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Preparation and Use of Novel (*S*)-β-Chlorodifluoromethyl-β-propiolactone as a Chiral Fluorinated Building Block

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Abstract: Novel chiral fluorinated building block, (*S*)-β-chlorodifluoromethyl-β-propiolactone with up to >99% ee was prepared using the Lewis acid catalyzed [2+2]cycloaddition of ketene with chlorodifluoroacetaldehyde followed by enzymatic resolution with a lipase. The lactone thus obtained readily underwent the Friedel-Crafts type acylation with aromatic compounds in the presence of a Lewis acid to afford the corresponding chiral β-hydroxy aryl ketones in good yields.

INTRODUCTION

β-lactones have not been only synthetic targets in natural products that exhibit biological activity[1] but also widely used as key synthetic intermediates to afford a variety of tetrahydrofurans,[2] γ-lactones,[3] and unnatural amino acids.[4] In contrast to γ- or δ-lactone, the high ring-strain of β-lactone shows an increased and different reactivity, which is demonstrated in decarboxylation[5] and Lewis acid promoted rearrangement.[6] We have previously observed efficient ring-opening reactions of β-alkyl-β-propiolactones with various alkyl metallic reagents involving the cleavage of a carbon-oxygen bond,[7] and recently reported the Lewis acid promoted acylation of aromatic compounds with chiral β-trichloromethyl-β-propiolactone as an acylating reagent which underwent an acyl-oxygen bond cleavage to give optically active 1-aryl-3-hydroxy-4,4,4-trichroro-1-butanones in good yields, making a strong contrast to simple β-alkyl-β-propiolactones.[8]

There have been current interests in the synthesis of organofluorine compounds in connection with imparted biological activities.[9] The unique properties of fluorine atoms on the activity have been applied to the fluorinated analogous of various types of compounds such as amino acids,[10] vitamin D_3,[11] nucleotides,[12] prostagrandines,[13] fatty acids,[14] and insect pheromones.[15] Furthermore, such interesting properties of fluorines were also found in the fields of liquid crystals.[16] In this paper, we would like to report an efficient synthetic method for a novel chiral β-lactone derivative having a chlorodifluoromethyl group in high enantiomeric purity using Lewis acid catalyzed [2+2]cycloaddition of ketene with chlorodifluoroacetaldehyde followed by lipase-catalyzed kinetic resolution of a racemic β-lactone. The reaction of β-chlorodifluoromethyl-β-propiolactone as a useful chiral synthon was further demonstrated by the Friedel-Crafts type reaction with aromatic compounds, affording the corresponding acylated products in good yields.

RESULTS AND DISCUSSIONS

Synthesis of a racemic β-lactone derivative possessing a chlorodifluoromethyl group was carried out using [2+2]cycloaddition of chlorodifluoroacetaldehyde **1** with ketene **2**[17] in the presence of an appropriate

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Lewis acid. Usual cycloaddition of ketene with unactivated carbonyl compounds such as acetaldehyde proceeds in good yields in the presence of a Lewis acid catalyst such as boron trifluoride diethyl etherate.[18] Cycloaddition of ketene with an activated aldehyde possessing an electron-withdrawing chlorodifluoromethyl group gave good results using weaker Lewis acids such as zinc iodide. Table 1 shows the effects of various Lewis acids on the [2+2]cycloaddition. The use of 1.0 equivalent of Lewis acid, *e.g.*, zinc iodide or magnesium bromide diethyl etherate in diethyl ether-dichloromethane, gave β-lactone 3 in reasonable yields (entries 1-4). On the other hand, the use of relatively strong Lewis acids such as aluminum chloride, aluminum bromide, and boron trifluoride diethyl etherate, resulted in decrease in product yields (entries 5-8), maybe due to the Lewis acid catalyzed polymerization of the produced lactone.[19] Furthermore, the use of protic acids such as *p*-toluenesulfonic acid monohydrate resulted in poor yield of the cycloaddition product (entry 9).

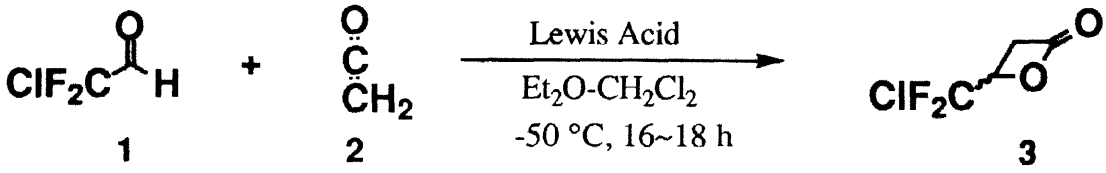

Table 1. Synthesis of β-Chlorodifluoromethyl-β-propiolactone 3 Promoted by Various Acids

Entry	Acid	equiv.	Yield (%)[a]
1	ZnI_2	0.1	55
2	ZnI_2	0.47	60
3	ZnI_2	1.0	67
4	$MgBr_2$•OEt_2	1.0	57
5	BF_3•OEt2	1.0	49
6	$AlCl_3$	1.0	42
7	$AlBr_3$	1.0	47
8	$EtAlCl_2$	1.0	40
9	PTS•H_2O	1.0	24

a) Yield determined by GC using *n*-decane as an internal standard.

In order to obtain β-chlorodifluoromethyl-β-propiolactone 3 in enantiomerically pure form, we attempted to synthesize a chiral β-propiolactone 3 by [2+2]cycloadditon between ketene and chlorodifluoroacetaldehyde using a chiral alkaloid, such as quinidine as a chiral catalyst according to the Wynberg's method.[20] This method, however, did not meet with satisfactory results, and β–propiolactone with poor enantiomeric excess (56%ee) was obtained in low yield (3%). Although other asymmetric [2+2] cycloadditions of ketene with aldehyde catalyzed by chiral Lewis acid have been investigated by a few groups, only moderate levels of optical yields have been attained. For example, the reaction of ketene with aldehyde catalyzed by bissulfonamide-trialkylaluminum complexes[21a] or 1,1'-binaphthalene-2,2'-diol derivatives[21b] yields optically active β-lactones in 56% ee or 74% ee, respectively. In the case of reaction with trimethylsilylketene and aldehyde catalyzed by methylaluminoimidazolines, the enantiomeric excess varies from 30 to 83% ee, depending on the structure of aldehydes.[21c] Consequently, we searched for alternative methods to prepare optically active β-lactone. High enantiomeric purity of β-lactones has been recently obtained in the enzymatic kinetic resolution of racemic β-alkyl-[22] and α-methylene-β-lactone[23] catalyzed by several lipases. Thus the lipase-catalyzed kinetic resolution was next examined. Firstly, we choosed lipase PS (*Pseudomonas* sp. lipase, Amano Pharmaceutical Co.), and the enzymatic kinetic resolution of racemic β–propiolactone 3 was conducted with 0.8 equivalent of alcohol in organic solvents at 30°C. The results are

summarized in Table 2.

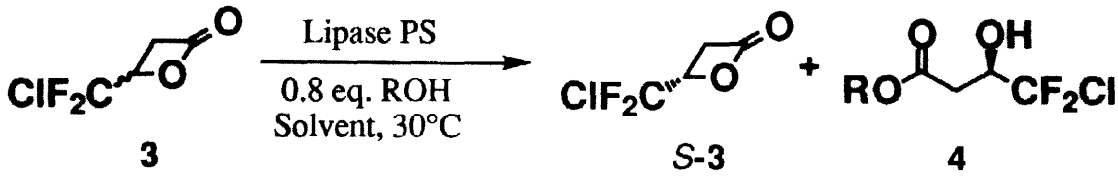

Table 2. Kinetic Resolution of β-Chlorodifluoromethyl-β-propiolactone with Various Alcohols in the presence of Lipase PS[a)]

Entry	ROH	Solvent	Time (h)	Conv.[b)] (%)	Lactone Yield (%)[c)]	Lactone ee (%)[d)]	Ester Yield (%)[c)]	Ester ee (%)[d)]	E[f)]
1	BuOH	Hexane	476	46	52	64	18	75	13
2	BuOH	THF	239	53	30	73	40	66	10
3	EtOH	Et_2O	43	53	43	97	40	81	38
4	BuOH	Et_2O	39	51	26[e)]	89	29	84	35
5	HexOH	Et_2O	69	58	39	99.9	36	73	46

a) Lipase PS (Amano) b) Calculated from c = ee(lactone)/[ee(lactone)+ee(ester)]. c) Yield determined by GC using *n*-decane as an internal standard. d) Optical purity determined by GC equipped with Chiral Dex G-TA or HPLC equipped with Chiralcel OJ. e) Isolated yield f) Calculated from E = ln{1-c[1+ee(ester)]}/ln{1-c[1-ee(ester)]}. [24]

The resolution of β-alkyl-β-lactone has been reported to need long reaction times, and the kinetic resolution using benzyl alcohol and porcine pancreas lipase (PPL) in acetone at 35 °C took place for 6 days to give the unchanged lactone (96% ee) and the ester (85% ee).[22] In the present case screening of the solvent and the alcohol using lipase PS at 30 °C indicated that the combined use of diethyl ether and 1-hexanol (entry 5) was more effective than that of alcohols such as ethanol and 1-butanol (entry 3, 4). Use of tetrahydrofuran and hexane exhibited the reduced activity even for prolonged reaction times (entry 1, 2). Under the conditions using diethyl ether and 1-hexanol at 30 °C, examination into the enzyme revealed that Novozyme 435 (immobilized lipase from *Candida antarctica*, Novo Nordisk Co.) was the most efficient biocatalyst for the resolution of β-chlorodifluoromethyl-β-propiolactone **3**, in which the reaction gave (*S*)-β-lactone **3** in 27% yield with 99.9% ee and the ring-opened (*R*)-β-hydroxy ester **4** (R = hexyl) in 20% yield with 82% ee, respectively (E = 74). The absolute configuration of the transformed β-hydroxy ester **4** (R = ethyl) showing the specific rotation of $[\alpha]_D^{23}$ = +13.9 (c 1.00, $CHCl_3$) was determined by comparison with that of the known derivative.[25] Thus the β-hydroxy ester **4** (R = ethyl) was determined to be (*R*)-configuration, and the remaining β-propiolactone **3** to be (*S*)-configuration.

To demonstrate the usefulness of β-chlorodifluoromethyl-β-propiolactone (*S*)-**3** as a chiral building block, acylation of aromatic compounds in the presence of Lewis acid was examined. The reaction using anisole as the aromatic compound and racemic β-chlorodifluoromethyl-β-propiolactone **3** was examined as a model reaction in the following manner: A solution of 3 eq. of Lewis acid in anisole was stirred for 30 min at -30 °C. To it was added a solution of racemic β-chlorodifluoromethyl-β-propiolactone **3** in anisole at -30 °C, and the mixture was warmed up to 0 °C for 1 h. After usual work up, the crude product was purified by silica gel column chromatography to afford 4-chloro-4,4-difluoro-3-hydroxy-1-(4-methoxyphenyl)-1-butanone and its *ortho* isomer.

The effect of Lewis acid was examined. In the case of aluminum chloride as a Lewis acid in anisole, the corresponding **5b** was obtained in good yield (78 %, *p* : *o* = 71 : 29), whereas the use of ethylaluminum dichloride provided **5b** in moderated yield (68 %, *p* : *o* = 83 : 17). The use of much weaker Lewis acid of diethylaluminum chloride gave the acylated product in poor yield (20 %) even for the prolonged reaction time

of 24 h. However, *p*-, *o*-regioselectivity of the acylated product was improved under these conditions, and the ratio of regioisomers showed an excellent *p*-selectivity (*p* : *o* = 95 : 5). Yields of acylation using the fluorinated lactone 3, however, were lower than those by the reaction of β-trichloromethyl-β-propiolactone.[8] In each case, regioselectivity was determined by ^{1}H-NMR spectrometry.

Various substituted benzene derivatives such as *m*-xylene, mesitylene, and β-methoxynaphthalene in the presence of aluminum trichloride could be subjected to the reaction with (*S*)-β-lactone, and the acylated products **5d**, **5e**, **5f** and **5g** were obtained as single regioisomers in good yields shown in Table 3. All products were confirmed to retain the configuration of the starting β-lactone by HPLC analysis.

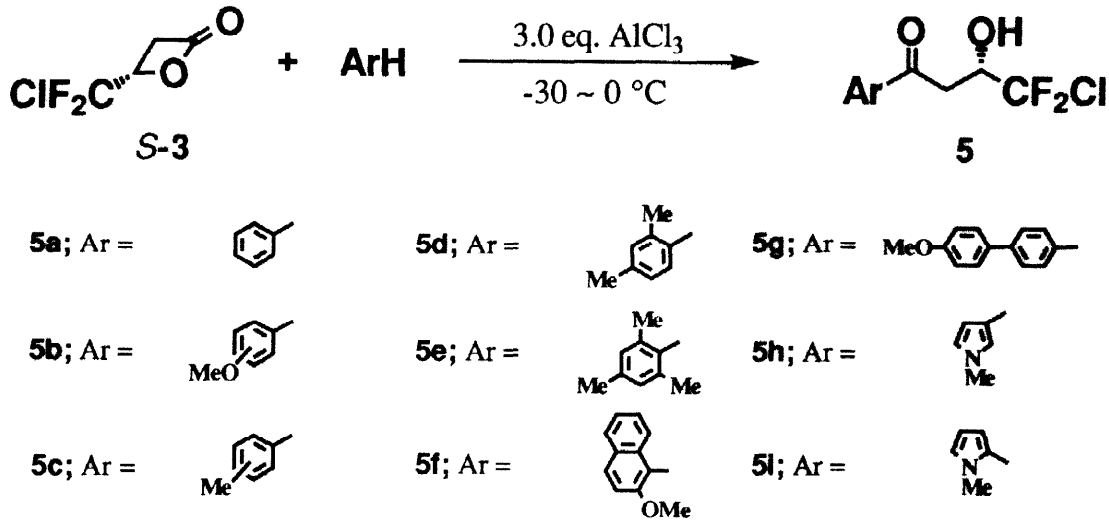

Table 3. Aromatic Acylations of Chiral β-Lactone *S*-3 with Various Aromatic Compounds

Entry	Time(h)	Product	Yield (%)	$[\alpha]_D^{23}$ in $CHCl_3$
1[a)]	2	**5a**	71	-18.8 (c 0.46)
2	1	**5b**[b)]	78	-18.1 (c 0.54)[d)]
3	1	**5c**[c)]	42	-21.2 (c 0.067)[d)]
4	1	**5d**	78	-20.3 (c 0.086)
5	1	**5e**	78	-8.8 (c 0.47)
6	1	**5f**	48	+8.8 (c 0.56)
7	1	**5g**	70	-9.0 (c 0.66)
8	1	**5h**	67	-35.3 (c 0.13)
		5i	11	-40.9 (c 0.067)

a) $EtAlCl_2$ was 3 eq. b) *p*-:*o*- = 71 : 29. c) *p*-:*o*- = 89 : 11. d) Optical rotation was measured as the mixture of regioisomers.

In summary, this paper describes an efficient method for the preparation of chiral novel β-chlorodifluoromethyl-β-propiolactone, which was synthesized by the [2+2]cycloaddition of chlorodifluoroacetaldehyde with ketene in the presence of Lewis acid as a catalyst followed by lipase-catalyzed resolution. Easily available chiral β-chlorodifluoromethyl-β-propiolactone is very important as a useful chiral building block as demonstrated by acylation of aromatic compounds to give the corresponding chiral acylated β-hydroxycarbonyl derivatives **5** having the expected stereochemistry, which retains completely the stereochemical integrity of the starting β-chlorodifluoromethyl-β-propiolactone in good yields.

EXPERIMENTAL SECTION

General Comments Gas-liquid phase chromatography (GLC) was performed using a Shimadzu GC-17A. ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained using JEOL JNM-EX270 and JEOL JNM-AL300 spectrometers. For ^{1}H NMR TMS at 0 ppm, for ^{13}C NMR $CDCl_3$ at 77.00 ppm center line, and for ^{19}F NMR C_6F_6 at -162.9 ppm served as internal standards unless otherwise stated. High performance liquid chromatography (HPLC) was carried out on a Shimadzu LC-10 System using a Daicel Chiralcel OJ column. Infrared spectra (IR) were recorded on a Nicolet Magna-IR spectrometer. Mass spectra were recorded on a JEOL JMS-DX 303HF spectrometer. Optical rotations were measured with a Horiba SEPA-200 polarimeter. All the melting points were uncorrected. All the chemicals were purchased from Nacalai Tesque, Inc., Aldrich Chemical Co. Inc., or Tokyo Kasei Kogyo, Co., Ltd. Dichloromethane was distilled over calcium hydride under nitrogen atmosphere and stored over molecular sieves 4A. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone ketyl radical before use. Purification of products was performed by column chromatography on silica gel (Merck Silica Gel-9385).

Representative Procedure for the Synthesis of Racemic β-Chlorodifluoromethyl-β-propiolactone (3): A solution of chlorodifluoroacetaldehyde[26] (1.67 g, 14.6 mmol) derived from chlorodifluoroacetic acid in dichloromethane (50 ml) was cooled to -50 °C. Ketene generated by pyrolysis of diketene[15] was bubbled to the solution during ca. 2 h. Simultaneously, a solution of anhydrous zinc iodide (4.67 g, 14.6 mmol) in diethyl ether (10 ml) was added dropwise during 1 h, and the resulting solution was stirred for 17 h at -50 °C. The reaction mixture was warmed to room temperature and poured into 10% aqueous $NaHCO_3$ solution. Aqueous layer was extracted with diethyl ether. The combined ethereal solutions were washed with 1 M HCl, and dried over anhydrous $MgSO_4$. Removal of the $MgSO_4$ and evaporation of the solvent gave a crude product. The mixture was purified by short silica gel column chromatography (eluting with diethyl ether : hexane) to give a pale yellow oil. 67% (Yield determined by GC using *n*-decane as an internal standard). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.85~4.75 (1H, m), 3.75 (1H, dd, J = 6.1 and 16.9 Hz), 3.58 (1H, dd, J = 4.0 and 16.9 Hz). ^{13}C-NMR (75.45 MHz, $CDCl_3$) δ 163.7, 129.4, 125.5, 121.6, 69.5, 69.0, 68.6, 41,2. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -69.19 (dd, J = 169.2 and 705.6 Hz). IR (neat) 1853, 1145, 995, 964, 894 cm^{-1}. MS (CI) *m/z* 157 [M+H$^+$] (100). HRMS (EI) Calcd for $C_3H_3ClF_2$ [M$^+$-CO_2]: 111.9891, found: 111.9930.

Representative Procedure for the Kinetic Resolution to Afford (*S*)-β-Chlorodifluoromethyl-β-propiolactone (*S*)-(3): A mixture of 3 (156 mg, 1 mmol), hexyl alcohol (61mg, 0.6 mmol), novozyme 435 (156 mg) and diethyl ether (12 ml) was stirred at 30 °C during the resolution, and the reaction conversion was assessed by GC. After 48 hrs, the lipase was filtered off and the filtrate was evaporated. The residue was purified by silica gel flash chromatography. $[\alpha]_D^{23}$ = -5.14 (c 1.01, $CHCl_3$). ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, IR and HRMS were identical with those of racemic β-chlorodifluoromethyl-β-propiolactone.

Hexyl 4-chloro-4,4-difluoro-(*R*)-3-hydroxybutyrate (4, R = Hexyl): $[\alpha]_D^{23}$ = 11.7 (c 0.40, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.53~4.40 (1H, m), 4.15 (2H, t, J = 6.7 Hz), 3.60~3.50 (1H), 2.80 (1H, dd, J = 3.3 and 16.7 Hz), 2.69 (1H, dd, J = 9.0 and 16.5 Hz), 1.70~1.55 (2H, m), 1.42~1.25 (6H, m), 0.90 (3H, t, J = 6.7 Hz). ^{13}C-NMR (75.45 MHz, $CDCl_3$) δ 170.73, 136.00, 128.78, 120.12, 72.39, 72.02, 71.64, 65.73, 35.44, 35.41, 35.38, 31.38, 28.43, 25.50, 22.52, 13.98. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -66.23 (dd, J = 167.4 and 450.1 Hz). MS (CI) *m/z* 259 [M+H$^+$] (100), 175 (67). HRMS (EI) Calcd for $C_{10}H_{15}ClF_2O_2$ [M$^+$-H_2O] : 240.0729, found: 240.0680.

Ethyl 4-chroro-4,4-difluoro-(*R*)-3-hydroxybutyrate (4, R = Ethyl): $[\alpha]_D^{23}$ = 13.9 (c 1.00, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.55~4.40 (1H, m), 4.22 (2H, q, J = 7.2 Hz), 3.65~3.30 (1H, brord), 2.80 (1H, dd, J = 3.3 and 16.5 Hz), 2.69 (1H, dd, J = 9 and 16.5 Hz), 1.30 (3H, t, J = 7.2 Hz). ^{13}C-NMR (75.45 MHz, $CDCl_3$) δ 170.72, 132.68, 128.77, 124.86, 72.29, 71.92, 71.55, 61.56, 35.51, 14.03. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -66.21 (dd, J = 165.1 and 426.0 Hz). MS (CI) *m/z* 203 [M+H$^+$]

(100). HRMS (EI) Calcd for $C_6H_7ClF_2O_2$ [M^+-H_2O] : 184.0103, found: 184.0111.

General Procedure of the Friedel-Craft Type Aromatic Acylation: Under a nitrogen atmosphere, $AlCl_3$ (120 mg, 0.9 mmol) was suspended in 1 mmol of aromatic compound and cooled to -30 °C. To it was added a solution of β-chlorodifluoromethyl-β-propiolactone (47 mg, 0.3 mmol) in 15 mmol of the aromatic compound over a period of 15 min, and the mixture was stirred for 3 h at ambient temperature. The reaction mixture was poured into ice cooled aq. HCl. The aqueous layer was extracted with three 100 ml portions of ether. The combined ethereal solutions were washed with 1 M HCl, and dried over anhydrous $MgSO_4$. Removal of the drying agent and evaporation of the solvent gave a crude product. The mixture was chromatographed on silica gel (eluting with ethyl acetate : hexane) to give the acylated product.

4-Chloro-4,4-difluoro-3-hydroxy-1-phenyl-1-butanone (5a): Yield 71%. $[\alpha]_D^{23}$ = -18.8 (c 0.46, $CHCl_3$). mp 69~70 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95~7.80 (2H, m), 7.61~7.50 (1H, m), 7.45~7.35 (2H, m), 4.70~4.60 (1H, m), 3.60~3.45 (1H, m), 3.37~3.30 (2H, m). ^{13}C-NMR (75.45 MHz, $CDCl_3$) δ 197.36, 136.08, 129.12, 128. 85, 128.22, 72.04, 71.67, 71.30, 39.03. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -65.74 (dd, J = 167.1 and 464.8 Hz). IR (KBr) 3400, 2967, 1686, 1268, 1092, 802 cm^{-1}. HRMS(EI) Calcd for $C_{10}H_9ClF_2O_2$ [M^+]: 234.0259, found: 234.0230.

4-Chloro-4,4-difluoro-3-hydroxy-1-(4-methoxyphenyl)-1-butanone (5b): Yield 78%. $[\alpha]_D^{23}$ = -18.1 (c 0.54, $CHCl_3$). mp 68~70 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.95 (2H, d, J=8.9 Hz), 6.96 (2H, d, J=8.9 Hz), 4.75~4.69 (1H, m), 3.98 (1H, OH), 3.88 (3H, s), 3.35~3.23 (2H, m). ^{13}C-NMR ($CDCl_3$, 270 MHz) δ 195.9, 164.3, 133.6, 130.6, 129.1, 113.9, 72.1, 71.7, 71.3, 55.5, 38.5. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -65.61 (dd, J = 165.4 and 461.4 Hz). IR (KBr) 3374, 1678, 1604, 1263, 1169, 1101 cm^{-1}. HRMS (EI) Calcd for $C_{11}H_{11}ClF_2O_3$ [M^+] : 264.0365, found: 264.0356.

4-Chloro-4,4-difluoro-3-hydroxy-1-(2- or 4-toluyl)-1-butanone (5c): Yield 42%. $[\alpha]_D^{23}$ = -21.2 (c 0.067, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.79 (*p*-, 2H, d, J = 8.3 Hz), 7.73~7.53 (*o*-, 2H, m), 7.20 (*p*-, 2H, d, J = 8.3 Hz), 7.40~7.20 (*o*-, 2H, m), 4.64 (1H, broad), 3.71~3.70 (1H, m), 3.30~3.27 (2H, m), 2.46 (*o*-, 3H, s), 2.36 (*p*-, 3H, s). ^{13}C-NMR (75.45 MHz, $CDCl_3$) δ 197.0, 145.1, 133.6, 132.3, 129.5, 129.2, 128.6, 128.36, 125.91, 72.11, 71.70, 68.34, 38.85, 21.69. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -65.67 (dd, J = 171.0 and 470.7 Hz). HRMS (EI) Calcd for $C_{11}H_{11}ClF_2O_2$ [M^+] : 248.0416, found: 248.0413.

4-Chloro-4,4-difluoro-3-hydroxy-1-(2,4-dimethylphenyl)-1-butanone (5d): Yield 78%. $[\alpha]_D^{23}$ = -20.3 (c 0.086, $CHCl_3$). mp 85~87 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 8.4 Hz), 7.02 (2H, m), 4.66~4.56 (1H, m), 3.79 (1H, broad) 3.24~3.22 (2H, m), 2.44 (3H, s), 2.29 (3H, s). ^{13}C-NMR (67.80 MHz, $CDCl_3$) δ 199.9, 143.3, 139.6, 133.5, 133.2, 129.6, 129.3, 126.7, 124.9, 72.3, 71.9, 71.5, 41.0, 21.7, 21.4. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -65.61 (dd, J = 167.3 and 459.6 Hz). IR (KBr) 3403, 1684, 1104, 1008, 812, 790 cm^{-1}. HRMS (EI) Calcd for $C_{12}H_{13}ClF_2O_2$ [M^+] : 262.0572, found: 262.0564.

4-Chloro-4,4-difluoro-3-hydroxy-1-(2,4,6-trimethyphenyl)-1-butanone (5e): Yield 78%. $[\alpha]_D^{23}$ = -8.8 (c 0.47, $CHCl_3$). mp 57~59 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.78 (2H, s), 4.70~4.68 (1H, m), 3.53 (1H, broad), 3.03~3.00 (2H, m), 2.22 (3H, s), 2.14 (6H, s). ^{13}C-NMR (67.80 MHz, $CDCl_3$) δ 207.5, 139.2, 138.1, 133.4, 132.7, 129.0, 128.7, 124.7, 71.6, 71.2, 70.8, 45.2, 21.7, 19.8. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -65.96 (dd, J = 165.5 and 430.1 Hz). IR (KBr) 3528, 1685, 1284, 1112, 1030, 963 cm^{-1}. HRMS (EI) Calcd for $C_{13}H_{15}ClF_2O_2$ [M^+] : 276.0729, found: 276.0726.

4-Chloro-4,4-difluoro-3-hydroxy-1-(2-methoxynaphtyl)-1-butanone (5f): Yield 48%. $[\alpha]_D^{23}$ = +8.3 (c 0.56, $CHCl_3$). Dec.p. 55 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.86~7.69 (2H, m), 7.45~7.21 (1H, m), 4.71~4.68 (1H, m), 3.92 (3H, s), 3.51 (1H, OH), 3.38 (1H, dd, J = 2.6 and 17.5 Hz), 3.20 (1H, dd, J = 9.2 and 17.5 Hz). ^{13}C-NMR (67.80 MHz, $CDCl_3$) δ 204.2, 154.6, 133.5, 132.7, 130.4, 129.1, 128.9, 128.3, 124.8, 124.4, 123.4, 123.2, 112.5, 112.4, 72.5, 72.1, 71.7, 56.5, 45.1. ^{19}F-NMR (254

MHz, $CDCl_3$) δ -65.90 (dd, J = 169.1 and 479.8 Hz). IR (KBr) 3474, 1684, 1514, 1254, 1108, 1072, 1023, 817, 748 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{13}ClF_2O_3$ [M^+] : 314.0521, found: 314.0522.

4-Chloro-4,4-difluoro-3-hydroxy-1-(4-methoxybiphenyl)-1-butanone (5g): Yield 70%. $[\alpha]_D^{23}$ = -9.0 (c 0.66, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.88~7.18 (8H, m), 4.72~4.70 (1H, m), 3.98 (3H, s), 3.71 (1H, s), 3.47 (2H, m). ^{13}C-NMR (67.80 MHz, $CDCl_3$) δ 198.8, 158.5, 139.4, 133.9, 133.1, 129.3, 129.1, 128.8, 126.8, 126.6, 112.2, 72.4, 71.9, 71.5, 55.8, 44.3. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -65.65 (dd, J = 167.3 and 483.5 Hz). IR (KBr) 3460, 1652, 1604, 1271, 1175, 1113, 1025, 1002, 813, 766, 698 cm^{-1}. HRMS (EI) Calcd for $C_{17}H_{15}ClF_2O_3$ [M^+] : 340.0677, found: 340.0647.

4-Chloro-4,4-difluoro-3-hydroxy-1-(2-*N*-methypyrolyl)-1-butanone (5h): Yield 67%. $[\alpha]_D^{23}$ = -35.3 (c 0.13, $CHCl_3$). Dec.p. 66 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.95~6.93(1H, m), 6.80(1H, s), 6.10~6.08 (1H, m), 4.55 (1H, broad), 4.18 (1H, broad), 3.86 (3H, s), 3.10 (2H, m). ^{13}C-NMR (67.80 MHz, $CDCl_3$) δ 187.2, 133.7, 132.5, 130.0, 129.3, 125.0, 120.7, 108.7, 72.5, 72.1, 71.7, 38.6, 37.7. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -65.76 (dd, J = 161.8 and 443.1 Hz). IR (KBr) 3437, 1634, 1402, 1110, 744 cm^{-1}. HRMS (EI) Calcd for $C_9H_{10}ClF_2NO_2$ [M^+] : 237.0368, found: 237.0327.

4-Chloro-4,4-difluoro-3-hydroxy-1-(3-*N*-methypyrolyl)-1-butanone (5i): Yield 11%. $[\alpha]_D^{23}$ = -40.9 (c 0.067, $CHCl_3$). Dec.p. 72 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.30~7.29 (1H, m), 6.61 (2H, s), 4.63~4.60 (1H, m), 4.23 (1H, broad), 3.71 (3H, s), 3.16 (1H, dd, J = 3.3 and 16.8 Hz), 3.07 (1H, dd, J = 8.6 and 16.8 Hz). ^{13}C-NMR (67.80 MHz, $CDCl_3$) δ 192.7, 133.5, 129.2, 127.4, 125.1, 124.8, 123.8, 109.5, 72.6, 72.2, 71.8, 38.7, 36.8. ^{19}F-NMR (254 MHz, $CDCl_3$) δ -65.74 (dd, J = 165.4 and 478.0 Hz). IR (KBr) 3395, 1652, 1534, 1187, 1102, 1029 cm^{-1}. HRMS (EI) Calcd for $C_9H_{10}ClF_2NO_2$ [M^+] : 237.0368, found: 237.0340.

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