Journal of Fluorine Chemistry 130 (2009) 1157–1163

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Chemo-enzymatic synthesis of spiro type gem-difluorocyclopropane as core molecule candidate for liquid crystal compounds

Toshiyuki Itoh [a,*], Manabu Kanbara [a], Shino Nakajima [a], Yusuke Sakuta [a], Shuichi Hayase [a], Motoi Kawatsura [a], Takashi Kato [b], Kazutoshi Miyazawa [b], Hidemitsu Uno [c]

[a] Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan
[b] Chisso Petrochemical Corporation, Goi Research Center, Research Laboratory I, 5-1 Goikaigan, Ichihara-shi, Chiba 290-8551, Japan
[c] Department of Chemistry and Biology, Graduate School of Science and Engineering, Ehime University, Matsuyama 790-8577, Japan

ARTICLE INFO

Article history:
Received 12 May 2009
Received in revised form 9 June 2009
Accepted 9 June 2009
Available online 18 June 2009

Keywords:
Spiro compounds
gem-Difluorocyclopropane
Lipase-catalyzed reaction
Helical twisting power
Liquid crystal

ABSTRACT

The synthesis of a novel spiro type gem-difluorocyclopropane building block, 1,1,7,7-tetrafluoro-2,8-bis(hydroxymethyl)dispiro[2.2.2.2]decane (**1**), has been accomplished in optically pure form using chemo-enzymatic reaction protocol. Various types of diesters or dialkyl ether were prepared from diol (+)-**1** or (−)-**1** in optically active form and their helical twisting power (HTP) was evaluated by addition of 1.0 wt% to a non-chiral nematic liquid crystal host. Although their HTP values were not significant, all compounds showed liquid crystal property with SmC* phase when they were dissolved (20 wt%) in achiral nematic host liquid crystal.

1. Introduction

The utility of cyclopropane derivatives in the construction of a variety of cyclic and acyclic organic compounds has been amply demonstrated [1]. 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 and biological properties [2]. Much attention has thus been paid to gem-difluorocyclopropane derivatives as a source for novel functional materials [3–5]. We have been synthesizing numerous novel molecules that have gem-difluorocyclopropane moieties through a chemo-enzymatic reaction strategy [4,5]. Development of new materials that have good electrooptical properties for LCD has now been recognized as a very important topic in the field of organic synthesis [6]. We reported that gem-difluorocyclopropane LC1 showed liquid crystal property (Fig. 1) [5d]. To gain insight into designing novel liquid crystalline compounds based on the gem-difluorocyclopropane molecules, we next designed difluorocyclopropane LC2 that has a benzene ring as a spacer unit between two gem-difluorocyclopropane moieties. However, the compounds showed no liquid crystalline property, while they had strong helical twisting power [5a]. The synthesis of a spiro shaped difluorocyclopropane derivative was reported by Miyazawa, de Meijere and co-workers; it was established that the compound showed ferroelectric liquid crystalline property [7]. We were stimulated by the results and planned to synthesize spiro type gem-difluorocyclopropane **1** and investigated its physical properties (Fig. 1).

2. Results and discussion

2.1. Synthesis of optically active 1,1,7,7-tetrafluoro-2,8-bis(hydroxymethyl)dispiro[2.2.2.2]decane (1) through chemo-enzymatic reaction

Synthesis of a *meso* and *dl* mixture of spiro gem-difluorocyclopropane **1** was accomplished following Scheme 1. Diene **5** was prepared using cyclohexane-1,4-dione as a starting material by Horner–Wadsworth–Emmons reaction in 97% yield [8], and subsequent diisobutylaluminum hydride (DIBAL) reduction of the ethoxycarbonyl groups of **4** to give **5** in 79% yield as an inseparable mixture [9]. Therefore, diol **5** was next converted to the corresponding dibenzyl ether **6** in 96% yield. Compound **6** was then subjected to the reaction with difluorocarbene produced from pyrolysis of sodium chlorodifluoroacetate [5a]; dibenzyl ether of 1,1,7,7-tetrafluoro-2,8-bis(hydroxymethyl)dispiro[2.2.2.2]decane was thus obtained and deprotection of the benzyl groups gave

* Corresponding author. Tel.: +81 857 31 5259; fax: +81 857 31 5259.
E-mail address: titoh@chem.tottori-u.ac.jp (T. Itoh).

0022-1139/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2009.06.007

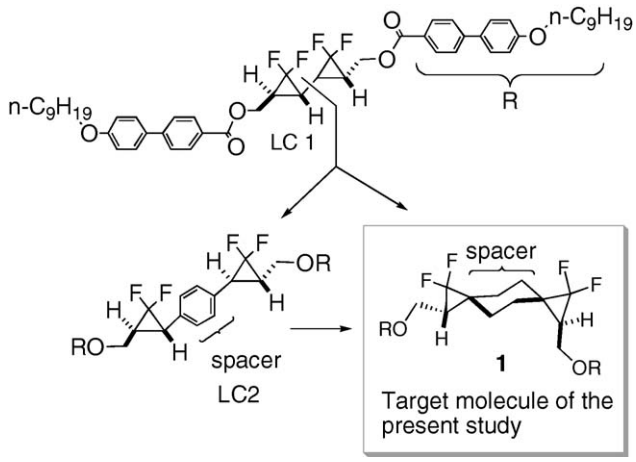
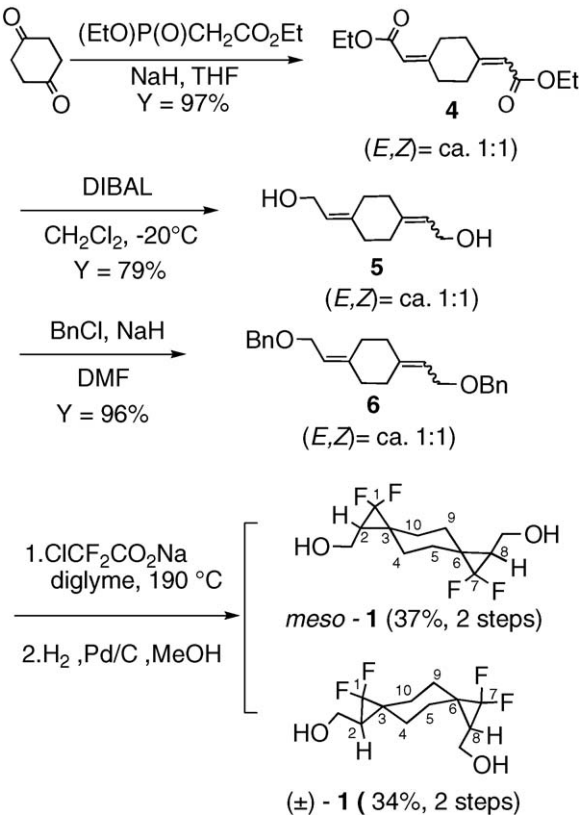


Fig. 1. Design of a core molecule as candidate for a liquid crystalline compound.

desired diol **1** as a mixture of *meso*- and *dl*-form (ca. 1:1), and separation of *meso*- and *dl*-isomers ((±)-**1**) of the diol was accomplished by silica gel flash column chromatography. (Scheme 1).

Fortunately, we succeeded in obtaining a good crystal of dibenzyl ether *meso*-**7** by recrystallization from a mixed solvent of acetone and hexane. As shown in Fig. 2 of the ORTEP view of *meso*-**7**, the two difluorocyclopropane rings locate at the opposite side in a very symmetrical manner [10].

Optical resolution of racemic **1** ((±)-**1**) was accomplished by lipase technology [11] following Scheme 2 and the results are shown in Table 1. Although we tested many commercial enzymes, only lipase SL-25 and lipase QL gave moderate results (entries 2 and 3): the highest E^* value [12] obtained for lipase QL catalyzed reaction was estimated to be 36 (entry 3). Although generally good results have been obtained for lipase SL-25 for the optical resolution of gem-



Scheme 1. Synthesis of spiro type bis-gem-difluorocyclopropane.

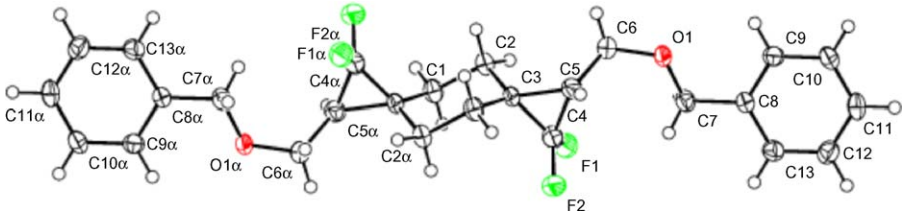
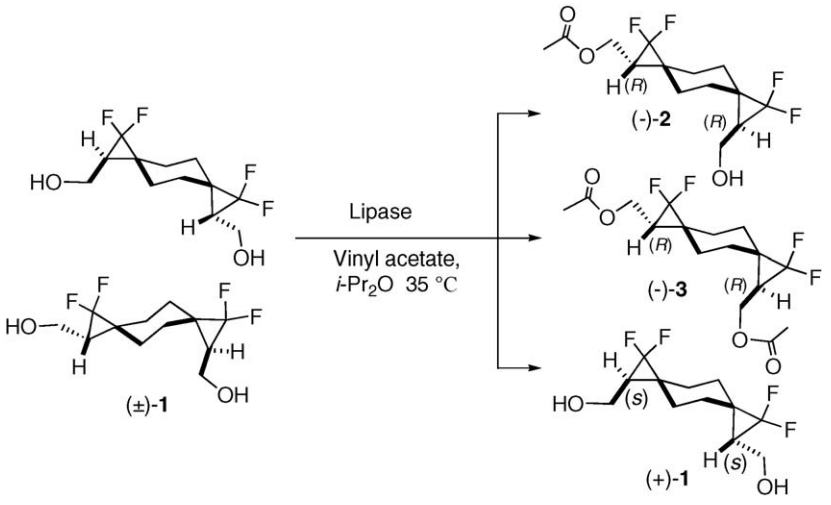


Fig. 2. ORTEP view of (*meso*)-spiro-gem-difluorocyclopropane derivative **7**. space group *P*21/*c*, *R* (reflections) = 0.0802 (1123).



Scheme 2. Optical resolution of (±)-**1** using lipase-catalyzed enantioselective transesterification.

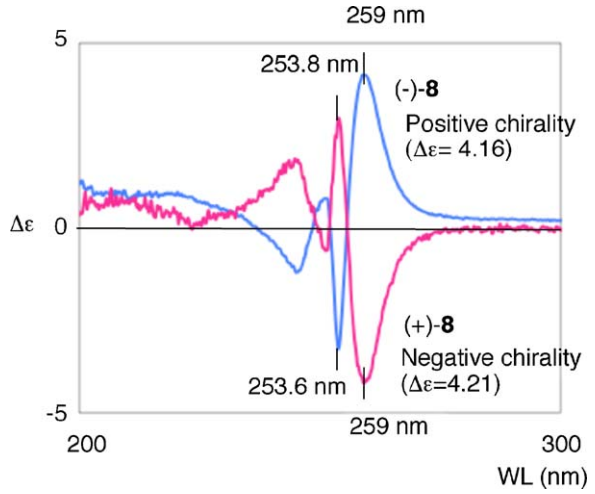


Fig. 3. CD spectra of (+)- and (−)-**8**.

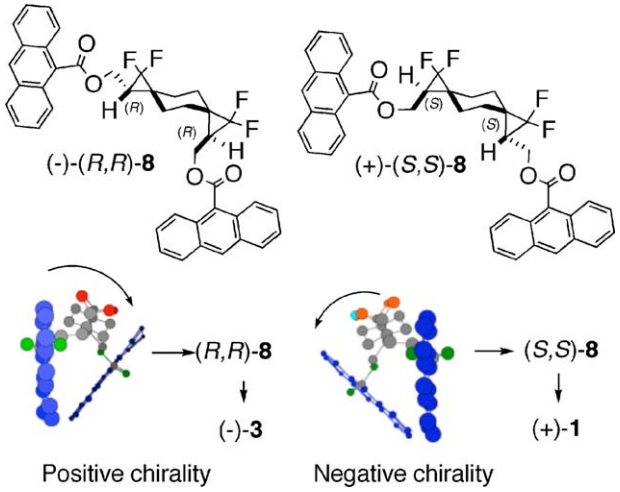
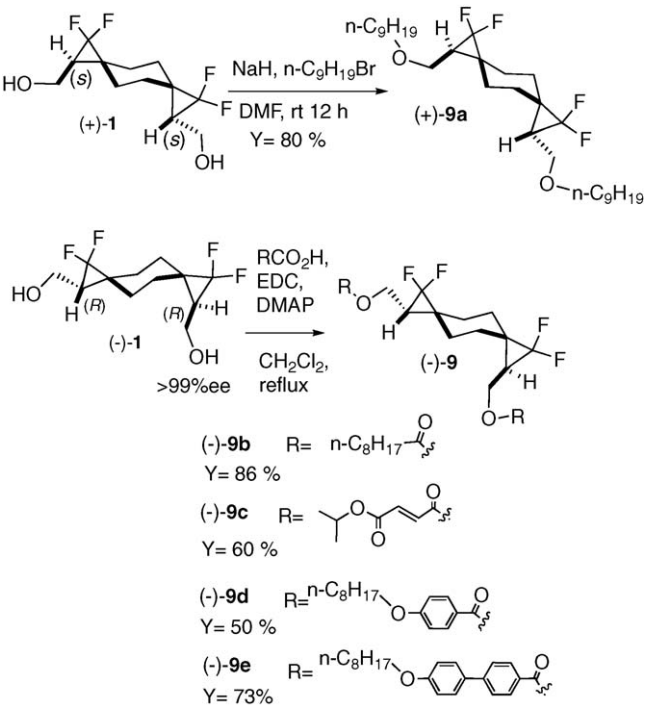


Fig. 4. Assignment of the stereochemistry of (−)- and (+)-**8** based on the Cotton effect of CD spectra.

difluorocyclopropane derivatives [5], the best enantioselectivity was observed when lipase QL was used as catalyst for this spiro type compound. In contrast, poor enantioselectivity was obtained for Novozym 435 (entry 1), and no reaction took place when lipase PS (entry 4) or lipase AY (entry 5) was employed as catalyst. Although the enantioselectivity of lipase QL-catalyzed reaction was moderate, since the lipase-catalyzed reaction was a kinetic resolution, we succeeded in obtaining optically pure diol (+)-**1** easily by repeating the reaction, and thus we accomplished the preparation of both enantiomers of diol **1** (Scheme 2).

The stereochemistry of the diol (+)-**1** was assigned as (*S,S*), and the diacetate (−)-**3** was (*R,R*), based on the CD exciton chirality method using the CD spectral results of bis-9-anthracenecarboxylate **8** (Figs. 3 and 4). The CD spectrum of the ester (−)-8, which was derived from (−)-**3**, exhibited a positive chirality on the large Cotton effect [259.0 and 253.6 nm (Δε 4.16), CH_3CN], while a negative chirality on the Cotton effect was observed by the ester (+)-**8** derived from (+)-**1** [259.0 and 253.8 nm (Δε 4.21), CH_3CN] (Fig. 3) [13,14]. This enantiofavoritism obtained from lipase QL in the transesterification of (±)-**1** was found to be the same as that of LC2 (R=H) in Fig. 1 [5a] because the cyclohexane group between the two gem-difluorocyclopropane rings seemed to cause no modification in the enantiofavoritism of the enzymes.



Scheme 3. Synthesis of LC compounds.

2.2. Helical twisting power and LC properties of spiro type gem-difluorocyclopropane derivatives

There is great interest in the field of liquid crystals in the application of chirality; chiral nematic (cholesteric) liquid crystals having a macro-helical structure are currently used in liquid crystal display devices [15]. The chiral nematic materials consist of an achiral host mixture of nematic liquid crystals and a chiral dopant with a large helical twisting power (HTP) [16]. Generally, the chiral nematic materials that are used in good LCD devices consist of an achiral host mixture of nematic liquid crystals and a chiral dopant with a large helical twisting power (HTP). Therefore it is very important to develop efficient chiral dopant materials with large HTP. The syntheses of fluorinated compounds that have

Table 1
Results of lipase-catalyzed transesterification of (±)-**1**.

Entry	Lipase	Time	%Yield of (−)-**2** (% ee)	%Yield of (−)-**3** (% ee)	%Yield of (+)-**1** (% ee)	E^*[a]
1	Novozym435	10 min	50 (22% ee)	10 (55% ee)	33 (49% ee)	6
2	SL-25	17 h	34 (62% ee)	29 (69% ee)	29 (57% ee)	10
3	PS	4 days	0	0	99 (0% ee)	–
4	QL	40 min	20 (65% ee)	28 (92% ee)	46 (41% ee)	36
5	AY	4 days	0	0	100 (0% ee)	–

[a] Since the reaction included two processes, E^* value was the result of two reactions. Here c^* means conv. which was calculated by the formula: $c^* = ee\mathbf{3}/(ee\mathbf{3} + ee\mathbf{1})$. Therefore the present E^* value is not the real E value [12] but a relative E value. $E^* = \ln[(1 - c^*)(1 + ee\mathbf{3})]/\ln[(1 - c^*)(1 - ee\mathbf{3})]$.

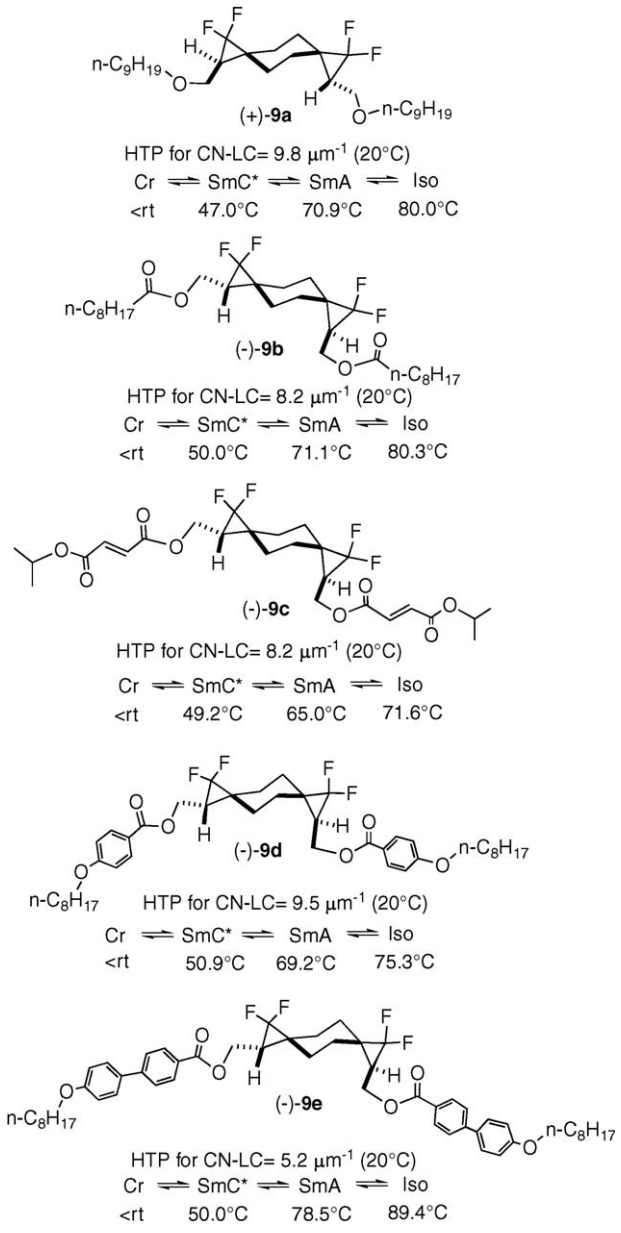


Fig. 5. HTP and LC properties of spiro-bis-gem-difluorocyclopropane derivatives.

large HTP have been reported by several groups [14]. Optically pure diol (+)-**1** was converted to bis-*n*-nonyl ether **9a** and four types of esters **9b**, **9c**, **9d**, and **9e** were prepared from (−)-**1** (>99% ee) (Scheme 3) and their liquid crystal properties were investigated (Fig. 5). All of them had helical twisting power (HTP) when 1.0 wt% was added to the achiral nematic liquid crystal [17]. The helical pitches in the chiral nematic phases were measured using Cano wedge cells [18]: 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 [19]; the results are summarized in Fig. 5.

Among them, compounds **9a** and **9d** showed a somewhat high HTP value, 9.8 and 9.5 μm^{-1}, respectively, values ca. 2-fold larger than that of cholesteryl caprylate (HTP = 4.4 μm^{-1}). Although we expected that high HTP power might be found for these compounds, the results are not particularly impressive. In addition, it was well established that introduction of isopropylfumalic acid moiety was very effective to obtain high HTP values. However, no significant enhancement was obtained by introduction of the isopropylfumaroyl group to this compound. Further, HTP values obtained from compounds **9a**–**9e** were inferior to the corresponding ones derived from 1,4-bis(2,2-difluoro-3-(hydroxymethyl)cyclopropyl)benzene derivatives [5a]. The compound **9e** with an extended molecular shape exhibits a monotoropic SmA phase with the transition temperatures of Cr 139.5 (SmA 130.2) Iso. On the contrary, none of the showed liquid crystal property for 1,4-bis(2,2,-difluoro-3-(hydroxymethyl)cyclopropyl)benzene derivatives that we reported previously [5a]. We found that chiral **9a**–**9e** showed liquid crystal properties when they were dissolved (20 wt%) in achiral nematic host liquid crystal (Cr 4 SmC 65 SmA 79 N 90 Iso (°C)). For example, the resulted mixture containing compounds (−)-**9d** and (−)-**9e** exhibited SmC* phase at 50.9 and 50.0 °C, respectively. Because it is believed that two gem-difluorocyclopropane rings of (−)-**1** have a helical shape as confirmed by CD spectroscopic analysis (see Fig. 3), this conformation might be responsible for this unique physical property of compound **1**.

3. Conclusion

In summary, we accomplished the chemo-enzymatic synthesis of chiral spiro type gem-difluorocyclopropane. The compounds have interesting properties; in particular, the compound (−)-**9e** with an extended molecular shape exhibits a monotoropic SmA phase. Compounds (+)-**9a**, (−)-**9b**, (−)-**9d** and (−)-**9e** showed liquid crystal property and exhibited SmC* phase 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 (500 MHz), ^{13}C NMR (125 MHz) and ^{19}F NMR (470 MHz) spectra were recorded in $CDCl_3$ unless otherwise noted on a JEOL JNM MH-500 spectrometer. Chemical shifts are expressed in δ value (ppm) downfield from tetramethylsilane (TMS) 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 and reported in cm^{-1}. CD spectra were measured by a JASCO J-820 spectrometer using CH_3CN as solvent. Optical purity was determined by HPLC analysis using chiralcel OD-H (Daicel). Helical twisted power of gem-difluorocyclopropane derivatives was estimated by the distance between the stripes appearing using a microscope in the Cano type wedge-shaped cell when 1.0 wt% of gem-difluorocyclopropane was dissolved in the achiral nematic host mixture consisting of cyanobenzene compounds: 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. 1,4-Bis(carboethoxymethylene)cyclohexane 4 [8]

To a solution of sodium hydride in tetrahydrofuran (THF) (9.0 ml) was added ethyl diethylphosphonoacetate (440 mg, 11 mmol) in THF (9.0 ml) at 0 °C *via* a cannula. After stirring for 1 h at rt, a solution of cyclohexane-1,4-dione (500 mg, 4.5 mmol)

in THF (10 ml) was added *via* a cannula. After 30 min, the dark brown colored mixture was quenched with saturated aq. NH_4Cl and 2 M HCl. The resulting mixture was extracted with ethyl acetate, dried ($MgSO_4$), concentrated, and purified using silica gel flash column chromatography (ethyl acetate/hexane, 10:1) to give **4** (1.1 g, 97%) as a colorless oil as an inseparable mixture of *E*:*Z* isomers in a ratio of ca. 1:1. R_f 0.48 (hexane/ethyl acetate = 7:1); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 1.26–1.30 (6H, m), 2.37–2.40 (4H, m), 2.98–3.02 (4H, m), 4.13–4.18 (4H, m), 5.69 (1H, s), 5.72 (1H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 14.2, 28.8, 29.5, 35.9, 37.3, 59.6, 59.7, 114.5, 114.6, 159.5, 159.9, 166.4, 166.5. Spectroscopic data of this compound were identical to those previously reported in the literature [8].

4.3. Diol 5 [9]

To a solution of **4** (1.4 g, 5.5 mmol) in toluene (10 ml) was added diisobutylaluminum hydride (DIBAL) (12 ml 1.5 M in toluene, 18 mmol) at −20 °C. After stirring for 3 h at rt, the reaction mixture was diluted with diethyl ether (Et_2O), and quenched with potassium fluoride and water, then extracted with ethyl acetate, dried ($MgSO_4$), and concentrated. Purification using silica gel column chromatography (ethyl acetate–hexane, 0:1 to 1:3) gave diol **5** (530 mg, 79%) as an inseparable mixture of *E*:*Z* mixture (ca. 1:1). ^{1}H NMR (500 MHz, ppm, acetone d_6) δ 2.16–2.18 (4H, m), 3.98–4.00 (4H, m), 4.76 (2H, s, OH), 5.28 (4H, t, J = 16 Hz, 9.0 Hz); ^{13}C NMR (125 MHz, ppm, CD_3OD) δ 29.8, 30.5, 38.0, 38.9, 58.6, 123.0, 142.6, 142.7. Spectroscopic data of this compound are identical to those previously reported in the literature [9].

4.4. Dibenzyl ether 6

A suspension of sodium hydride (NaH) (1.50 g, 9.0 mmol) in 20 ml of N,N-dimethylformamide (DMF) was cooled to 0 °C with stirring and a DMF (20 ml) solution of diol **5** (500 mg, 3.0 mmol) was added dropwise. To this mixture was added a DMF (10 ml) solution of benzyl bromide (1.50 g, 9.0 mmol) and the mixture was stirred at rt for 10 h, then the reaction was quenched by addition of water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. Silica gel thin layer chromatography (TLC) (ethyl acetate/hexane, 1:7) afforded dibenzyl ether **6** (1.00 g) in 96% yield. R_f 0.48 (hexane/ethyl acetate = 7:1); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 2.20 (4H, s), 2.23 (4H, s), 4.04 (4H, d, J = 6.8 Hz), 4.51 (4H, s), 5.42 (2H, t, J = 7.3 Hz), 7.26–7.35 (10H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 28.9, 29.5, 36.7, 65.6, 65.6, 71.8, 71.9, 118.9, 119.0, 127.4, 127.6, 128.2, 138.3, 143.0, 143.1; IR (KBr, cm^{-1}); 3030, 2845, 1452, 1099, 1067, 1028, 736.8, 698.2; Anal. Calcd for $C_{24}H_{28}O_2$; C, 82.72; H, 8.10. Found: C, 81.99; H, 8.28.

4.5. Dibenzyl ether of 1,1,7,7-tetrafluoro-2,8-bis(hydroxymethyl)dispiro[2.2.2.2]decane 7

To a dry diglyme (30 ml) solution of **6** (9.1 g, 26 mmol) was added a diglyme (60 ml) solution of sodium chlorodifluoroacetate (40 g, 260 mmol) at 190 °C during 4 h with vigorous stirring. After being stirred at 190 °C for an additional 1 h, the reaction mixture was allowed to cool to 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 to dryness. Separation of *dl*- and *meso*-**7** was successful and we obtained pure *meso*-**7** by recrystallization from hexane.

meso-7: R_f 0.55 (ethyl acetate/hexane = 1:4); m.p. 70–72 °C; ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 1.50–1.71 (10H, m), 3.53–3.62 (4H, m), 4.46–4.60 (4H, m), 8.28–7.37 (10H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$); 23.3–23.4 (m), 29.8, 30.6–30.9 (m), 63.3, 72.8, 116.2 (dd, $J_{C\text{-}F}$ = 295 Hz, 288 Hz), 127.7, 127.8, 128.4, 137.9; ^{19}F NMR (470 MHz, ppm, $CDCl_3$) δ 13.8 (2F, d, J = 161 Hz), 24.3 (1F, dd, J = 35.0 Hz, 17.3 Hz), 24.6 (1F, dd, J = 35.0 Hz, 17.3 Hz); IR (KBr, cm^{-1}); 2860, 1458, 1447, 1236; Anal. Calcd for $C_{26}H_{28}F_4O_2$; C, 69.63; H, 6.29. Found: C, 69.56; H, 6.17.

dl-**7**: R_f 0.48 (ethyl acetate/hexane = 1:4); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 1.49–1.65 (8H, m), 3.56–3.62 (4H, m), 4.45–4.48 (2H, m), 4.53–4.57 (2H, m), 7.28–7.38 (10H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 22.9, 29.5, 30.6–30.9 (m), 63.4 (d, $J_{C\text{-}F}$ = 3.8 Hz), 72.7, 116.0 (dd, $J_{C\text{-}F}$ = 289 Hz, 6.7 Hz), 127.67, 127.73, 128.4, 137.9; ^{19}F NMR (470 MHz, ppm, $CDCl_3$, C_6F_6) δ 14.1 (2F, d, J = 161 Hz), 24.6 (2F, dt, J = 127 Hz, 17.3 Hz); IR (KBr, cm^{-1}) 2860, 1458, 1236, 1194, 993, 741; Anal. Calcd for $C_{26}H_{28}F_4O_2$; C, 69.63; H, 6.29. Found: C, 69.56; H, 6.17.

4.6. 1,1,7,7-Tetrafluoro-2,8-bis(hydroxymethyl)dispiro[2.2.2.2]decane ((±)-1)

Palladium carbon (20 wt%) (697 mg, 5 mol%) was added to a methanol (200 ml) solution of a *dl* and *meso* mixture of dibenzyl ether **7** (11.7 g, 26.2 mmol), which was then saturated with H_2 gas. After stirring for 15 h at rt, the reaction mixture was filtered through a sintered glass filter with a Celite pad to remove Pd-C, and the filtrate was concentrated, and purified using silica gel flash column chromatography (ethyl acetate/hexane, 1:10 to 1:2) to give *meso*-**1** (2.4 g, 37%), *dl*-**1** (2.6 g, 34%).

dl-(±)-**1**: R_f 0.08 (ethyl acetate/hexane = 1:2); m.p. 68–70 °C; ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 1.57–1.64 (2H, m), 1.66–1.85 (8H, m), 3.75–3.80 (4H, m), 4.98 (2H, s, OH); ^{13}C NMR (125 MHz, ppm, CD_3OD) δ 23.8, 24.0, 30.6, 30.8, 32.1 (t, $J_{C\text{-}F}$ = 9.7 Hz), 34.1 (t, $J_{C\text{-}F}$ = 9.6 Hz), 56.3, 117.8 (dd, $J_{C\text{-}F}$ = 295 Hz, 287 Hz); ^{19}F NMR (470 MHz, ppm, CD_3OD) δ 14.6 (2F, dd, J = 161 Hz, 17.4 Hz), 26.5 (2F, dt, J = 161 Hz, 17.4 Hz); IR (KBr, cm^{-1}) 3337, 2864, 1560, 1508, 1236, 1188, 1132, 980.0; Anal. Calcd for $C_{12}H_{16}F_4O_2$; C, 53.71; H, 6.01, Found: C, 52.50; H, 6.13.

meso-**1**: R_f 0.32 (ethyl acetate/hexane = 1:2); m.p. 70–72 °C; ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 1.60 (1H, t, J = 7.3 Hz), 1.61 (1H, t, J = 7.8 Hz), 1.53–1.56 (6H, m), 1.60–1.68 (2H, m), 3.54–3.64 (4H, m), 4.77 (2H, s, OH); ^{13}C NMR (125 MHz, ppm, CD_3OD) δ 24.2, 30.9 (t, $J_{C\text{-}F}$ = 9.0 Hz), 32.0 (t, $J_{C\text{-}F}$ = 9.1 Hz), 29.3, 34.2, 56.2, 117.9 (dd, $J_{C\text{-}F}$ = 293 Hz, 285 Hz); ^{19}F NMR (470 MHz, ppm, CD_3OD) δ 14.7 (2F, dd, J = 161 Hz, 40.5 Hz), 26.6 (2F, dd, J = 156 Hz, 11.8 Hz); IR (KBr, cm^{-1}) 3337, 2864, 1474, 1236, 1190, 1119, 1092, 968; Anal. Calcd for $C_{12}H_{16}F_4O_2$; C, 53.73; H, 6.01. Found: C, 53.31; H, 5.86.

4.7. Lipase-catalyzed optical resolution of (±)-1

To a solution of (±)-**1** (90 mg, 0.34 mmol) and vinyl acetate (86 mg, 1.0 mmol) in diisopropyl ether (*i*-Pr_2O) (1.7 ml) was added lipase QL (45 mg, 50 wt%) and the mixture was stirred at 35 °C for 40 min. The reaction course was monitored by silica gel TLC. The reaction mixture was filtered through a sintered glass filter with a Celite pad to remove the lipase, and the filtrate was concentrated. Silica gel flash column chromatography (ethyl acetate–hexane, 4:1 to 1:0) to give diacetate **3** (34 mg, 28%), monoacetate **2** (21 mg, 20%), and diol **1** (41 mg, 46%).

Diacetate (−)-**3**: 92% ee, $[\alpha]_D^{25}$ −7.18 (c 1.7, MeOH); R_f 0.72 (ethyl acetate/hexane = 1:1); ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 1.65–1.75 (10H, m), 2.05 (6H, s), 4.15–4.21 (2H, m), 4.22–4.27 (2H, m); ^{13}C NMR (125 MHz, ppm, CD_3OD) δ 20.8, 24.0, 30.3, 30.6–30.7 (m), 32.5 (t, $J_{C\text{-}F}$ = 9.6 Hz), 59.3 (d, $J_{C\text{-}F}$ = 4.8 Hz), 117.2 (dd, $J_{C\text{-}F}$ = 293 Hz, 286 Hz); ^{19}F NMR (470 MHz, ppm, CD_3OD) δ 15.5 (2F, d, J = 156 Hz), 26.4 (2F, dd, J = 161 Hz, 11.3 Hz); IR (KBr, cm^{-1}) 2963, 2868, 1744, 1448, 1369, 1232, 1194, 966.0; Anal. Calcd for $C_{16}H_{20}F_4O_4$; C, 57.83; H, 4.85. Found: C, 55.90; H, 4.53.

Monoacetate (−)-**2**: 65% ee, $[\alpha]_D^{24}$ −2.20 (c 1.1, $CHCl_3$), $[\alpha]_D^{25}$ −0.76 (c 1.0, MeOH); R_f 0.72 (ethyl acetate/hexane = 1:1); ^{1}H NMR

(500 MHz, ppm, $CDCl_3$) δ 1.51–1.75 (10H, m), 2.09 (3H, s), 3.37–3.89 (2H, m), 4.19–4.20 (2H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 20.9, 22.9–23.2 (m), 29.4–29.6 (m), 31.0 (dt, $J_{C\text{-}F}$ = 9.6 Hz, 2.9 Hz), 31.2 (t, $J_{C\text{-}F}$ = 9.6 Hz), 33.1 (t, $J_{C\text{-}F}$ = 9.6 Hz), 56.5 (t, $J_{C\text{-}F}$ = 4.8 Hz), 58.4 (t, $J_{C\text{-}F}$ = 3.4 Hz), 115.3 (dd, $J_{C\text{-}F}$ = 221.7 Hz, 72.9 Hz), 117.0 (dd, $J_{C\text{-}F}$ = 289 Hz, 73.0 Hz), 171.0; ^{19}F NMR (470 MHz, ppm, $CDCl_3$) δ 13.2 (1F, dd, J = 136 Hz, 40.0 Hz), 13.5 (1F, dd, J = 118 Hz, 35.0 Hz), 24.3 (1F, ddd, J = 159 Hz, 25 Hz, 12 Hz), 24.8 (1F, dd, J = 159 Hz, 12 Hz); IR (KBr, cm^{-1}) 2963, 2868, 1744, 1448, 1369, 1232, 1194, 966.0.

Diol (+)-**1**: 41% ee, $[\alpha]_D^{26}$ +4.29 (c 2.1, MeOH); R_f 0.08 (ethyl acetate/hexane = 1:2); m.p. 118–120 °C; ^1H NMR (500 MHz, ppm, CD_3OD) δ 1.44–1.68 (10H, m), 3.62–3.70 (4H, m); ^{13}C NMR (125 MHz, ppm, CD_3OD) δ 23.2 (d, $J_{C\text{-}F}$ = 4.8), 30.2 (d, $J_{C\text{-}F}$ = 4.8 Hz), 31.5 (t, $J_{C\text{-}F}$ = 9.5 Hz), 33.4 (t, $J_{C\text{-}F}$ = 9.5 Hz), 117.2 (dd, $J_{C\text{-}F}$ = 284 Hz, 7.6 Hz); ^{19}F NMR (470 MHz, ppm, CD_3OD, C_6F_6) δ 14.6 (2F, d, J = 161 Hz), 26.4 (2F, dd, J = 161 Hz, 11.3 Hz); IR (KBr, cm^{-1}) 3337, 2864, 1560, 1508, 1236, 1188, 1132, 978. Optically pure (+)-**1** was obtained after recrystallization from methanol: $[\alpha]_D^{23}$ +9.06 (c 1.1, MeOH), >99% ee. Optical purity of diol **1** was determined by HPLC analysis using chiralcel OD-H as diacetate **3**, hexane/2-propanol (9:1), 35 °C; R_t (*R,R*) = 17 min, R_t (*meso*) = 11 min, and R_t (*S,S*) = 9.3 min.

4.8. Preparation of (−)-8 and (+)-8 for CD spectroscopic analysis

A mixture of (−)-**1** (37.0 mg, 0.14 mmol, 96% ee) which was prepared from (−)-**3** by alkaline hydrolysis, 9-anthracene carboxylic acid (92 mg, 0.41 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (79 mg, 0.41 mmol), 4-(N,N-dimethylamino)pyridine (DMAP) (17 mg, 0.14 mmol) in CH_2Cl_2 (3.0 ml) was stirred for 60 h at 50 °C. After being cooled to rt, the solvent was removed by evaporation and the residue was subjected on silica gel TLC (hexane/ethyl acetate = 2:1) to give (−)-**8** (11.0 mg, 0.01 mmol) in 12% yield. Since reactivity of (−)-**1** was very poor, 80% of starting diol (−)-**1** was recovered: $[\alpha]_D^{21}$ −2.60 (c 1.00 $CHCl_3$); R_f 0.80 (hexane/ethyl acetate = 2/1); ^1H NMR (500 MHz, ppm, $CDCl_3$) δ 1.26–1.27 (4H, s), 1.59–1.88 (6H, m), 4.61–4.65 (2H, m), 4.76 (2H, dd, J = 12.2 Hz, 8.2 Hz), 7.44–7.47 (8H, m), 7.51–7.54 (8H, m), 7.96 (8H, dd, J = 9.8 Hz, 8.2 Hz), 8.50 (2H, d, J = 5.7 Hz); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 20.3, 23.1–23.4 (m), 29.2–29.7 (m), 31.0–31.9 (m), 54.8, 58.1, 59.5, 60.4, 77.0 (t, $J_{C\text{-}F}$ = 31.7 Hz), 115.4 (t, $J_{C\text{-}F}$ = 288 Hz), 124.7, 125.5, 127.1, 128.6, 128.7, 130.9, 141.7, 141.8, 142.3, 169.4; ^{19}F NMR (470 MHz, ppm, $CDCl_3$) δ 24.0 (1F, dd, J = 43.0 Hz, 12.0 Hz), 24.3 (2F, d, J = 34.0 Hz), 24.6 (1F, dd, J = 26.0 Hz, 12.0 Hz); IR (neat, cm^{-1}) 2963, 2926, 2874, 1719, 1449, 13350 1333, 1227, 1194, 1055, 739; HRMS (MALDI-TOF MS, matrix: SA) found 676.2238 ($C_{42}H_{32}F_4O_6$, calcd: 676.2200). Using (+)-**1** (94% ee) as a starting material, (+)-**8** was obtained in a similar yield: $[\alpha]_D^{21}$ +3.60 (c 1.00 $CHCl_3$). CD spectra of (−)-**8** or (+)-**8** was measured as CH_3CN solution (8.87×10^{-4} M) at 15 °C using 1.00 cm cell.

4.9. Synthesis of (+)-9a

To a suspension of NaH (48 mg, 1.2 mmol) in DMF (2.0 ml) was added a DMF (1.0 ml) solution of (+)-**1** (>99% ee) at 0 °C, then a DMF (1.0 ml) solution of *n*-nonylbromide (250 mg, 1.2 mmol) was added and the mixture was stirred at rt for 12 h. The reaction was quenched by addition of water and extracted with diethyl ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and purified by silica gel flash column chromatography (ethyl acetate/hexane, 0:1 to 1:10) to afford (+)-**9a** (170 mg) in 80% yield: $[\alpha]_D^{23}$ +2.74 (c 0.96, $CHCl_3$); R_f 0.53 (ethyl acetate/hexane = 1:7); ^1H NMR (500 MHz, ppm, $CDCl_3$) δ 0.88 (6H, t, J = 6.9 Hz), 1.27–1.31 (24H, m), 1.54–1.66 (14H, m), 3.33–3.38 (2H, m), 3.44–3.48 (2H, m), 3.52–3.56 (4H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 14.07, 22.67, 22.97 (d, $J_{C\text{-}F}$ = 4.8 Hz), 26.15, 29.29–29.67 (m), 30.73 (t, $J_{C\text{-}F}$ = 9.5 Hz), 31.88, 63.76 (d, $J_{C\text{-}F}$ = 4.8 Hz), 70.79, 116.13 (dd, $J_{C\text{-}F}$ = 294 Hz, 286 Hz); ^{19}F NMR (470 MHz, ppm, $CDCl_3$) δ 13.7 (2F, d, J = 161 Hz), 24.40 (2F, dd, J = 161 Hz, 17.4 Hz); IR (KBr, cm^{-1}) 2926, 2856, 2804, 2743, 1474, 1414, 1375, 1261, 1236, 1194; Anal. Calcd for $C_{30}H_{52}F_4O_2$; C, 69.20; H, 10.07. Found: C, 69.15; H, 10.51.

4.10. Synthesis of (−)-9b

Using the same method as described above, (−)-**9b** was prepared in 86% yield starting from (−)-**1** (>99% ee): $[\alpha]_D^{24}$ −5.49 (c 1.0, $CHCl_3$); R_f 0.70 (ethyl acetate/hexane = 1:4); ^1H NMR (500 MHz, ppm, $CDCl_3$) δ 0.88 (6H, t, J = 6.9 Hz), 1.27–1.29 (18H, m), 1.55–1.65 (16H, m), 2.32 (4H, t, J = 7.6 Hz), 416–4.24 (4H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 14.04, 22.61, 22.95 (d, $J_{C\text{-}F}$ = 4.8 Hz), 24.90, 29.11–29.56 (m), 31.06 (t, $J_{C\text{-}F}$ = 9.5 Hz), 31.78, 34.20, 58.04 (d, $J_{C\text{-}F}$ = 5.7 Hz), 115.41 (dd, $J_{C\text{-}F}$ = 293 Hz, 286 Hz,), 173.56; ^{19}F NMR (470 MHz, ppm, $CDCl_3$) δ 13.55 (2F, d, J = 161 Hz), 24.32 (2F, dd, J = 161 Hz, 11.8 Hz); IR (KBr, cm^{-1}) 2934, 2860, 1747, 1474, 1283, 1198, 1140, 1123, 972; Anal. Calcd for $C_{30}H_{48}F_4O_4$; C, 65.67; H, 8.82. Found: C, 65.80; H, 8.66.

4.11. Synthesis of (−)-9c

Using the same method as described above, (−)-**9c** was prepared in 60% yield starting from (−)-**1** (>99% ee): $[\alpha]_D^{23}$ −1.03 (c 1.4, $CHCl_3$); R_f 0.55 (ethyl acetate/hexane = 4:1): ^1H NMR (500 MHz, ppm, $CDCl_3$) δ 1.30 (12H, d, J = 6.0 Hz), 1.58–1.78 (10H, m), 4.31–4.39 (4H, m), 5.21 (2H, sep, J = 6.5 Hz), 6.86 (4H, brs); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 21.70, 23.02 (d, $J_{C\text{-}F}$ = 3.8 Hz), 29.17 (t, $J_{C\text{-}F}$ = 9.6 Hz), 29.43 (d, $J_{C\text{-}F}$ = 3.8 Hz), 31.00 (t, $J_{C\text{-}F}$ = 9.6 Hz), 59.10 (d, $J_{C\text{-}F}$ = 3.8 Hz), 69.16, 115.18 (dd, $J_{C\text{-}F}$ = 293 Hz, 285 Hz), 132.43, 135.03, 164.21, 164.80; ^{19}F NMR (470 MHz, ppm, $CDCl_3$) δ 13.57 (2F, dd, J = 141 Hz, 47 Hz), 24.3 (2F, dd, J = 141 Hz, 47 Hz); IR (KBr, cm^{-1}) 2986, 2943, 1715, 1645, 1472, 1456, 1389, 1375, 1352, 1298; Anal. Calcd for $C_{26}H_{32}F_4O_8$; C, 56.93; H, 5.88. Found: C, 57.02; H, 5.69.

4.12. Synthesis of (−)-9d

Using the same method as described above, (−)-**9d** was prepared in 50% yield starting from (−)-**1** (>99% ee): $[\alpha]_D^{22}$ −8.43 (c 0.83, $CHCl_3$); R_f 0.63 (ethyl acetate/hexane = 1:4); m.p. 44–45 °C; ^1H NMR (500 MHz, ppm, $CDCl_3$) δ 0.888 (6H, t, J = 6.9 Hz), 1.24–1.83 (34H, m), 3.96 (4H, t, J = 6.7 Hz), 4.34–4.38 (2H, m), 4.46–4.50 (2H, m), 6.85 (4H, d, J = 9.2 Hz), 7.94 (4H, d, J = 8.7 Hz); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 14.06, 22.63, 23.07, 25.97, 29.09–29.59 (m), 31.18 (t, $J_{C\text{-}F}$ = 9.5 Hz), 31.78, 58.43 (d, $J_{C\text{-}F}$ = 4.8 Hz), 68.21, 114.17, 115.55 (dd, $J_{C\text{-}F}$ = 296 Hz, 289 Hz), 121.75, 131.51, 163.18, 166.10; ^{19}F NMR (470 MHz, ppm, $CDCl_3$) 13.77 (2F, d, J = 161 Hz), 24.52 (2F, ddd, J = 172 Hz, 161 Hz, 11.3 Hz); IR (KBr, cm^{-1}) 2926, 2856, 1719, 1607, 1578, 1510, 1474, 1421, 1389, 1256, 997; Anal. Calcd for $C_{42}H_{56}F_4O_6$; C, 68.83; H, 7.70. Found: C, 68.94; H, 7.42.

4.13. Synthesis of (−)-9e

Using the same method as described above, (−)-**9e** was prepared in 73% yield starting from (−)-**1** (>99% ee): $[\alpha]_D^{24}$ −2.91 (c 1.5, $CHCl_3$); R_f 0.34 (ethyl acetate/hexane = 7:1); ^1H NMR (500 MHz, ppm, $CDCl_3$) δ 0.893 (6H, t, J = 6.9 Hz), 1.26–1.85 (30H, m), 3.97 (4H, t, J = 6.6 Hz), 4.37–4.41 (2H, m), 4.55–4.59 (2H, m), 6.92 (4H, d, J = 8.7 Hz), 7.45 (4H, d, J = 8.7 Hz), 7.52 (4H, d, J = 8.3 Hz), 8.02 (4H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, ppm, $CDCl_3$)

δ 14.08, 22.65, 23.12, 26.04, 29.24–29.69 (m), 31.27 (t, $J_{C\text{-}F}$ = 9.1 Hz), 31.81, 58.75 (d, $J_{C\text{-}F}$ = 4.8 Hz), 68.10, 114.86, 115.52 (dd, J = 296 Hz, 289 Hz), 126.47, 127.59, 128.26, 130.00, 131.81, 145.56, 159.47, 166.29; ^{19}F NMR (470 MHz, ppm, $CDCl_3$); 13.91 (2F, d, J = 161 Hz), 24.62 (2F, ddd, J = 173 Hz, 161 Hz, 11.8 Hz); IR (KBr, cm^{-1}) 2924, 2855, 1713, 1605, 1524, 1499, 1474, 1310, 1277, 1244; Anal. Calcd for $C_{54}H_{64}F_4O_6$; C, 73.28; H, 7.29. Found: C, 73.81; H, 7.75.

Acknowledgments

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors are grateful to Meito Sangyo Co., Ltd., for providing the lipase.

References

[1] For a review see: A. de Meijere (Ed.), Cyclopropanes and Related Rings, Chem. Rev. 103 (2003) 931–1648.
[2] Reviews see:
(a) I. Ojima (Ed.), Fluorine in Bioorganic and Medicinal Chemistry, Wiley–Blackwell, London, UK, 2009;
(b) K. Uneyama, Organofluorine Chemistry, Blackwell Publishing, London, 2006;
(c) V.A. Soloshonok (Ed.), Fluorine-Containing Synthons, ACS Symposium Series 911, Oxford University Press/American Chemical Society, Washington, DC, 2005;
(d) T. Hiyama, Organofluorine Compounds Chemistry and Applications, Springer-Verlag, Berlin, Heidelberg, 2000.
[3] Reviews for the synthesis of gem-difluorocyclopropanes see:
(a) M.J. Tozer, T.F. Herpin, Tetrahedron 52 (1996) 8619–8683;
(b) M. Fedorynski, Chem. Rev. 103 (2003) 1099–1132.
[4] For our most recent review see:
(a) T. Itoh, in: I. Ojima (Ed.), Fluorine in Bioorganic and Medicinal Chemistry, Wiley–Blackwell, London, UK, 2009 , pp. 313–355 (Chapter 12).
[5] (a) T. Itoh, M. Kanbara, M. Ohashi, S. Hayase, M. Kawatsura, T. Kato, K. Miyazawa, H. Uno, J. Fluorine Chem. 128 (2007) 1112–1120;
(b) K. Ninomiya, K. Tanimoto, N. Ishida, D. Horii, M. Sisido, T. Itoh, J. Fluorine Chem. 127 (2006) 651–656;
(c) T. Itoh, N. Ishida, K. Mitsukura, S. Hayase, K. Ohashi, J. Fluorine Chem. 125 (2004) 775–783;
(d) T. Itoh, N. Ishida, M. Ohashi, R. Asep, H. Nohira, Chem. Lett. 32 (2003) 494–495;
(e) T. Itoh, N. Ishida, K. Mitsukura, K. Uneyama, J. Fluorine Chem. 112 (2001) 63–68;
(f) T. Itoh, K. Mitsukura, N. Ishida, K. Uneyama, Org. Lett. 2 (2000) 1431–1434;
(g) K. Mitsukura, S. Korekiyo, T. Itoh, Tetrahedron Lett. 40 (1999) 5739–5742;
(h) T. Itoh, K. Mitsukura, M. Furutani, Chem. Lett. (1998) 903–904.
[6] For a good review see: B. List, A. Doehring, F.M.T. Hechavarria, A. Job, T.R. Rios, Tetrahedron, 62 (2005) 476–482.
[7] K. Miyazawa, D.S. Yufit, J.A.K. Howard, A. de Meijere, Eur. J. Org. Chem. (2000) 4109.
[8] P.S. Engel, R.L. Allgren, W.-K. Chae, R.A. Leckonby, N.A. Marron, J. Org. Chem. 44 (1979) 4233–4239.
[9] G.H. Posner, S.H.T. Lee, H.J. Kim, S. Peleg, P. Dolanc, T.W. Kenslerc, Bioorg. Med. Chem. 13 (2005) 2959–2966.
[10] Crystallographic data for compound **7** have been deposited to the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 731672. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: data_request@ccdc.cam.ac.uk.
[11] For a nice recent review on lipase technology in organic syntheses see:, T. Matsuda (Ed.), Future Directions in Biocatalysis, Elsevier Bioscience, The Netherlands, 2007.
[12] We used E^* value for evaluating the lipase enantioselectivity because the reaction included two steps (monoester formation and subsequent rapid formation of diacetate). For the E value see: C.-S. Chen, Y. Fujimoto, G. Girdauskas, C.J. Sih, J. Am. Chem. Soc. 102 (1982) 7294–7298.
[13] (a) S. Egusa, M. Sisido, Y. Imanishi, Bull. Chem. Soc. Jpn. 59 (1986) 3175–3178;
(b) B. Weckerle, P. Schreier, H.-U. Humpf, J. Org. Chem. 66 (2001) 8160–8164.
[14] For CD exciton theory, see: N. Harada, K. Nakanishi, Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry, University Science Books/Oxford University Press, Mill Valley, CA/Oxford, 1983.
[15] For a good review see: P. Kirsch, M. Bremer, Angew. Chem. Int. Ed. 39 (2000) 4216–4235.
[16] A.N. Collins, G.N. Sheldrake, J. Crosby, Chirality in Industry II, John Wiley and Sons, Ltd., Chichester, UK, 1997 (Chapter 13).
[17] (a) Y. Aoki, K. Matsushima, T. Taroura, T. Hirose, H. Nohira, Mol. Cryst. Liq. Cryst. 398 (2003) 189–193;
(b) K. Tojo, Y. Aoki, M. Yasutake, T. Hirose, J. Fluorine Chem. 127 (2006) 620–626;
(c) P. Kirsch, T. Mergner, J. Fluorine Chem. 127 (2006) 146–149;
(d) T. Yamaguchi, T. Inagaw, H. Nakazumi, S. Irie, M. Irie, Chem. Mater. 12 (2000) 869–871;
(e) M. Acimis, E.B. Karaman, J. Colloid Interface Sci. 300 (2006) 1–6.
[18] T. Kato, M. Ushioda, K. Miyazawa, Liq. Cryst. 33 (2006) 543–548.
[19] R. Cano, Bull. Soc. Fr. Miner. Crystallogr. 91 (1968) 20–27.