PREPARATION OF α-METHYLENE-γ-BUTYROLACTONES WITH DIFLUOROMETHYLENE FUNCTIONALITIES

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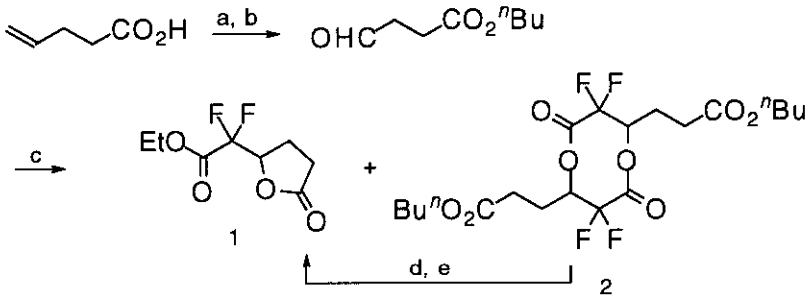
Abstract- 4-(1,1-Difluoro-2-ethoxycarbonyl)methyl-γ-butyrolactone (**1**) was prepared from the Reformatsky-type reaction of *n*-butyl 3-formylpropanoate with ethyl bromodifluoroacetate in Zn-THF system, and compound (**1**) was converted to α-methylene-γ-butyrolactone derivatives with a difluoromethylene unit at γ-position.

In recent years, fluorinated materials have been receiving much attention in various fields such as pharmacology or functionalized materials because of their unique biological and physical properties.[1,2] Particularly, the difluoromethylene group is preferred due to its ability to act as a hydrogen donor, allowing the possibility to interact with solvents and biological molecules.[3] Recently, we have reported the biological activity of chiral 4,4-difluoro-threonine[4] and 4-difluoromethyl-α-methylene-γ-butyrolactone.[5] As a continuation of our interest in the synthesis of materials modified with a difluoromethylene unit, which often exhibit unique biological properties such as aggregation pheromone analogues, we examined the synthesis of α-methylene-γ-butyrolactone derivatives with a difluoromethylene unit at 4-position.

RESULTS AND DISCUSSION

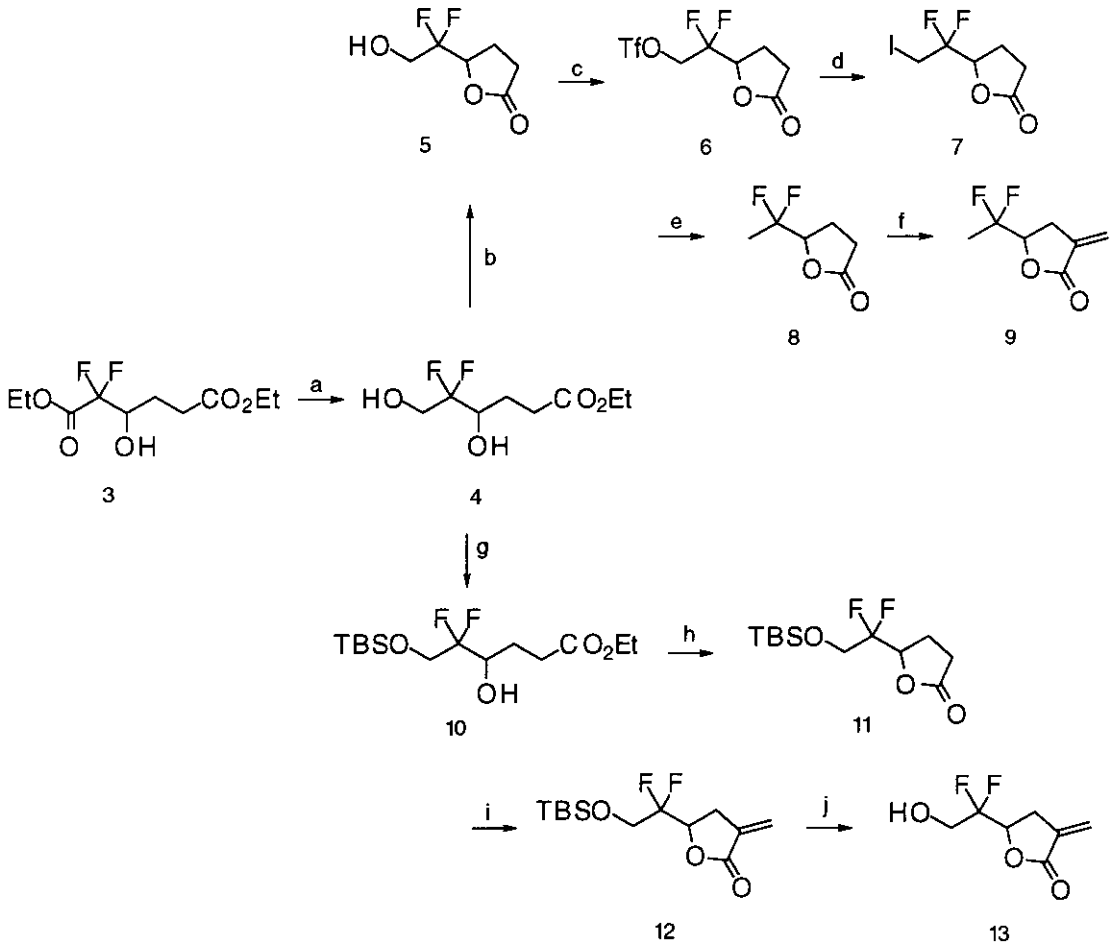
To obtain various types of α-methylene-γ-butyrolactone derivatives with a difluoromethylene unit at 4-position, the synthesis of 4-(1,1-difluoro-2-ethoxycarbonyl)methyl-γ-butyrolactone (**1**) as a key intermediate in this process, was examined as shown in Scheme 1. In this reaction, compounds (**1**) and (**2**) were obtained from the reaction of *n*-butyl 3-formyl-

propanoate prepared from 4-pentenoic acid with ethyl bromodifluoroacetate in Zn-THF system in the ratio (**1** : **2** =3.4 : 1). After separating both compounds by column chromatography (silica gel, 35% AcOEt-hexane), compound (**2**) was hydrolyzed by NaOEt-EtOH system, and then converted to compound (**1**) by the lactonization in the TsOH-benzene system.



Scheme 1. (a) cat. TsOH, *n*-BuOH, reflux. (quant) (b) OsO_4, $NaIO_4$, THF-H_2O (77%) (c) Zn, $BrCF_2CO_2Et$, THF (51%) (d) cat. NaOEt, EtOH (71%) (e) cat. TsOH, benzene (98%)

For the purpose to prepare aggregation pheromone analogues, we examined the reduction of ester group with sodium borohydride. In general, it is known that the reduction of ester group with sodium borohydride does not proceed. However, the ester group in compound (**1**) activated with a difluoromethylene unit was reduced to give diol (**4**) in $NaBH_4$-EtOH system. Treatment of the diol (**4**) with *p*-toluenesulfonic acid in benzene gave 4-(2-hydroxy-1,1-difluoroethyl)-γ-butyrolactone (**5**) in 95% yield. The triflate (**6**), prepared from alcohol (**5**), reacted selectively with sodium iodide in acetone to give the compound (**7**) in good yield . The compound (**7**) then reacted with AIBN-*n*-Bu_3SnH system to give aggregation pheromone analogue (**8**) of *Trogoderma glabrum* . Forthermore, the synthesis of 4-(1,1-difluoroethyl)-α-methylene-γ-butyrolactone (**9**) was acheived by introduction of the methylene group at α-position (Scheme 2). The compound (**1 0**) derived from compound (**4**) was also transformed to compund (**1 1**) with *p*-toluenesulfonic acid in benzene, and then a synthesis of 4-(1,1-difluoro-2-hydroxyethyl)-α-methylene-γ-butyrolactone (**1 3**) possessing 1,1-difluoro-2-hydroxyethyl group attached to the 4-position of α-methylene-γ-butyrolactone was achieved by introduction of the methylene group at α-position (Scheme 2).



Scheme 2. (a) $NaBH_4$, EtOH (64%) (b) cat. TsOH, benzene, reflux (95%) (c) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2 (90%) (d) NaI, acetone (quant) (e) cat. AIBN, *n*-Bu_3SnH (75%) (f) LDA, $CH_2NMe_2^+ I^-$, MeI (g) TBSCl, imidazole, DMF (quant.) (h) cat. TsOH, benzene (i) LDA, $CH_2NMe_2^+ I^-$, MeI (j) TBAF, THF

EXPERIMENTAL

General : All commercially available reagents were used without further purification. Chemical shifts 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 $CFCl_3$ in $CDCl_3$ using VXR 500 instrument. Yields quoted are those of the products actually isolated.

n-Butyl 4-pentenoate

The solution of 4-pentenoic acid (0.204 mL, 2.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid in *n*-butanol (2 mL) was stirred at 130 °C. After 1 h of stirring at that temperature, the solvent was removed *in vacuo*. The residual oil was purified by column chromatography (silica gel, 10% AcOEt-hexane) to give *n*-butyl 4-pentenoate (313 mg) in quantitative yield. ^{1}H NMR ($CDCl_3$): δ 0.94 (3 H, t, *J*=7.6 Hz), 1.34-1.43 (2 H, m), 1.57-1.64 (2 H, m), 2.34-2.43 (4 H, m), 4.08 (2 H, t, *J*= 6.8 Hz), 4.98-5.09 (2 H, m), 5.78-5.87 (1 H, m); ^{13}C NMR ($CDCl_3$): δ 13.8, 19.3, 29.0, 30.8, 33.7, 64.3, 115.5, 136.8, 173.1. IR (neat): ν 1738, 1175 cm^{-1}.

n-Butyl 3-formylpropanoate

Into a solution of *n*-butyl 4-pentenoate (10.9 g, 70 mmol) and a catalytic amoumt of osumium tetraoxide in tetrahydrofuran-water (2 : 1, 350 mL), sodium metaperiodate (29.9 g, 140 mmol) was added at rt. After 3 h of stirring at rt, 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 *n*-butyl 3-formylpropanoate (8.52 g) in 77% yield.^{1}H NMR ($CDCl_3$): δ 0.94 (3 H, t, *J*=7.6 Hz), 1.34-1.42 (2 H, m), 1.58-1.65 (2 H, m), 2.63 (2 H, t, *J*= 6.6 Hz), 2.80 (2 H, td, *J*= 6.4, 0.5 Hz), 4.10 (2 H, t, *J*= 6.6 Hz), 9.82 (1H, m);^{13}C NMR ($CDCl_3$): δ 13.7, 19.1, 26.6, 30.6, 38.6, 64.7, 172.4, 200.2. IR (neat): ν 1734, 1179 cm^{-1}.

*4-(1,1-Difluoro-2-ethoxycarbonyl)methyl-γ-butyrolactone (**1**)*

To a solution of *n*-butyl 4-pentenoate (1.35 g, 8.53 mmol) and zinc (837 mg, 12.8 mmol) in tetrahydrofuran (85 mL), ethyl bromodifluoroacetate (1.42 mL, 11.1 mmol) was added at 0 °C under an argon atmosphere. After 2 h 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 ether. The combined organic extracts were dried over $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 35% AcOEt-hexane) to give 4-(1,1-difluoro-2-ethoxycarbonyl)methyl-γ-butyrolactone (**1**) (910 mg) and dimer (**2**) (610 mg, 1.29 mmol) in 51% and 15% yields, respectively. ^{1}H NMR ($CDCl_3$): δ 1.38 (3 H, t, *J*=7.1 Hz), 2.41-2.48 (2 H, m), 2.52-2.60 (1 H, m), 2.63-2.72 (1 H, m), 4.39 (2 H, q,

J=7.1 Hz), 4.92-5.00 (1 H, m);^{13}C NMR ($CDCl_3$): δ 13.9, 20.6 (q, *J*=1.8 Hz), 26.7 (d, *J*=1.6 Hz), 63.7, 76.5 (dd, *J*=32.8, 24.9 Hz), 112.8 (dd, *J*=257, 251 Hz), 162.0 (dd, *J*=32.1, 29.7 Hz), 175.5;^{19}F NMR ($CDCl_3$): δ -125 (dd, *J*=273, 16.8 Hz), -117 (dd, *J*=273, 6.1 Hz);IR (neat): ν 1797 cm^{-1};HRMS calcd for $C_8H_{10}O_4F_2$ $(M)^+$ 208.0546, found 208.0538.

*4,8-Bis{(2-n-butoxycarbonyl)ethyl}-3,3,7,7-tetrafluoro-2,6-dioxo-1,5-dioxocane (**2**)*

^{1}H NMR ($CDCl_3$): δ 0.96 (6 H, t, *J*=7.3 Hz), 1.34-1.46 (4 H, m), 1.69-1.75 (4 H, m), 2.41-2.49 (4 H, m), 2.52-2.60 (2 H, m), 2.63-2.72 (2 H, m), 4.33 (4 H, t, *J*=6.8 Hz), 4.91-5.00 (2 H, m);^{13}C NMR ($CDCl_3$): δ 13.6, 18.9, 20.6 (q, *J*=1.8 Hz), 26.7 (d, *J*=1.5 Hz), 30.2, 67.4, 76.5 (dd, *J*=33.1, 25.0 Hz), 112.8 (dd, *J*=257, 251 Hz), 162.1 (dd, *J*=32.4, 29.8 Hz), 175.4; ^{19}F NMR ($CDCl_3$): δ -125 (dd, *J*=273, 16.8 Hz), -117 (dd, *J*=273, 6.1 Hz); IR (neat): ν 1800 cm^{-1}.

*Ethyl 2,2-difluoro-5-ethoxycarbonyl-3-hydroxypentanoate (**3**)*

To a solution of 4,8-bis{(2-*n*-butoxycarbonyl)ethyl}-3,3,7,7-tetrafluoro-2,6-dioxo-1,5-dioxocane (605 mg, 1.28 mmol), a catalytic amount of sodium ethoxide in ethanol (13 mL) was added at 80 °C under an argon atmosphere. After 2 days of stirring at that temperature, the solvent was removed. The residue was diluted with ether, and then the mixture was quenched with 1 *N* HCl. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 30% AcOEt-hexane) to give ethyl 2,2-difluoro-5-ethoxycarbonyl-3-hydroxypentanoate (**3**) (462 mg) in 71% yield.^{1}H NMR ($CDCl_3$): δ 1.27 (3 H, t, *J*=7.1 Hz), 1.37 (3 H, t, *J*=7.3 Hz), 1.88-1.98 (1 H, m), 2.01-2.09 (1 H, m), 2.51-2.64 (2 H, m), 3.00 (1 H, *J*=6.6 Hz), 4.07-4.19 (3 H, m), 4.16 (2 H, q, *J*=7.3 Hz), 4.37 (2 H, q, *J*=7.1 Hz);^{13}C NMR ($CDCl_3$): δ 13.9, 14.1, 24.2 (q, *J*=1.9 Hz), 30.1, 61.0, 63.2, 71.0 (t, *J*=24.6 Hz), 114.6 (dd, *J*=256, 252 Hz), 163.6 (dd, *J*=32.8, 30.9 Hz), 174.0;^{19}F NMR ($CDCl_3$): δ -124 (dd, *J*=264, 16.8 Hz), -116 (dd, *J*=264, 6.1 Hz); IR (neat): ν 3467, 1761, 1735 cm^{-1}.

*Ethyl 5,5-difluoro-4,6-dihydroxyhexanoate (**4**)*

Into the flask containing sodium borohydride (1.21 g, 32.1 mmol), a solution of ethyl 2,2-difluoro-5-ethoxycarbonyl-3-hydroxypentanoate (8.17 g, 32.1 mmol) in ethanol (160 mL)

was added at rt under an argon atmosphere. After 30 min of stirring at that temperature, the mixture was quenched with NH_4Cl powder. On removal of the solvent, the residue was diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 65% AcOEt-hexane) to give ethyl 5,5-difluoro-4,6-dihydroxyhexanoate (**4**) (4.34 g) in 64% yield.^{1}H NMR ($CDCl_3$): δ 1.27 (3 H, t, *J*=7.1 Hz), 1.88-1.96 (1 H, m), 2.03-2.10 (1 H, m), 2.44-2.50 (1 H, m), 2.55 (1 H, ddd, *J*=17.1, 7.6, 6.1 Hz), 2.61 (1 H, ddd , *J*=17.1, 7.8, 5.9 Hz), 3.31 (1 H, d, *J*=5.9 Hz), 3.84-4.04 (3 H, m), 4.17 (2 H, q, *J*=7.1 Hz);^{13}C NMR ($CDCl_3$): δ 14.0, 24.3 (t, *J*=3.2 Hz), 30.3, 60.9, 61.6 (dd, *J*=32.9, 28.1 Hz), 70.0 (dd, *J*=29.8, 25.4 Hz), 121.2 (dd, *J*=247, 245 Hz), 174.4;^{19}F NMR ($CDCl_3$): δ -126 (dtd, *J*=258, 16.8, 10.7 Hz), -119 (dddd, *J*=258, 18.3, 12.2, 6.1 Hz); IR (neat): 3426, 1715 cm^{-1}; HRMS calcd for $C_8H_{14}O_4F_2$ $(M)^+$ 212.0859, found 212.0874.

*4-(2-Hydoxy-1,1-difluoroethyl)-γ-butyrolactone (**5**)*

To a solution of ethyl 5,5-difluoro-4,6-dihydroxyhexanoate (**4**) (5.86 g, 27.6 mmol) in benzene (140 mL), a catalytic amount of *p*-toluenesulfonic acid was added at 90 °C. After 2 h of stirring at 90 °C, the solvent was removed *in vacuo*. Oily materials were purified by column chromatography (silica gel, 65% AcOEt-hexane) to give 4-(2-hydoxy-1,1-difluoroethyl)-γ-butyrolactone (**5**) (4.33 g) in 95% yield.^{1}H NMR ($CDCl_3$): δ 2.24 (1 H, s), 2.35-2.71 (4 H, m), 3.88-4.04 (2 H, m), 4.86 (1 H, dddd, *J*=21.2, 8.3, 4.4, 2.4 Hz);^{13}C NMR ($CDCl_3$): δ 20.3 (dd, *J*=3.9, 2.1 Hz), 27.2 (d, *J*=1.6 Hz), 61.3 (dd, *J*=34.8, 26.2 Hz), 75.4 (dd, *J*=37.9, 25.2 Hz), 120.0 (dd, *J*=247, 244 Hz), 176.9;^{19}F NMR ($CDCl_3$): δ -128 (ddt, *J*=266, 21.4, 7.6 Hz), -120 (dddd, *J*=266, 22.9, 13.7, 3.1 Hz); IR (neat): ν 3441, 1790 cm^{-1}; HRMS calcd for $C_6H_8O_3F_2$ $(M)^+$ 166.0441, found 166.0453.

*4-{1,1-Difluoro-2-(trifluoromethanesulfonyloxy)ethyl}-γ-butyrolactone (**6**)*

To a solution of 4-(2-hydoxy-1,1-difluoroethyl)-γ-butyrolactone (**5**) (1.0 g, 6.02 mmol) in dichloromethane (30 mL), diisopropylethylamine (1.26 mL, 7.22 mmol) and trifluoromethanesulfonic anhydride (1.21 mL, 7.22 mmol) was added at 0 °C. After 30 min of stirring at 0 °C, the mixture was quenched with water. The organic layer was separated and the

aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 35% AcOEt-hexane) to give 4-{1,1-difluoro-2-(trifluoromethanesulfonyloxy)ethyl}-γ-butyrolactone (**6**) (1.61 g) in 90% yield.^{1}H NMR ($CDCl_3$): δ 2.42-2.73 (4 H, m), 4.70-4.81 (3 H, m);^{13}C NMR ($CDCl_3$): δ 20.1 (dd, *J*=3.9, 1.7 Hz), 26.8, 70.5 (dd, *J*=38.7, 26.1 Hz), 74.7 (dd, *J*=37.5, 24.6 Hz), 117.1 (t, *J*= 248 Hz), 118.6 (q, *J*=318 Hz), 175.2;^{19}F NMR ($CDCl_3$): δ -128 (ddt, *J*=272, 22.9, 6.1 Hz), -119 (dt, *J*=272, 16.8 Hz), -75.2; IR (neat): ν 1802 cm^{-1}.

*4-(1,1-Difluoro-2-iodoethyl)-γ-butyrolactone (**7**)*

To a solution of 4-{1,1-difluoro-2-(trifluorometanesulfonyloxy)ethyl}-γ-butyrolactone (**6**) (1.51 g, 5.07 mmol) in acetone (50 mL), sodium iodide (988 mg, 6.59 mmol) was added at rt. After 3 h of stirring at that temperature, the solvent was removed *in vacuo*. The residue was diluted with ether, and 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 $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 40% AcOEt-hexane) to give 4-(1,1-difluoro-2-iodoethyl)-γ-butyrolactone (**7**) (1.40 g) in quantitative yield.^{1}H NMR ($CDCl_3$): δ 2.32-2.74 (4 H, m), 3.48-3.66 (2 H, m), 4.91 (1 H, ddd, *J*=22.0, 8.3, 0.7 Hz);^{13}C NMR ($CDCl_3$): δ 0.3 (dd, *J*=30.8, 27.2 Hz), 20.9 (dd, *J*=3.7, 1.7 Hz), 26.9 (d, *J*=1.8 Hz), 76.3 (dd, *J*=38.8, 26.6 Hz), 118.2 (dd, *J*=247, 243 Hz), 175.5;^{19}F NMR ($CDCl_3$): δ -114 (ddd, *J*=253, 22.9, 6.1 Hz), -120 (dt, *J*=253, 18.3 Hz); IR (neat): ν 1790 cm^{-1}; HRMS calcd for $C_6H_7O_2F_2I$ $(M)^+$ 275.9457, found 275.9448.

*4-(1,1-Difluoroethyl)-γ-butyrolactone (**8**)*

To a solution of 4-(1,1-difluoro-2-iodoethyl)-γ-butyrolactone (**7**) (247 mg, 0.895 mmol) and *n*-butyltin hydride (0.31 mL, 1.16 mmol) in benzene (10 mL), a catalytic amount of 2,2'-azobis(isobutyronitrile) was added at 90 °C. After 30 min of stirring at 90 °C, the mixture was quenched with saturated KF aq. and the precipitate was filtered. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 35% AcOEt-hexane) to give 4-(1,1-difluoroethyl)-γ-butyrolactone

(**8**) (101 mg) in 75% yield.^{1}H NMR ($CDCl_3$): δ 1.72 (3 H, t, *J*=19.0 Hz), 2.30-2.46 (2 H, m), 2.53 (1 H, ddd, *J*=18.1, 10.5, 1.5 Hz), 2.64 (1 H, ddd, *J*=18.1, 9.8, 1.5 Hz), 4.53 (1 H, dddd, *J*=19.3, 8.7, 4.6, 3.2 Hz);^{13}C NMR ($CDCl_3$): δ 20.4 (dd, *J*=26.7, 25.1 Hz), 21.0 (dd, *J*=3.8, 2.4 Hz), 27.2 (d,*J*=1.7 Hz), 79.0 (dd, *J*=37.1, 27.9 Hz), 121.5 (dd, *J*=243, 238 Hz), 176.3;^{19}F NMR ($CDCl_3$): δ -111 (dquint, *J*=255, 18.3 Hz), -104 (ddq, *J*=255, 18.3, 3.1 Hz); IR (neat): ν 1793 cm^{-1}; HRMS calcd for $C_6H_8O_2F_2$ $(M)^+$ 150.0492, found 150.0479.

*4-(1,1-Difluoroethyl)-α-methylene-γ-butyrolactone (**9**)*

To a solution of diisopropylamine (0.377 mL, 2.69 mmol) in tetrahydrofuran (10 mL), *n*-butyllithium (1.6 M in hexane, 1.68 mL, 2.69 mmol) was added at -78 °C under a nitrogen atmosphere. After 10 min of stirring, 4-(1,1-difluoroethyl)-γ-butyrolactone (**8**) (308 mg, 2.06 mmol) in tetrahydrofuran (10 mL) was added at -78 °C. After 1 h of stirring, *N,N*-dimethylmethyleneammonium iodide (575 mg, 3.11 mmol) was added and stirred for 1 h. The solvent was removed and diluted with methanol. Methyl iodide (2 mL) was added to the mixture and the whole was stirred for 24 h. On removal of the solvent, the residue was diluted with dichloromethane and aqueous 5% $NaHCO_3$ solution was added to the mixture and vigurously stirred. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 35 % AcOEt-hexane) to give 4-(1,1-difluoroethyl)-α-methylene-γ-butyrolactone (**9**) (100 mg) in 30 % yield.^{1}H NMR ($CDCl_3$): δ 1.73 (3 H, t, *J*=19.0 Hz), 3.04 (1 H, ddt, *J*=18.1, 8.3, 2.9 Hz), 3.10 (1 H, ddt, *J*=18.1, 4.9, 2.7 Hz), 4.56 (1 H, dddd, *J*=17.8, 8.3, 5.1, 3.2 Hz), 5.74 (1 H, t, *J*=2.4 Hz), 6.30 (1 H, t, *J*=2.4 Hz);^{19}F NMR ($CDCl_3$): δ -112 (dquit, *J*=255, 18.3 Hz), -104 (dtd, *J*=255, 18.3, 3.1 Hz); IR (neat): ν 1778, 1665 cm^{-1}; HRMS calcd for $C_7H_8O_2F_2$ $(M)^+$ 162.0492, found 162.0485.

*Ethyl 6-t-butyldimethylsilyloxy-5,5-difluoro-4-hydroxyhexanoate (**10**)*

To a solution of ethyl 5,5-difluoro-4,6-dihydroxyhexanoate (**4**) (2.12 g, 10.0 mmol) and imidazole (749 mg, 11.0 mmol) in dimethylformamide (10 mL), *t*-butyldimethylsilyl chloride (1.66 g, 11.0 mmol) was added at rt under an argon atmosphere. After the mixture was stirred overnight, the mixture was quenched with aqueous 5% $NaHCO_3$ solution and diluted with ether. The organic layer was separated and the aqueous layer was extracted with ether.

The combined organic extracts were dried over $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 30% AcOEt-hexane) to give ethyl 6-*t*-butyldimethylsilyloxy-5,5-difluoro-4-hydroxyhexanoate (**10**) (3.23 g) in quantitative yield.^{1}H NMR ($CDCl_3$): δ 0.10 (6 H, d, *J*=0.7Hz), 0.90 (9 H, s), 1.26 (3 H, t, *J*=7.1 Hz), 1.86-1.95 (1 H, m), 2.01-2.09 (1 H, m), 2.55 (2 H, td, *J*=7.3, 2.2 Hz), 2.82 (1 H, d, *J*=6.1 Hz), 3.84 (1 H, q, *J*=11.5 Hz), 3.91-4.02 (2 H, m), 4.14 (2 H, q, *J*=7.1 Hz);^{13}C NMR ($CDCl_3$): δ -5.6, 14.1, 18.2, 24.5 (t, *J*=3.2 Hz), 25.7, 30.5, 60.6, 62.8 (dd, *J*=35.4, 30.8 Hz), 70.2 (dd, *J*=29.3, 25.3 Hz), 121.0 (t, *J* = 246 Hz), 174.0;^{19}F NMR ($CDCl_3$): δ -125 (dddd, *J*=256, 16.8, 12.2, 7.6 Hz), -118 (dddd, *J*=256, 16.8, 10.7, 4.6 Hz); IR (neat): ν 3448, 1735, 1718 cm^{-1}.

*4-(2-t-Butyldimethylsilyloxy-1,1-difluoroethyl)-γ-butyrolactone (**11**)*

To a solution of ethyl 6-*t*-butyldimethylsilyloxy-5,5-difluoro-4-hydroxyhexanoate (**10**) (324 mg, 1.0 mmol) in benzene (10 mL), a catalytic amount of pyridinium *p*-toluenesulfonate was added at 90 °C. After 20 h of stirring at 90 °C, the solvent was removed *in vacuo*. Oily materials were purified by column chromatography (silica gel, 20% AcOEt-hexane) to give 4-(2-*t*-butyldimethylsilyloxy-1,1-difluoroethyl)-γ-butyrolactone (**11**) (230 mg) in 82% yield.^{1}H NMR ($CDCl_3$): δ 0.98 (3 H, d, *J*=0.5 Hz), 0.10 (3 H, s), 0.90 (6H, s), 0.91 (3 H, s), 2.31-2.40 (1 H, m), 2.43-2.57 (2 H, m), 2.60-2.68 (1 H, m), 3.83 (1 H, dt, *J*=11.5, 6.4 Hz), 3.95 (1 H, ddd, *J*=25.9, 11.5, 4.6 Hz), 4.84 (1 H, dddd, *J*=21.2, 8.5, 4.6, 2.7 Hz);^{13}C NMR ($CDCl_3$): δ -5.7, -3.7, 18.1, 20.2 (dd, *J*=3.8, 2.2 Hz), 25.6, 27.1 (d, *J*=1.6 Hz), 61.9 (dd, *J*=38.3, 26.4 Hz), 74.8 (dd, *J*=37.8, 24.9 Hz), 120.0 (t, *J*=245 Hz), 176.2;^{19}F NMR ($CDCl_3$): δ -128 (ddt, *J*=263, 21.4, 4.6 Hz), -120 (dddd, *J*=263, 25.9, 12.2, 3.1 Hz); IR (neat): ν 1794 cm^{-1}.

*4-(2-t-Butyldimethylsilyloxy-1,1-difluoroethyl)-α-methylene-γ-butyrolactone (**12**)*

n-Butyllithium (1.6 M in hexane, 8.31 mL, 13.3 mmol) was added to a solution of diisopropylamine (1.86 mL, 13.3 mmol) in THF (40 mL) at -78 °C under an argom atmosphere. After 10 min of stirring, 4-(2-*t*-butyldimethylsilyloxy-1,1-difluoroethyl)-γ-butyrolactone (**11**)(2.88 g, 10.3 mmol) in tetrahydrofuran (40 mL) was added to the mixture at -78 °C. After 1 h of stirring, *N,N*-dimethylmethyleneammonium iodide (2.83 g, 15.3 mmol) was added and stirred for 1h. On removal of the solvent, the residue was diluted with methanol. To the mixture, methyl iodide (10 mL) was added, and the whole was stirred for

24 h. Aqueous 5% $NaHCO_3$ solution was added to the mixture, and the whole was vigurously stirred. 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*. Oily materials were purified by column chromatography (silica gel, 10% AcOEt-hexane) to give 4-(2-*t*-butyldimethyl-silyloxy-1,1-difluoroethyl)-α-methylene-γ-butyrolactone (**1 2**) (1.53 g) in 51% yield and starting material (**1 1**) (683 mg) was recovered in 24% yield.^{1}H NMR ($CDCl_3$): δ 0.10 (3 H, s), 0.11 (3 H, s), 0.90 (9 H, s), 3.05 (1 H, ddt, *J*=17.8, 9.0, 2.9 Hz), 3.16 (1 H, ddt, *J*=17.8, 4.9, 2.7 Hz), 3.85 (1 H, td, *J*=11.7, 6.6 Hz), 3.99 (1 H, ddd, *J*=25.9, 11.5, 4.6 Hz), 4.87 (1 H, dddd, *J*=20.0, 9.0, 4.9, 2.7 Hz), 5.73 (1 H, t,*J*=2.7 Hz), 6.30 (1 H, t, *J*=2.9 Hz);^{13}C NMR ($CDCl_3$): δ -5.6, 18.2, 25.6, 26.1 (dd, *J*=4.4, 2.4 Hz), 61.8 (dd, *J*=38.1, 26.4 Hz), 71.8 (dd, *J*=38.3, 25.1 Hz), 119.7 (dd, *J*=246, 245 Hz), 123.2, 132.4, 169.1;^{19}F NMR ($CDCl_3$): δ -129 (ddt, *J*=264, 19.8, 6.1 Hz), -120 (dddd, *J*=264, 25.9, 12.2, 3.1 Hz); IR (neat): ν 1783, 1667 cm^{-1}.

*4-(1,1-Difluoro-2-hydroxyethyl)-α-methylene-γ-butyrolactone (**1 3**)*

To a solution of 4-(2-*t*-butyldimethylsilyloxy-1,1-difluoroethyl)-α-methylene-γ-butyrolactone (**1 2**) (800 mg, 2.74 mmol) in tetrahydrofuran (30 mL), tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 3.29 mL, 3.29 mmol) was added at 0 °C. After 10 min of stirring, the mixture was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$. On removal of the solvent, oily materials were purified by column chromatography (silica gel, 50% AcOEt-hexane) to give 4-(1,1-difluoro-2-hydroxyethyl)-α-methylene-γ-butyrolactone (**1 3**) (428 mg) in 88% yield.^{1}H NMR ($CDCl_3$): δ 2.28 (1 H, t, *J*=6.8 Hz), 3.09 (1 H, ddt, *J*=17.8, 9.0, 2.9 Hz), 3.18 (1 H, dtd, *J*=17.8, 4.9, 2.7 Hz), 3.89-4.07 (2 H, m), 4.49 (1 H, dddd, *J*=20.5, 8.8, 4.6, 2.2 Hz), 5.77 (1 H, t, *J*=2.4 Hz), 6.32 (1 H, t, *J*=2.9 Hz);^{13}C NMR ($CDCl_3$): δ 26.1 (dd, *J*=4.5, 2.3 Hz), 61.2 (dd, *J*=34.9, 26.0 Hz), 72.4 (dd, *J*=38.2, 25.1 Hz), 119.7 (dd, *J*=248, 243 Hz), 123.9, 132.1, 169.7;^{19}F NMR ($CDCl_3$): δ -129 (ddt, *J*=266, 21.4, 7.6 Hz), -121 (dddd, *J*=266, 23.7, 13.7, 2.3 Hz);IR (neat):ν 3442, 1776, 1666 cm^{-1}; HRMS calcd for $C_7H_8O_3F_2$ $(M)^+$ 178.0441, found 178.0449.

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