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gem-Difluorocyclopropane as core molecule candidate for liquid crystal compounds

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Abstract

The synthesis of a novel chiral *gem*-difluorocyclopropane building block has been accomplished using chemo-enzymatic reaction protocol; the prochiral diol of 1,4-bis(2,2-difluoro-3-(hydroxymethyl)cyclopropyl)benzene (**5**) was converted to the corresponding chiral diacetate by *Pseudomonas* lipase (lipase SL-25, Meito)-catalyzed transesterification with vinyl acetate as acyl donor with >99% enantiomeric excess. Various types of diesters or dialkyl ether were prepared from the diol and their helical twisting power (HTP) was evaluated by addition of 1.0 wt% to a non-chiral nematic liquid crystal host; the HTP was significantly dependent on the structure of ester or ether moieties and diester of diol **5** with isopropylfumalic acid showed the largest HTP.

Keywords: *gem*-Diflurocyclopropane; Lipase-catalyzed reaction; Enantiomerically pure; Liquid crystal; Chiral dopant; Helical twisted power

1. Introduction

The substitution of a fluorine atom on an organic molecule can alter the chemical reactivity due to the strong electron-withdrawing nature of the fluorine, thus making it possible to create a new molecule that exhibits unique physical properties [1]. The utility of cyclopropane derivatives in the construction of a variety of cyclic and acyclic organic compounds has been amply demonstrated [2]. We have been synthesizing novel molecules that have *gem*-difluorocyclopropane moieties [3] using our original chiral *gem*-diflurocyclopropane **1** and bis-*gem*-diflurocyclopropane **2** as building blocks [4]. CD spectroscopic analysis of 9-anthracenecarboxylic acid diester of **2** showed that the tetrafluorobicyclopropane group exists with a helical shape configuration; this seems to suggest that a unique helically shaped compound may be produced from *gem*-diflurocyclopropanes as building blocks [4h]. Recently, synthesis of a unique helically shaped compound which possesses a 7,7-difluorospiro [2.0.2.1] heptane moiety has been reported by Miyazawa, de Meijere and co-workers; it was established that the compound showed ferroelectric liquid crystalline property [5]. We were stimulated by the results and prepared 4′-*n*-nonyloxybiphenyl derivatives **3** and **4** and found that both compounds indeed showed liquid crystalline properties with different modes; compound **4** showed SmC* phase, while compound **3** showed only SmA phase (Fig. 1) [4e]. Recently liquid crystal displays (LCD) have become an inseparable part of our daily life. Therefore, development of new materials that have good electrooptical properties for LCD has now been recognized as a very importanttopic in the filed of organic synthesis [6]. To gain insight into designing novel liquid crystalline compounds based on the *gem*-difluorocyclopropane molecules, we designed difluorocyclopropane **6** that has a benzene ring as a spacer unit between two *gem*-difluorocyclopropane moieties and is derived from compound **5** (Fig. 1). In this paper we report the results of the syntheses of novel *gem*-difluorocyclopropane compound **5** in optically active form and investigation of properties of their derivatives in liquid crystal chemistry.

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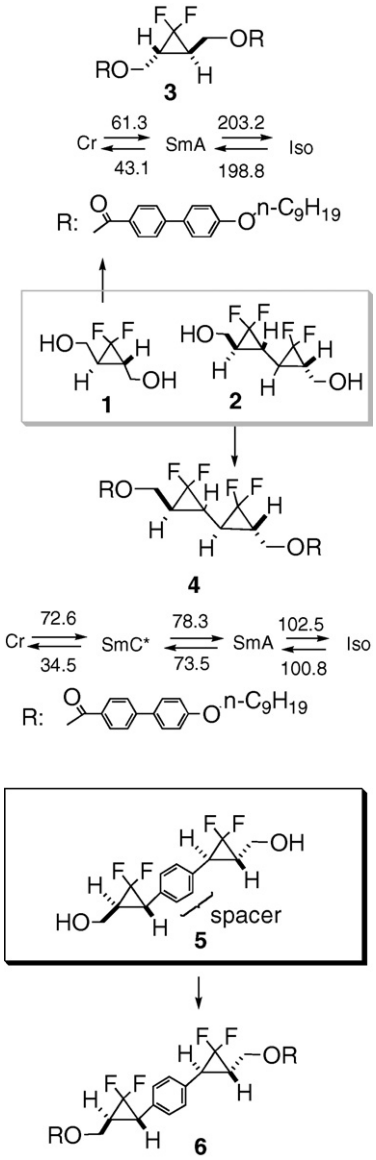


Fig. 1. Core molecules for liquid crystals that have *gem*-difluorocyclopropane moiety.

2. Results and discussion

2.1. Synthesis of optically active 1,4-bis(2,2-difluoro-3-(hydroxymethyl)cyclopropyl)benzene (5) using chemo enzymatic reaction

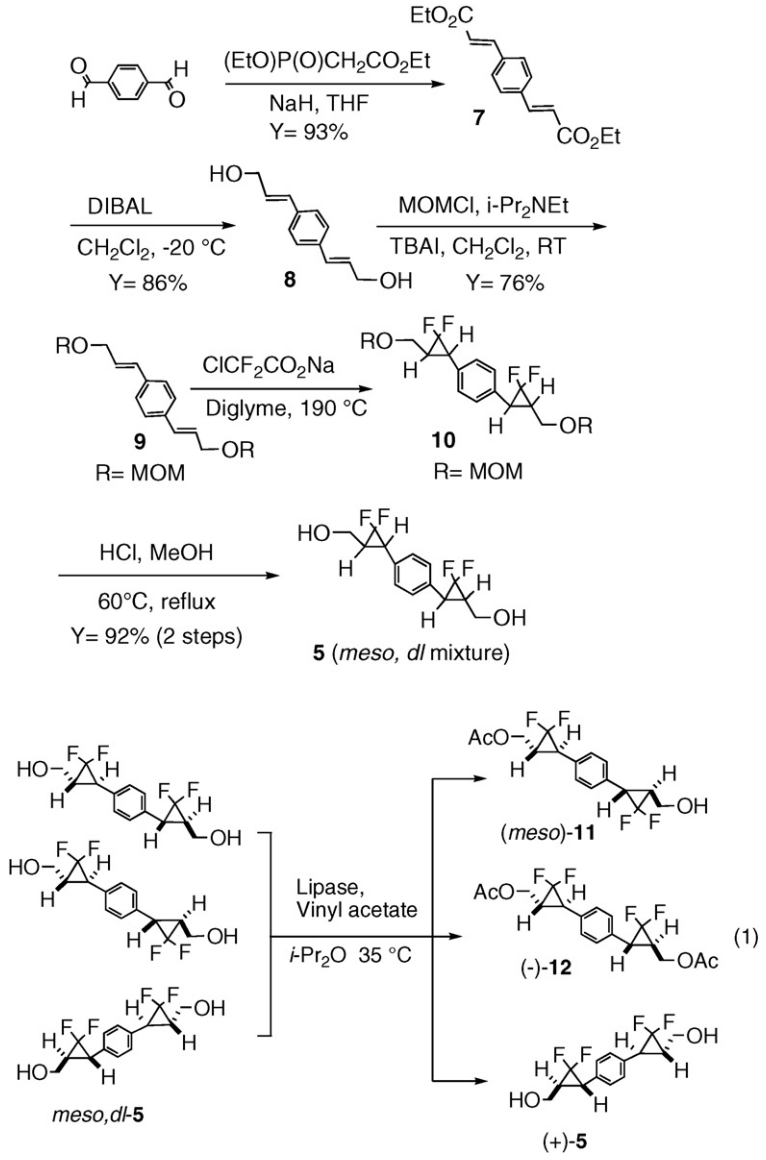
Synthesis of a racemic and DL mixture of *gem*-difluorocyclopropane **5** was accomplished following Scheme 1. (*E*,*E*)-Diene **7** was prepared using terephthaldicarboxaldehyde as a starting material by Horner-Wadsworth-Emmons reaction in 93% yield [6], and subsequent diisobutylalminum hydride (DIBAL) reduction of the ethoxycarbonyl groups of **7** to give 1,4-bis((*E*)-2-hydroxy-1-propenyl)benzene (**8**) in 86% yield [7]. We initially prepared benzyl ether derivative **9** (R = Benzyl) and converted it to the *gem*-difluorocyclopropane; the corresponding *gem*-difluorocyclopropane was obtained in excellent yield, however, we soon recognized that benzyl ether was not appropriate for the protecting group because significant decomposition of the difluorocyclopropane moieties took place during the de-protection step of the benzyl group by hydrogenation. So, diol **8** was converted to bis-methoxymethyl (MOM) ether **9** which was subjected to the reaction with difluorocarbene produced from pyrolysis of sodium chlorodifluoroacetate; bis-*gem*-difluorocyclopropane **10** was thus obtained and de-protection of the MOM ether groups gave desired compound **5** in excellent yield (92% from **10**) as a mixture of *meso*- and DL-form (1:1). Fortunately, we succeeded in obtaining a good crystal of *meso*-**5** by recrystallization from a mixed solvent of acetone and hexane. As shown in Fig. 2 of the ORTEP view of *meso*-**5**, there was an interesting difference in the crystalline structure found between **5** and **2**: the two difluorocyclopropane rings of **5** locate at the same plane, while they locate at the opposite site for bis-*gem*-diflurocyclopropane **2** [3h].

Optical resolution of racemic **5** was accomplished by lipase technology [9] and the results are shown in Table 1. Lipase SL-25, Lipase PS, and Lipase QL gave good results (Entries 1–3). With Lipase SL-25 being the best enzyme from the standpoint of enantioselectivity among them. The highest E^* value [10] obtained for Lipase SL-25 catalyzed reaction was estimated to be 55 (Entry 1). The most rapid reaction was observed when lipase QL was used as catalyst, though the enantioselectivity remained at a moderate level (Entry 3). In contrast, no enantioselctivity was obtained for Novozym 435 (Entry 4), nor did any reaction take place when lipase AY was employed as catalyst (Entry 5). Since the lipase-catalyzed reaction was a kinetic resolution, we succeeded in obtaining optically pure diol (+)-**5** easily, and thus handed both enantiomers of diol **5**.

An interesting point was found in the enantiofavoritism of the enzymatic reactions. (−)-Diacetate **12** and (+)-diol **5** were obtained for three enzymatic reactions (Entries 1–3). Monoacetate **11** was converted to diol **5** and assigned to be the *meso* form because the diol showed no specific rotation value and ^{1}H NMR spectra coincided with those of *meso*-**5**. According to the sign of specific rotation value of diacetate **12**, it was assumed that the produced (−)-diacetate **12** was (*R*,*S*,*S*,*R*)-isomer, and that, (+)-diol **12** unreacted was (*S*,*R*,*R*,*S*)-isomer [4d,4h]; these three lipases prefer to react with the hydroxyl group that has (*R*)-configuration. On the other hand, we had previously established that the same enzymes, SL-25 and QL, reacted with bis-*gem*-difluorocyclopropane **1** or **2** with (*S*)-enatiofavoritism [4d,4h]. This seems to mean that the phenyl group between the two *gem*-difluorocyclopropane rings seemed to cause a modification in the enantiofavoritism of these enzymes.

2.2. Helical twisting power of gem-diflurocyclopropane derivatives

Optically pure diol **5** was converted to bis-*n*-nonyl ether **6a** and four types of esters **6b**, **6c**, **6d**, and **6e** and their liquid crystal property was investigated. Although we expected that liquid crystal properties might be found for these compounds, none showed this property. Chiral nematic liquid crystals having macro helical structure are currently used in LCD



Scheme 1.

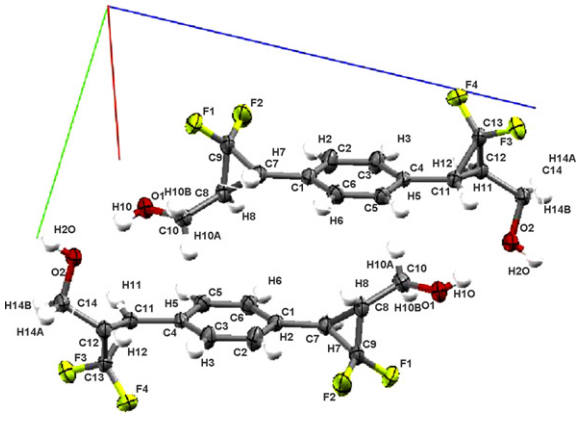


Fig. 2. ORTEP view of *meso*-**5**.

devices [6]; the chiral nematic materials consist of achiral host mixtures of nematic liquid crystals and a chiral dopant with helical twisting power [HTP][11]. Generally, the chiral nematic materials that are used in good LCD devices consist of achiral host mixture of nematic liquid crystals and a chiral dopnat with a large helical twisting power (HTP). Therefore, it is very important to develop efficient chiral dopant materials with having large HTP. The syntheses of fluorinated compounds that have large HTP have been reported by several groups [12–15]. So we investigated the HTP of our *gem*-difluorocyclopropane compounds **6a**–**6e** and found that all of them had helical twisting power (HTP) when 1.0 wt% was added to the host achiral nematic liquid crystal [16]. The helical pitches in the chiral nematic phases were measured using Cano wedge cells [17]: the HTP can be calculated by $(pc)^{-1}$, where p is the pitch of the chiral nematic phase in μm and c is the mass fraction of the chiral dopant [17], and the results are summarized in Fig. 3.

Table 1
Results of lipase-catalyzed acylation of *meso*- and DL-**5**

Entry	Lipase	Time	Yield of **11**[a] (*meso*)	Yield of **12**[a,b] (% ee)	Yield of **5**[a,b] (% ee)	c^{*}[c]	E^{*}[c]
1	Lipase SL-25	105 min	43%	29% (90% ee)	28% (88% ee)	0.49	55
2	Lipase PS	180 min	38%	31% (75% ee)	31% (80% ee)	0.52	17
3	Lipase QL	20 min	41%	47% (61% ee)	3% (99% ee)	0.62	23
4	Novozym435	5 min	0%	82% (0.8% ee)	0% (–)	–	–
5	Lipase AY	2 days	0%	0% (–)	99% (0% ee)	–	–

[a] Isolated yield.
[b] Determined by HPLC analysis using Chiralcel OD-H (hexane:*i*-PrOH = 4:1).
[c] Since the reaction included two processes, E^{*} value was the result of two reactions. $E^{*} = \ln[(1 - c)(1 - \text{ee}12)]/\ln[(1 - c)(1 + \text{ee}12)]$, here $c^{*} = \text{ee}5/(\text{ee}12 + \text{ee}5)$.

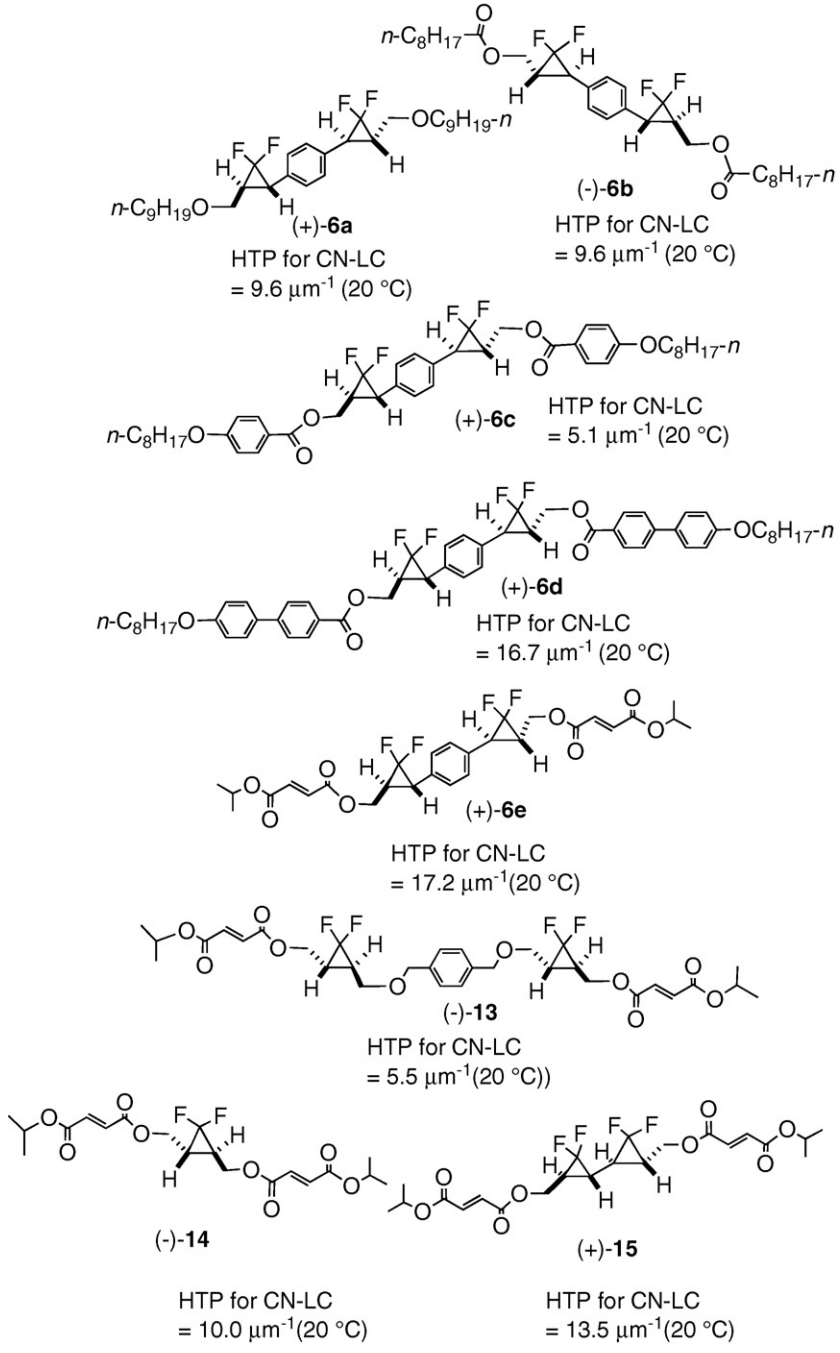


Fig. 3. Helical twisting power of various cyclopropane derivatives.

Among them, compounds **6c**, **6d**, and **6e** showed large HTP values, 19.6, 16.7 and 17.2 μm^{-1}, respectively, values ca. four-fold larger than that of cholesteryl caprylate (HTP = 4.4 μm^{-1}). The HTP values were significantly dependent on the ester group, and it was found that introduction of isopropylfumalic acid moiety was very effective to obtain high HTP values.

To gain insight in the role of the benzene ring between *gem*-difluorocyclopropane for helical twisting power, we prepared three types of bis-isopropylfumalate derivatives, (−)-**13**, (−)-**14**, and (+)-**15**, but all these had smaller HTP values than **6e**. Flexibility of the *gem*-difluorocyclopropane moiety seems to play an important part in determining the helical twisting ability, and the rigid form of the core part of the molecule seems to be important for obtaining high HTP, because the lowest HTP value was obtained for (−)-**13**. It was thus established that *gem*-difluorocyclopropane compound showed good property as a chiral dopant that caused helical twisting of achiral host mixture of nematic liquid crystal compounds.

3. Conclusion

In summary, we accomplished the synthesis of various types of unique diether or diester based on optically active bis-hydroxymethyl-*gem*-difluorocyclopropane compounds as building blocks. These compounds have interesting properties; in particular, compounds (+)-**6c**, (+)-**6d** and (+)-**6e** acted caused helical twisting when they were dissolved in achiral nematic host liquid crystal. We are hopeful that these unique properties might be identified allowing further investigation of our novel *gem*-difluorocyclopropane compounds.

4. Experimental

4.1. General procedures

Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Wako gel C-300 and Wako gel B5F were used for the flash column chromatography and thin-layer chromatography (TLC). ^{1}H NMR spectra, ^{13}C NMR spectra and ^{19}F NMR spectra were recoded on JEOL JNM MH-500 spectrometer. Chemical shifts are expressed in δ value (ppm) downfield from tetramethylsilane (TMS) in $CDCl_3$ as the internal reference. The ^{19}F NMR spectra were reported in ppm downfield from C_6F_6 as the internal reference. IR spectra were obtained on SHIMADZU FT-IR 8000 spectrometers. Optical purity was determined by HPLC analysis using chiralcel OD-H (Daicel). Helical twisted power of *gem*-difluorocyclopropane derivatives were estimated by the distance between the stripes appeared using a microscope in the Cano's type wedge-shaped when 1.0 wt% of *gem*-diflurocyclopropane was dissolved in the achiral nematic host mixture consisted of cyanobenzene compopunds: 1-cyano-4-(*trans*-4-*n*-propylcyclohexyl)benzene, 1-cyano-4-(*trans*-4-*n*-heptylcyclohexyl)benzene, 4-cyano-4′-(*trans*-4-*n*-heptylcyclohexyl)biphenyl (24:36:25:15 by weight). The physical properties of the host mixture are T_{NI} = 72.4 °C, $\Delta\varepsilon$ = 11.0, Δn = 0.137.

4.2. (E)-Diethyl p-phenylenediacrylate (7) [7]

To a solution of the sodium hydride in tetrahydrofuran (THF) (60 mL) was added ethyl diethylphosphonoacetetate (17 g, 75 mmol) in THF (60 mL) at 0 °C and the mixture was stirred for 2 h at rt, then terephthalaldehyde (4.0 g, 30 mmol) in THF (60 mL) was added. After being stirred for 30 min at the same temperature, the reaction was quenched by addition of saturated aq. NH_4Cl and 2 M HCl. Extraction with ethyl acetate, dried over $MgSO_4$, concentrated under vacuum, and purified by silica gel flash column chromatography (ethyl acetate–hexane, 0:1–1:5) gave (*E*)-diester **7** (3.3 g) in 93% yield: R_f 0.5 (hexane/ethyl acetate = 4:1); mp 114–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (6H, t, J = 7.3 Hz), 4.21–4.23 (4H, m), 6.40 (2H, d, J = 16.1 Hz), 7.47 (4H, s), 7.60 (2H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.18, 60.48, 119.21, 128.36, 136.01, 143.25, 166.55; IR (KBr, cm^{-1}) 3393, 1701, 1632, 1512, 1448, 1474, 1420, 1366, 1323, 1306; Anal. Calcd for $C_{12}H_{14}O_2$; C, 75.76; H, 7.42. Found: C, 70.22; H, 7.23.

4.3. 1,4-Bis(3-hydroxy-1-((E)-propenyl)benzene (8) [8]

To a solution of **7** (14 g, 50 mmol) in toluene (280 mL) was added diisobutylaluminum hydride (230 mL, 1.5 M in toluene, 230 mmol) at −20 °C and the reaction mixture was stirred for 12 h allowed to RT. The reaction was quenched by addition of potassium fluoride and water, then extracted with ethyl acetate, dried over $MgSO_4$, and concentrated under vacuum. Recrystallization in ether gaive diol **8** (8.2 g) in 86% yield: R_f 0.34 (hexane/ethyl acetate/methanol = 4:4:1); ^{1}H NMR (500 MHz, $CDCl_3$ + D_3COD) δ 2.11 (2H, s), 4.27–4.29 (4H, m), 6.33–6.37 (2H, m), 6.56–6.60 (2H, m), 7.35 (4H, s); ^{13}C NMR (125 MHz, D_3COD) δ 63.67, 127.64, 129.89, 131.18, 137.65; IR (KBr, cm^{-1}) 3751, 3726, 3269, 3024, 2839, 2718, 2446, 1911, 1655, 1541.

4.4. 1,4-Bis((E)-3-(methoxymethoxy)prop-1-enyl)benzene (9)

To dichloromethane (340 mL) solution of **8** (13 g, 68 mmol) were added diisopropylethylamine (22 g, 170 mmol) and chloromethoxymethane at 0 °C and the mixture was stirred for 3 h at rt and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated. Silica gel flash column chromatography (ethyl acetate–hexane, 20:1–4:1) afforded di-MOM-ether **9** (14 g) in 76% yield: R_f 0.30 (hexane/ethyl acetate = 4:1); mp 65–67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (6H, s), 4.16–4.17 (4H, m), 4.64 (4H, s) 6.21–6.24 (2H, m), 6.53–6.56 (2H, m), 7.28 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.20, 67.73, 95.59, 125.50, 126.63, 132.06, 136.03; IR (KBr, cm^{-1}) 3854, 3751, 1653, 1558, 1508, 1458, 1381, 1211, 1146, 1097.

4.5. 1,4-Bis(2,2-difluoro-3-(methoxymethoxymethyl)cyclopropyl)benzene (**5**)

To a dry diglyme (20 mL) solution of di-MOM-ether **9** (14 g, 52 mmol) was added 150 mL of diglyme solution of sodium chlorodifluoroacetate (87 g, 570 mmol) drop wise at 190 °C over 4 h with vigorous stirring. After being kept at 190 °C for an additional 2 h, the reaction mixture was allowed to cool to room temperature (rt), then the mixture was poured into ice water and extracted with hexane and ethyl acetate. The combined organic layers were washed with brine and water, dried over $MgSO_4$ and evaporated under reduced pressure to give di-MOM-ether **10**. Since it was difficult to remove diglyme at this stage, this was used for the nxet reaction without further purification.

To the methanol (200 mL) solution of di-MOM-ether **10** was added conc. hydrochloric acid drop wise and stirred under reflux conditions for 2 h. After being cooled to rt, the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel flash column chromatography (ethyl acetate–hexane, 5:1–4:1) afforded diol **5** (14 g) in 92% yield as a mixture of *meso* and DL mixture (2 steps): R_f 0.32 (hexane/ethyl acetate = 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (2H, sex, J = 6.7 Hz), 2.54 (2H, q, J = 7.4 Hz), 3.53 (6H, s), 3.74 (4H, d, J = 12.0 Hz), 4.65 (4H, s), 7.18 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) 29.13 (t, J_{C-F} = 95.4 Hz), 31.33 (t, J_{C-F} = 105 Hz), 55.21, 63.91, 96.17, 113.25 (t, J_{C-F} = 288 Hz), 128.14, 132.19; ^{19}F NMR (470 MHz, $CDCl_3$) 11.49–11.59 (m), 36.45 (d, J = 35.2 Hz); IR (neat, cm^{-1}) 3854, 3651, 2889, 2827, 1524, 1474, 1389, 1271, 1219, 1180.

Recrystallization from acetone and hexane gave pure *meso*-**5** and X-ray crystallographic analysis was successfully carried out.

(*meso*)-**5**: R_f 0.14 (acetone/hexane = 1:2); mp 158–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (2H, sex. d, J = 5.5, 2.3 Hz), 2.63–2.67 (2H, m), 3.71–3.75 (2H, m), 3.77–3.81 (2H, m), 7.21 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.2 (q, J = 10.6 Hz), 59.6 (d, J_{C-F} = 3.8 Hz), 115.2 (t, J_{C-F} = 289 Hz), 129.2, 133.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ 23.3 (qd, J = 144, 69, 11.5 Hz); IR (KBr, cm^{-1}); 3269, 3032, 2914, 2853, 2613, 1526, 1477, 1414, 1250, 1177; Anal. Calcd for $C_{14}H_{14}F_4O_2$; C, 57.93; H, 4.86. Found: C, 57.77; H, 4.81.

Crystal and refinement data for *meso*-**5**: $C_{14}H_{14}F_4O_2$, formula weight = 394.41, triclinic, space group $P1_1$ (#2), a = 5.6338 Å, b = 8.9410, c = 13.133 Å, V = 629.87 Å^3, Z = 2, d_{calc} = 1.53 g cm^{-3}, $R(Rw)$ = 0.0536 for 2795 diffraction data with $I > 3.00\sigma$ (I) and 182 valuable.

4.6. Lipase-catalyzed optical resolution of (±)-**5**

To solution of **5** (60 mg, 0.21 mmol, racemic:*meso* = 1:1) and vinyl acetate (36 mg, 0.42 mmol) in diisopropyl ether (1.1 mL) was added Lipase SL-25 (30 mg, 50 wt%) and the mixture was stirred at 35 °C for 1.8 h. The reaction course was monitored by silica gel TLC. Lipase was removed by filtration through a sintered glass filter with a Celite pad and the filtrate was concentrated under vacuum. Silica gel TLC (acetone–hexane, 2:1) gave (−)-diacetate **12** (23 mg, 29%), monoacetate **11** (32 mg, 48%), and (+)-diol **5** (22 mg, 28%):

*Monoacetate **11***: $[\alpha]_D^{29}$ − 1.83 (c 1.2, MeOH), a mixture of *meso*-**11** and a small amount of (−)-**11**; R_f 0.32 (acetone/hexane = 1:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (1H, s), 2.03 (3H, s) 2.11–2.19 (2H, m), 3.80–3.82 (1H, m), 3.81–3.90 (1H, m), 4.15–4.20 (1H, m), 4.25–4.30 (1H, m), 7.12 (4H, d, J = 2.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 27.8 (t, J_{C-F} = 9.6 Hz), 30.8 (t, J_{C-F} = 11.6 Hz), 31.1 (t, J_{C-F} = 8.6 Hz), 31.3 (t, J_{C-F} = 10.6 Hz), 59.1 (d, J_{C-F} = 3.9 Hz), 60.7 (d, J_{C-F} = 4.8 Hz), 113.2 (td, J_{C-F} = 212, 77.8 Hz), 128.1 (d, J_{C-F} = 5.7 Hz), 131.9 (d, J_{C-F} = 107 Hz), 171.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ 24.34–26.44 (m); IR (neat, cm^{-1}) 3854, 3751, 3690, 3676, 3398, 2891, 1707, 1560, 1524, 1508.

4.6.1. Diacetate (−)-**12**

90% ee: $[\alpha]_D^{29}$ − 36.3 (c 1.2, MeOH), >99% ee: $[\alpha]_D^{29}$ − 40.3 (c 1.0, MeOH). Enantiomeric excess of (−)-**12** was deyermined by HPLC analysis using Chiralcel OD-H, hexane/2-propanol (9:1), 35 °C. Rt (R,R) = 17 min, R_t (*meso*) = 11 min, and R_t (S,S) = 9.3 min.; R_f 0.50 (acetone/hexane = 1:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09 (6H, s), 2.23 (2H,s ex, J = 7.8 Hz), 4.10–4.25 (2H, m), 4.31–4.35 (2H, m), 7.17 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 27.9 (t, J_{C-F} = 9.6 Hz), 31.4 (t, J_{C-F} = 10.5 Hz), 60.6 (d, J_{C-F} = 4.8 Hz), 112.8 (t, J_{C-F} = 289 Hz), 128.2, 131.8, 170.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ 24.37–26.49 (m); IR (neat, cm^{-1}) 3854, 3751, 3690, 3676, 3651, 2963, 1742, 1701, 1560, 1508.

4.6.2. Diol (+)-**5**

88% ee: $[\alpha]_D^{29}$ + 18.9 (c 1.1, MeOH), >99% ee: $[\alpha]_D^{29}$ + 22.5 (c 1.0, MeOH). Enantiomeric excess of (+)-**5** was determined by HPLC analysis using Chiralcel OD-H, hexane/2-propanol (4:1), 35 °C. R^t (R,R) = 8.8 min, R_t (*meso*) = 11 min, and R_t (S,S) = 10.0 min; R_f 0.14 (acetone/hexane = 1:2); mp 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (2H, s), 2.15–2.17 (2H, m), 2.56–2.59 (2H, m), 3.81–3.86 (2H, m), 3.90–3.95 (2H, m), 7.17 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.60 (t, J_{C-F} = 11.4 Hz), 32.09 (t, J_{C-F} = 9.54 Hz), 59.12, 115.19 (t, J_{C-F} = 286 Hz), 128.93, 133.38; ^{19}F NMR (470 MHz, $CDCl_3$) δ 24.65–25.68 (m); IR (neat, cm^{-1}) 3906, 3854, 3751, 3690, 3676, 3651, 3368, 2893, 1701, 1647; Anal. Calcd for $C_{14}H_{14}F_4O_2$; C, 57.93; H, 4.86. Found: C, 57.77; H, 4.84.

4.7. Results of lipase PS-catalyzed reaction

Diacetate **12**: 75% ee, $[\alpha]_D^{28}$ − 32.9 (c 1.1, MeOH), Y = 31%.
Monoacetate **11**: $[\alpha]_D^{28}$ + 2.00 (c 1.0, MeOH), Y = 46%.
Diol **5**: 80% ee, $[\alpha]_D^{28}$ + 13.2 (c 1.3, MeOH), Y = 24%.

4.8. Results of lipase QL-catalyzed reaction

Diacetate **12**: 61% ee, $[\alpha]_D^{28}$ − 42.3 (c 1.0, MeOH), Y = 47%.
Monoacetate **11**: $[\alpha]_D^{28}$ + 13.1 (c 0.9, MeOH), Y = 41%.
Diol **5**: >99% ee, $[\alpha]_D^{28}$ + 29.0 (c 0.2, MeOH), Y = 3%.

4.9. Results of Novozyme 435-catalyzed reaction

Diacetate **12**: 0.8% ee, $[\alpha]_D^{25}$ − 1.2 (c 1.0, MeOH), Y = 82%.

4.10. Synthesis of (+)-*6a*

To a DMF (1.0 mL) suspension of sodium hydride (110 mg, 0.38 mmol) was added a DMF (2.0 mL) solution of diol (+)-**5** (110 mg, 0.38 mmol, >99% ee) at 0 °C and the mixture was stirred for 5 h at rt. To this mixture was added water and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, evaporated and purified by silica gel flash column chromatography (ethyl acetate:hexane = 1:20) gave (+)-**6a** (160 mg) in 78% yield: $[\alpha]_D^{24}$ − 36.6 (c 1.0, $CHCl_3$); R_f 0.56 (ethyl acetate/hexane = 1:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.880 (6H, t, J = 7.33 Hz), 1.26–1.36 (20H, m), 1.56–1.61 (4H, m), 2.13 (2H, sex, J = 7.3 Hz), 2.53 (2H, dd, J = 14.7, 7.8 Hz), 3.41–3.46 (2H, m), 3.48–3.53 (2H, m), 3.59–3.63 (2H, m), 3.69–3.73 (2H, m), 7.18 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.1, 29.3 (t, J_{C-F} = 10.6 Hz), 29.4, 29.5, 29.7, 31.1 (t, J_{C-F} = 11.5 Hz), 31.9, 66.7 (d, J_{C-F} = 3.84 Hz), 70.8, 113.4 (t, J_{C-F} = 289 Hz), 128.2, 132.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ 25.4 (ddd, J = 726, 144, 11.5 Hz); IR (KBr, cm^{-1}) 3906, 2926, 2856, 1686, 1647, 1560, 1508, 1375, 1267, 1111; Anal. Calcd for $C_{30}H_{50}F_4O_2$; C, 70.82; H, 9.29. Found: C, 70.28; H, 9.00.

4.11. Synthesis of (−)-*6b*

To a mixture of (−)-**5** (220 mg, 0.69 mmol, >99% ee), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide ethylene dichloride (EDC) (63 mg, 0.33 mmol), nonanoic acid (380 mg, 2.1 mmol), and 4-*N*,*N*′-dimethylaminopyridine (DMAP) (270 mg, 2.2 mmol) in 10 mL of dichloromethane (CH_2Cl_2) was added 0.25 mL of triethylamine (Et_3N) at 0 °C and the mixture was stirred for 5 h at 60 °C, then cooled to rt and was extracted with Et_2O. The combined organic layers were washed with water and 2 M HCl, dried over $MgSO_4$, evaporated, and purified by silica gel flash column chromatography (ethyl acetate–hexane, 1:50–1:6) to give diester (−)-**6b** (350 mg) in 90% yield: $[\alpha]_D^{28}$ − 52.6 (c 1.0, $CHCl_3$); R_f 0.58 (ethyl acetate/hexane = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.860–0.889 (6H, m), 1.25–1.35 (20H, m), 1.60–1.66 (4H, m), 2.24 (2H, quin, J = 7.8 Hz), 2.34 (4H, t, J = 7.3 Hz), 2.64 (2H, dd, J = 14.6, 7.8 Hz), 4.23–4.27 (2H, m), 4.33–4.36 (2H, m), 7.18 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.6, 24.9, 28.1 (t, J_{C-F} = 10.5 Hz), 29.0, 29.1, 31.5 (t, J_{C-F} = 11.5 Hz), 31.7, 34.1, 60.4 (d, J_{C-F} = 18.2 Hz), 112.9 (t, J_{C-F} = 289 Hz), 128.3, 131.9, 173.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ 24.4–26.6 (m); IR (KBr, cm^{-1}); 2928, 2856, 1736, 1719, 1707, 1524, 1458, 1221, 1161, 1111; Anal. Calcd for $C_{28}H_{30}F_4O_4$; C, 67.35; H, 8.12. Found: C, 67.44; H, 8.58.

Compounds (+)-**6c**, (+)-**6d**, and (+)-**6e** were prepared using optically pure diol (+)-**5** following to the similar method.

4.12. (+)-*6c*

R_f 0.50 (ethyl acetate/hexane = 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.888 (6H, t, J = 7.3), 1.26–1.37 (16H, m), 1.44–1.47 (4H, m), 1.80, (4H, quin, J = 6.9 Hz), 2.36 (2H, sex, J = 6.4 Hz), 2.73 (2H, dd, J = 14.2, 7.3 Hz), 4.01 (4H, t, J = 6.4 Hz), 4.45–4.49 (2H, m), 4.54–4.58 (2H, m), 6.91 (4H, d, J = 9.2 Hz), 7.20 (4H, s), 7.99 (4H, d, J = 8.71 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.6, 25.9, 28.3 (t, J_{C-F} = 9.6 Hz), 29.2 (t, J_{C-F} = 13.4 Hz), 31.5 (t, J_{C-F} = 11.5 Hz), 31.7, 60.8, 68.2, 113.0 (t, J_{C-F} = 289 Hz), 114.1, 121.7, 128.3, 131.7, 132.0, 163.2, 166.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ 25.6 (ddd, J = 587, 155, 17.3 Hz); IR (KBr, cm^{-1}); 3854, 3651, 2924, 2849, 1707, 1609, 1514, 1254, 1105, 1009.

$[\alpha]_D^{24}$ + 19.4 (c 1.0, $CHCl_3$); Anal. Calcd for $C_{44}H_{54}F_4O_6$; C, 70.01; H, 7.21. Found: C, 69.27; H, 7.16.

4.13. (+)-*6d*

R_f 0.42 (ethyl acetate/hexane = 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.878–0.905 (6H, m), 1.25–1.39 (20H, m), 1.81 (4H, q, J = 7.8 Hz), 2.39 (2H, sex, J = 7.3 Hz), 2.76 (2H, dd, J = 15, 7.8 Hz), 4.00 (4H, t, J = 6.4 Hz), 4.50–4.54 (2H, m), 4.59–4.62 (2H, m), 6.87 (4H, d, J = 8.7 Hz), 7.22 (4H, s), 7.56 (4H, d, J = 8.7 Hz), 7.63 (4H, d, J = 8.7 Hz), 8.09 (4H, d, J = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 28.2, (t, J_{C-F} = 9.6 Hz), 29.2, 29.3, 31.6 (t, J_{C-F} = 9.6 Hz), 31.8, 61.2, 68.1, 113.0 (t, J_{C-F} = 290 Hz), 115.3, 126.5, 127.6, 128.3, 128.4, 130.2, 132.0 (d, J_{C-F} = 2.9 Hz), 145.6, 159.5, 166.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ 24.7–26.7 (m); IR (KBr, cm^{-1}); 3854, 3427, 2928, 2854, 1719, 1605, 1474, 1267, 1180, 1109; $[\alpha]_D^{26}$ + 13.8 (c 0.90, $CHCl_3$); Anal. Calcd for $C_{56}H_{62}F_4O_6$; C, 74.15; H, 6.89. Found: C, 75.09; H, 6.68.

4.14. (+)-*6e*

$[\alpha]_D^{23}$ + 31.0 (c 1.0, $CHCl_3$); R_f 0.36 (ethyl acetate/hexane = 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (12H, d, J = 6.3 Hz), 2.29 (2H, sex, J = 7.3 Hz), 2.69 (2H, q, J = 7.3 Hz), 4.39 (2H, m), 4.48 (2H, m), 5.12 (2H, seq, J = 6.0 Hz), 6.87 (4H, d, J = 1.8 Hz), 7.19 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) d 21.8 (d, J_{C-F} = 3.8 Hz), 27.9 (t, J_{C-F} = 10.6 Hz), 31.7 (t, J_{C-F} = 10.6 Hz), 61.6 (d, J_{C-F} = 4.7 Hz), 69.2 (d, J_{C-F} = 7.7 Hz), 112.8 (t, J_{C-F} = 290 Hz), 128.4, 131.9, 132.4 (t, J_{C-F} = 3.8 Hz), 135.1 (t, J_{C-F} = 2.9 Hz), 164.2, 164.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 25.5 (ddd, J = 720, 144, 11.6 Hz); IR (KBr, cm^{-1}) 3414, 2856, 1734, 1481, 1393, 1267, 1175, 1034, 964; Anal. Calcd for $C_{28}H_{30}F_4O_4$; C, 67.35; H, 8.12. Found: C, 67.27; H, 7.89.

4.15. Synthesis of (−)-*13*

4.15.1. Synthesis of 1,4-bis(2,2-difluoro-(3-t-butyldiphenylsilyloxymethyl)cyclopropylmethoxymethyl)benzene (−)-*16*

To a suspension of NaH (23 mg, 0.57 mmol, 60% in mineral oil) in 1.0 mL of THF was added 2,2-difluoro-3-(*t*-butyldiphenylsiliyoxymethyl)cyclopropylmethanol (143 mg, 0.38 mg,

>99% ee) [4d] at 0 °C under argon atmospheric conditions and the mixture was stirred for 1 h at the same temperature. To this mixture was added 1,4-di(bromomethyl)benzen (50 mg, 0.19 mmol) and the resulting mixture was stirred for 15 h at rt. The reaction was quenched by the addition of several pieces of ice and was extracted with ether. The combined organic layers were dried over $MgSO_4$ and evaporated and purified by silica gel flash chromatography to give (−)-**16** (135 mg, 0.16 mmol) in 83% yield: $[\alpha]_D^{18}$ − 4.0 (c 1.0, $CHCl_3$); R_f 0.7 (hexane/ethyl acetate = 4:1; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (18H, s), 1.48–1.62 (4H, m), 3.37–3.51 (4H, m), 3.68 (4H, d, J = 6.0 Hz), 4.44 (4H, dd, J = 18.5, 11.5 Hz), 7.21–7.60 (24H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.13, 25.98 (t, J_{C-F} = 10.6 Hz), 26.73, 28.46 (t, J_{C-F} = 10.0 Hz), 60.15 (d, J_{C-F} = 4.3 Hz), 66.04 (d, J_{C-F} = 4.3 Hz), 72.10, 114.20 (t, J_{C-F} = 287.0 Hz), 127.71, 129.77, 133.20, 133.30, 133.53, 137.42; ^{19}F NMR (471 MHz, $CDCl_3$) δ 22.91 (dd, J = 161.3, 14.4 Hz), 24.05 (dd, J = 161.2, 14.4 Hz); IR (neat, cm^{-1}) 2858, 1474, 1427, 1396, 1362, 1259, 1192, 1092, 102, 802.

*4.15.2. Synthesis of (−)-**13***

To a 4.1 mL of THF solution of (−)-**16** (347 mg, 0.41 mmol) was added a 1.0 mL THF solution of tetrabutylammonium fluoride (1.01 mmol) at rt and the mixture was stirred for 15 h at rt, then the solvent was removed by evaporation under vacuum conditions to give diol (−)-**17** (127 mg) which was subjected to the next esterification without further purification. To a mixture of EDC (130 mg, 0.68 mmol), fumalic acid monoisopropyl ester (108 mg, 0.68 mmol) and (−)-**17** (127 mg, 0.34 mmol, crude) in CH_2Cl_2 (2.4 mL) was added DMAP (17 mg, 0.14 mmol) at one portion under argon at 0 °C. The mixture was stirred for 4 h at rt, then removed the solvent by evaporation and the residue was extracted with ethyl acetate. The combined organic layers were washed with water, dried over $MgSO_4$, and evaporated. Silica gel flash column chromatography (hexane/ethyl acetate = 20:1–4:1) gave (−)-**13** (120 mg, 0.18 mmol) in 54 % yield (two steps): $[\alpha]_D^{22}$ − 12.0 (c 1.3, $CHCl_3$); R_f 0.2 (hexane/ethyl acetate = 4:1; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (12H, d, J = 6.0 Hz), 1.73–1.82 (4H, m), 3.43–3.53 (4H, m), 4.10–4.32 (4H, m), 4.44 (4H, dd, J = 18.0, 11.5 Hz), 5.00–5.09 (2H, m), 6.77 (4H, s), 7.23 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.62, 24.99 (t, J_{C-F} = 10.8 Hz), 26.76 (t, J_{C-F} = 10.0 Hz), 60.23, 65.51, 69.02, 72.25, 113.46 (t, J_{C-F} = 287 Hz), 127.65, 132.41, 134.85, 137.27, 164.15, 164.65; ^{19}F NMR (471 MHz, $CDCl_3$) δ 23.49 (t, J = 168 Hz); IR (neat, cm^{-1}) 2872, 1717, 1645, 1456, 1261, 1157, 1107, 989, 777; Anal. Calcd for $C_{32}H_{38}F_4O_{10}$; C, 58.35; H, 5.82. Found: C, 58.29; H, 5.72.

*4.16. Syntheses of (−)-**14** and (+)-**15***

The syntheses of (−)-**14** and (+)-**15** were accomplished using diol (−)-**1** and (+)-**2** following to the same method of the synthesis of (−)-**6b** in 44% yield and 46% yield, respectively.

*4.16.1. (−)-(**14**)*

$[\alpha]_D^{20}$ − 13.2 (c 1.0, $CHCl_3$); R_f 0.4 (hexane/ethyl acetate = 4:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (12H, d, J = 6.2 Hz), 1.92–1.99 (2H, m), 4.19–4.32 (4H, m), 5.05–5.14 (2H, m), 6.81 (4H, d, J = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.64, 25.60 (t, J_{C-F} = 10.6 Hz), 60.78, 69.08, 112.93 (t, J_{C-F} = 287.0 Hz), 132.18, 135.11, 164.08, 164.62; ^{19}F NMR (471 MHz, $CDCl_3$) δ 23.42 (s); IR (KBr, cm^{-1}) 2984, 1717, 1647, 1456, 1377, 1224, 1157, 1109, 988; Anal. Calcd for $C_{19}H_{24}F_2O_8$; C, 54.54; H, 5.78. Found: C, 53.97; H, 5.72.

*4.16.2. (+)-(**15**)*

$[\alpha]_D^{27}$ + 20.2 (c 1.0, $CHCl_3$); R_f 0.4 (hexane/ethyl acetate = 4:1); mp 90–95 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (12H, d, J = 6.2 Hz), 1.67–1.75 (4H, m), 4.18–4.33 (4H, m), 5.07–5.16 (2H, m), 6.83 (4H, d, J = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.70, 22.92 (t, J_{C-F} = 10.6 Hz), 25.91 (t, J_{C-F} = 10.4 Hz), 60.73 (d, J_{C-F} = 3.9 Hz), 69.16, 112.38 (t, J_{C-F} = 288.0 Hz), 132.19, 135.13, 164.19, 164.71; ^{19}F NMR (471 MHz, $CDCl_3$) δ 24.32 (dd, J = 163.0, 10.1 Hz), 24.90 (dd, J = 162.7, 12.9 Hz); IR (KBr, cm^{-1}); 1713, 1643, 1456, 1265, 1173, 1109, 986, 779, 426; Anal. Calcd for $C_{22}H_{26}F_4O_8$; C, 53.44; H, 5.30. Found: C, 53.28; H, 5.32.

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