^{-1} ; R_f = 0.28 (20% AcOEt-Hexane).

(*S*)-(-)-Ethyl 2,2-difluoro-3-(*t*-butyldimethylsilyloxy)octanoate (6). To a solution of (*S*)-(-)-ethyl 2,2-difluoro-3-hydroxyoctanoate (**1**) (975 mg, 4.35 mmol){$[\alpha]_D^{30}$ -21.3 (*c* 1.10, $CHCl_3$); 92% ee} in anhydrous *N*,*N*-dimethylformamide (2 mL), imidazole (355 mg, 5.22 mmol) and *t*-butyldimethylsilyl chloride (787 mg, 5.22 mmol) was added at room temperature under argon atmosphere. After 2 days of stirring at room temperature, the mixture was quenched with saturated $NaHCO_3$, and then diluted with hexane. The organic layer was separated and the aqueous layer was extracted with hexane. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 5% AcOEt-Hexane) to give ether (**6**) (1.39g, 4.11 mmol) in 95% yield; $[\alpha]_D^{28}$ -6.9 (*c* 1.14, $CHCl_3$); 92%

ee; ^{1}H NMR ($CDCl_3$): δ 0.08-0.09 (6H, m), 0.87-0.91 (12H, m), 1.24-1.70 (11H, m), 1.35 (3H, t, *J* = 7.08 Hz), 3.98-4.06 (1H, m), 4.26-4.36 (2H, m); ^{13}C NMR ($CDCl_3$): δ -4.82 (t, *J* = 1.62 Hz), -4.57, 13.96, 13.99, 18.14, 22.51, 25.06, 25.71, 31.24 (t, *J* = 2.63 Hz), 31.78, 62.61, 73.04 (t, *J* = 25.68 Hz), 115.39 (t, *J* = 254.20 Hz), 163.75 (t, *J* = 31.85 Hz); ^{19}F NMR ($CDCl_3$): δ -116.99, -114.27 (ABX, J_{F-F} = 254.83, J_{F-H} = 12.21, J_{F-H} = 9.15 Hz); IR (neat): ν 1775, 1762 (C=O) cm^{-1} ; R_f = 0.72 (20% AcOEt-Hexane).

(*R*)-(+)-Ethyl 2,2-difluoro-3-(*t*-butyldimethylsilyloxy)octanoate (6). In the above reaction, (*R*)-(+)-ethyl 2,2-difluoro-3-hydroxyoctanoate (**1**) {$[\alpha]_D^{26}$ +19.5 (*c* 0.98, $CHCl_3$); 81% ee} was used, and worked up similarly, giving (*R*)-(+)-Ethyl 2,2-difluoro-3-(*t*-butyldimethylsilyloxy)octanoate (**6**), {$[\alpha]_D^{26}$ +6.0 (*c* 1.18, $CHCl_3$)}.

(4-Hydroxy-3-methoxyphenyl)ethanal (8). Into a solution of eugenol (5 g, 30.5 mmol) and catalytic amount of $NaHCO_3$ in methanol-dichloromethane (1:2, 200 mL), ozone gas was bubbled at -78 ℃. After 1.5 hr of stirring at that temperature, the mixture was quenched with dimethylsulfide (22.4 mL, 305 mmol). The whole was warmed to room temperature, and the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 50% AcOEt-Hexane) to give aldehyde (**7**) (4.36 g, 26.2 mmol) in 86% yield; ^{1}H NMR ($CDCl_3$): δ 3.61 (2H, d, *J* = 2.44 Hz), 3.89 (3H, s), 5.62 (1H, s), 6.69 (1H, d, *J* = 1.96 Hz), 6.71-6,74 (1H, m), 6.91 (1H, d, *J* = 8.06 Hz), 9.72 (1H, t, *J* = 2.44 Hz); ^{13}C NMR ($CDCl_3$): δ 50.08, 55.90, 112.15, 114.97, 122.50, 123.41, 145.04, 147.02, 200.03 ; IR (neat): ν 3427 (OH), 1721 (C=O) cm^{-1} ; R_f = 0.24 (40% AcOEt-Hexane).

(4-Hydroxy-3-methoxyphenyl)ethylaldehyde propanedithioacetal (9). To a solution of aldehyde (**8**) (3.65 g, 22.0 mmol) in anhydrous dichloromethane (200 mL), 1,3-propanedithiol (6.63 mL, 66.0 mmol) and boron trifluoride etherate was added at room temperature under argon atmosphere. After 1.5 hr of stirring at that temperature, the mixture was quenched with saturated NaOH aq. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 30% AcOEt-Hexane) to give thioacetal (**9**) (4.60 g, 17.9 mmol) in 81% yield; mp 96.5-99.6 ℃ (recrystalization, AcOEt-Hexane); ^{1}H NMR ($CDCl_3$): δ 1.85 (1H, dtt, *J* = 14.16, 10.99, 4.15 Hz), 2.11 (1H, dtt, *J* = 14.16, 4.15, 2.93 Hz), 2.78-2.89 (4H, m), 2.95 (2H, d, *J* = 7.32 Hz), 3.89 (1H, s), 4.21 (1H, t, *J* = 7.32 Hz), 5.53 (1H, s) , 6.73-6.77 (2H, m), 6.84-6.87 (1H, m); ^{13}C NMR ($CDCl_3$): δ 25.73, 30.50, 41.48, 48.91, 55.85, 111.56, 114.20, 121.96, 129.07, 144.55, 146.25; IR (neat): ν 3422 (OH), 1603 (C=O) cm^{-1} ; R_f = 0.67 (50% AcOEt-Hexane).

(*S*)-(+)-[6]-2,2-Difluoro-4,4-(1,3-propanedithioacetyl)gingerol-*t*-butyldimethylsilylether (10).. To a solution of thioacetal (**9**) (300 mg, 1.17 mmol) in freshly dried tetrahydrofuran (5 mL), *n*-BuLi (2.5 *M* in hexane, 1.03 mL, 2.57 mmol) was dropwise at 0 ℃ under argon atmosphere. After 30 min of stirring at 0 ℃, ether (**6**) (396 mg, 1.17 mmol) in fleshly dried tetrahydrofuran (5 mL) was added to the solution at -78 ℃. After 1 hr of stirring at that temperature, the mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 20% AcOEt-Hexane) to give thioacetal (**10**) (420 mg, 0.765 mmol) in 65% yield; $[\alpha]_D^{28}$ +32.6 (c 1.15, $CHCl_3$); 92% ee; ^{1}H NMR ($CDCl_3$): δ 0.11 (3H, s), 0.12 (3H, s), 0.86-0.92 (12H, m), 1.24-1.60 (8H, m), 1.67 (1H, qt, *J* = 12.94, 3.41 Hz), 1.91-1.98 (1H, m), 2.55-2.67 (2H, m), 2.80 (1H, ddd, *J* = 14.89, 12.69, 2.44 Hz), 3.13 (1H ddd , *J* = 15.87, 13.91, 2.68 Hz), 3.24 (1H, d, *J* = 14.90 Hz), 3.47 (1H, d, *J* = 14.90 Hz), 3.89 (3H, s), 4.25-4.34 (1H, m), 5.56 (1H, s), 6.85 (2H, d, *J* = 0.73 Hz), 6.89 (1H, s); ^{13}C NMR ($CDCl_3$): δ -4.81, -4.07 (t *J* = 1.37 Hz), 14.01, 14.21, 18.25, 22.49, 23.38, 25.01 (t, *J* = 1.57 Hz), 25.90, 27.72, 28.12, 31.38 (t, *J* = 2.53 Hz), 31.89, 40.85 (t, *J* = 5.36 Hz), 55.90, 60.41 (t, *J* = 2.63 Hz), 72.78 (t, *J* = 24.37 Hz), 113.64, 113.77, 118.66 (t, *J* = 262.40 Hz), 124.18, 125.62, 145.09, 145.89, 191.69 (t, *J* = 25.50 Hz); ^{19}F NMR ($CDCl_3$): δ -108.32, -107.41 (ABX, J_{F-F} = 268.56, J_{F-H} = 10.68, J_{F-H} = 10.68 Hz); IR (neat): ν 3551 (OH) , 1739 (C=O) cm^{-1} ; R_f = 0.30 (20% AcOEt-Hexane).

(*R*)-(-)-[6]-2,2-Difluoro-4,4-(1,3-propanedithioacetyl)gingerol-*t*-butyldimethylsilylether (10). In the above reaction, (*R*)-(+)-ether (**6**) was used, giving (*R*)-(-)-(**10**), $[\alpha]_D^{19}$ -26.8 (*c* 0.82, $CHCl_3$).

(*S*)-(-)-[6]-2,2-Difluorogingerol-*t*-butyldimethylsilylether (11). To a solution of thioacetal (**10**) (390 mg, 0.711 mmol), excess of Raney Ni (W-2) in anhydrous ethanol (10 mL) was added under argon atmosphere. After the solution was stirred for 2 days at 80 ℃, the precipitates was filtered, and then the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 20% AcOEt-Hexane) to give ether (**11**) (13.1 g, 36.0 mmol) in 95% yield; $[\alpha]_D^{28}$ -14.7 (*c* 1.08, $CHCl_3$); 92% ee; ^1H NMR ($CDCl_3$): δ 0.07 (3H, s), 0.09 (3H, s), 0.86-0.90 (12H, m), 1.17-1.35 (4H, m), 1.37-1.48 (2H, m), 1.51-1.62 (2H, m), 2.79-2.90 (2H, m), 2.92-3.07 (2H, m), 3.87 (3H, s), 3.97-4.05 (1H, m), 5.47 (1H, s), 6.66-6.69 (2H, m), 6.82 (1H, d, *J* = 8.06 Hz); ^{13}C NMR ($CDCl_3$): δ -4.72, -4.62 (d, *J* = 1.97 Hz), 1.98, 18.12, 22.45, 25.01 (t, *J* = 1.32 Hz), 25.79, 28.21, 31.37 (t, *J* = 2.37 Hz), 41.07, 55.81, 60.44, 72.68 (t, *J* = 26.29 Hz), 111.06, 114.48, 116.73 (dd, *J* = 257.50, 254.95 Hz), 120.92, 132.24, 144.13, 146.52, 201.30 (dd, *J* = 29.65, 28.25 Hz); ^{19}F NMR ($CDCl_3$): δ -119.45, -114.43 (ABX, $J_{F\text{-}F}$ = 257.88, $J_{F\text{-}H}$ = 12.21, $J_{F\text{-}H}$ = 10.68 Hz); IR (neat): ν 3554 (OH) , 1742 (C=O) cm^{-1} ; R_f = 0.44 (20% AcOEt-Hexane).

(*R*)-(+)-[6]-2,2-Difluorogingerol-*t*-butyldimethylsilylether (11). In the above reaction, (*R*)-(-)-(**10**), $[\alpha]_D^{19}$ -26.8 (*c* 0.82, $CHCl_3$) was used, giving (+)-(**11**), $[\alpha]_D^{24}$ +14.1 (*c* 1.13, $CHCl_3$).

(*S*)-(-)-[6]-2,2-Difluorogingerol (12). To a solution of ether (**11**) (275 mg, 0.618 mmol) in anhydrous tetrahydrofuran (4 mL), tetrabutylammonium fluoride (1.0 *M*, 0.742 mL, 0.742 mmol) was added under argon atmosphere. After 30 min of stirring at room temperature, the mixture was quenched with water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 30% AcOEt-Hexane) to give difluorogingerol (**12**) (165 mg, 0.499 mmol) in 81% yield; $[\alpha]_D^{27}$ -4.9 (c 1.13, $CHCl_3$); 92% ee; ^1H NMR ($CDCl_3$): δ 0.86 (3H, t, *J* = 7.08 Hz), 1.25-1.65 (8H, m), 2.01 (1H, d, *J* = 6.60 Hz), 2.88 (2H, t, *J* = 7.33 Hz), 3.02 (2H, d, *J* = 7.33 Hz), 3.88 (3H, s), 3.96-4.06 (1H, m), 5.49 (1H, s), 6.67-6.71 (2H, m), 6.83 (1H, d, *J* = 7.82 Hz); ^{13}C NMR ($CDCl_3$): δ 13.93, 22.48, 24.90, 28.17, 28.99 (dd, *J* = 2.98, 1.87 Hz), 31.46, 39.91, 55.88, 71.10, (dd, *J* = 27.55, 24.82 Hz), 111.06, 114.46, 115.76 (dd, *J* = 258.10, 254.10 Hz), 120.87, 132.13, 144.02, 146.51, 201.68 (dd, *J* = 31.30, 28.20 Hz); ^{19}F NMR ($CDCl_3$): δ -126.06, -115.42 (ABX, $J_{F\text{-}F}$ = 274.67, $J_{F\text{-}H}$ = 16.78, $J_{F\text{-}H}$ = 6.11 Hz); IR (neat): ν 3457 (OH), 1740 (C=O) cm^{-1} ; HRMS, calc.330.1641, obs.330.1637 ; R_f = 0.17 (20% AcOEt-Hexane).

(*R*)-(+)-[6]-2,2-Difluorogingerol (12). In the above reaction, (*R*)-(+)-(**11**), $[\alpha]_D^{24}$ +14.1 (*c* 1.13, $CHCl_3$) was used, giving (*R*)-(+)-[6]-2,2-Difluorogingerol (**12**), $[\alpha]_D^{24}$ +4.4 (*c* 1.54, $CHCl_3$).

Enzymatic resolution of Ethyl 2,2-difluoro-3-hydroxyoctanoate (1) *General procedure.*

Method **A**: To a solution of alcohol (**1**) (224 mg, 1 mmol) and lipase (6000 unit / mmol) in 20 mL water at 30 ℃. After the solution was stirred overnight, the mixture was quenched with 1 *N* HCl. The enzyme was filtrated on celite, and oily materials were extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. Hydrolysis conversion was determined by ^{19}F NMR integral intensity. The residual oil was diluted with diethyl ether, and was alkalized with saturated $NaHCO_3$ aq. The organic layer was separated and dried over $MgSO_4$. On removal of the solvent, the residual oil was purified by bulb-to-bulb distillation (5 mmHg, oil bath; 120 ℃) to give alcohol (**1**).

The aqueous layer was acidified with 1 *N* HCl, and extracted with diethyl ether. The organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*, giving 2,2-difluoro-3-hydroxyoctanoic acid.

Method **B**: To a solution of alcohol (**1**) (224 mg, 1 mmol) and lipase (6000 unit / mmol) in 20 mL water at 30 ℃. After the solution was stirred and added 1 *N* NaOH (1.0 mL) to keep neutral pH. When all amount of 1 *N* NaOH was added, the reaction was quenched with 1 *N* HCl, and then worked-up similarly.

Method **C**: To a solution of alcohol (**1**) (224 mg, 1 mmol) and lipase (6000 unit / mmol) in 20 mL buffer at 30 ℃. After the solution was stirred overnight, the mixture was quenched with 1*N* HCl, and then worked-up similarly.

Esterification. After a solution of 2,2-difluoro-3-hydroxyoctanoic acid (m.p. 106-109℃) and catalytic amount of *p*-toluenesulfonate in ethanol (10 mL) was stirred for 2 hr at 80 ℃, the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 20% AcOEt-Hexane), and purified by bulb-

to-bulb distillation (5 mmHg, oil bath; 120 ℃) to give (*R*)-(+)-alcohol (**1**), $[\alpha]_D^{26}$ +19.5 (*c* 0.98 $CHCl_3$), 81% ee.

Enzymatic resolution of Ethyl 2,2-difluoro-3-hydroxy-4-octenoate (2) - To a solution of ethyl 2,2-difluoro-3-hydroxy-4-octenoate (**2**) (1.11 g, 5 mmol) and lipase/2S (6000 unit / mmol) in 500 mL water at 30 ℃. After 10 hr of stirring, the mixture was quenched with 1 *N* HCl. The enzyme was filtrated on celite, and oily materials were extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. Hydrolysis conversion (60%) was determined by ^{19}F NMR integral intensity. The residual oil was diluted with diethyl ether, and alkalized with saturated $NaHCO_3$ aq. The organic layer was separated and dried over $MgSO_4$. On removal of the solvent, the residual oil was purified by column chromatogrphy to give ethyl 2,2-difluoro-3-hydroxy-4-octenoate (**2**), $[\alpha]_D^{18}$ -7.3 (*c* 1.04, $CHCl_3$) in 33% yield. The aqueous layer was acidified with 1 *N* HCl, and extracted with diethyl ether. The organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*, giving 2,2-difluoro-3-hydroxy-4-octenoic acid.

Reduction of Ethyl 2,2-difluoro-3-hydroxy-4-octenoate (2) - Into a steel vessel, a solution of ethyl 2,2-difluoro-3-hydroxy-4-octenoate (**2**), $[\alpha]_D^{18}$ -7.3 (*c* 1.04, $CHCl_3$), and 10% Pt-C (cat.) in ethanol (40 mL) was added, and the the whole was stirred for 2 days at room temperature under hydrogen (10 atm). The precipitate was filtrated and then the solvent was removed. The residual oil was purified by column chromatography to give ethyl 2,2-difluoro-3-hydroxyoctanoate (**1**), $[\alpha]_D^{20}$ -23.5 (*c* 1.03, $CHCl_3$) in 95% yield.

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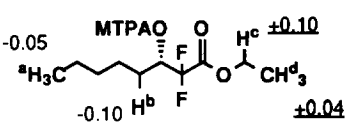
(12) The absolute configuration were determined by modified Mosher's method. ^1H NMR chemical shifts in $CDCl_3$ of the selected protons after converting (-)-(**1**) to the corresponding MTPA esters: (S)-MTPA ester, δ 0.83 (a), 1.32 (b), 1.70 (c), 4.30 (d), (R)-MTPA ester, δ 0.88, 1.28, 1.80, 4.20. Numbers in the drawing represents Δδ values. See, Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.



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