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Optical Resolution of 5-Alkyl-δ-Valerolactones and Synthesis of Optically Active 5-Fluoroalkanols

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ABSTRACT Optical resolutions of 5-alkyl-δ-valerolactones were carried out by derivatization to the diastereomeric amides, in which (*R*)-(+)-1-(1-naphthyl)ethylamine or (*S*)-(−)-1-phenylethylamine were used as resolving agents. Optically active 5-fluoroalkanols, useful intermediates for fluorinated ferroelectric liquid crystals, were derived from the resolved lactones in four steps without racemization.

KEYWORDS optically active 5-alkyl-δ-valerolactones, optically active 5-fluoroalkanols, optical resolution

INTRODUCTION

Optically active fluorinated compounds are interesting organic materials and have often been used for pharmacological studies [1]. In these days they also collect interest in liquid crystal studies since they can be important intermediates of ferroelectric liquid crystals applicable for flat panel display [2,3]. We have been working on fluorinated ferroelectric liquid crystals in order to achieve short response time and have found that the optically active 5-fluorodecanol derivatives showed the shortest response time [4,5].

In the previous paper, we have reported a 9-step synthetic method of 5-fluoroalkanols starting from optically active 1,2-epoxyalkanes [5]. However, this method has limitation that only (*S*)-(−)-5-fluoroalkanols are available as (*R*)-(+)-epoxyalkanes are commercially available. We made a new synthetic strategy for both enantiomers of 5-fluoroalkanols starting from optically active δ-valerolactones in order to develop more convenient and practical method. Previously optically active δ-valerolactones have been produced by extracting natural resources [6], by asymmetric synthesis [7], or by fermenting bakers' yeast [8]. However, these methods gave only one enantiomer of the optically active δ-valerolactones and/or gave them in low yields, so that further investigations were required for our purpose. We have previously reported a convenient resolution of 5-pentyl-δ-valerolactone (δ-decalactone) by means of

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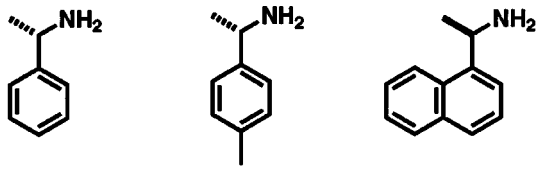


(*S*)-(−)-1-phenylethylamine | (*S*)-(−)-1-*p*-tolylethylamine | (*R*)-(+)-1-(1-naphthyl)ethylamine

CHART 1 Resolving agents examined.

diastereomeric amide formation method [9]. Here we report a further investigation to obtain a series of optically active 5-alkyl-*δ*-valerolactones that were different in the alkyl chain length by diastereomeric amide formation method and their conversion to optically active 5-fluoroalkanols in four steps.

RESULTS AND DISCUSSION

Optical Resolution of 5-alkyl-*δ*-valerolactones 1-n

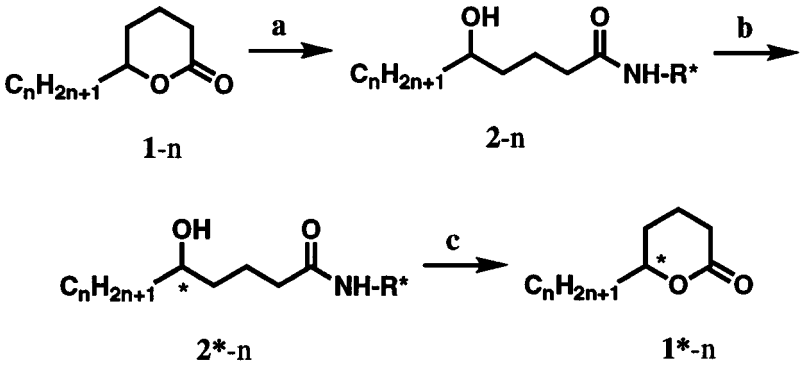
The optical resolutions of the racemic 5-alkyl-*δ*-valerolactones **1**-n were carried out by the diastereomeric amide derivatization method. The diastereomeric amides **2**-n were obtained by reaction of the lactones **1**-n with optically active amines as resolving agents. Three resolving agents were applied to the procedure (Chart 1), and optically active 1-(1-naphthyl)ethylamine (NEA) and/or 1-phenylethyl amine (PEA) gave good results. That is, both diastereomers were easily separated by recrystallization from proper solvents (Scheme 1).

The amides **2**-n were recrystallized from pure or mixed solvents to separate each of the diastereomers (Table 1). The choice of an appropriate solvent depended on the length of the alkyl group. The longer the alkyl groups, the lower polarity of the solvents was chosen. By three or four times of recrystallization, high diastereomeric purity of each diastereomer was obtained (>90% d.e.). Each diastereomer was hydrolyzed under acidic conditions, and the product was cyclized without racemization to afford the optically active 5-alkyl-*δ*-valerolactones **1***-n in high yield and optical purity. The absolute configurations of the lactones were determined by comparison with a natural product of (*S*)-(−)-5-hexyl-*δ*-valerolactone [6], and the others [7,8] (see Experimental section).

Synthesis of Optically Active 5-fluoroalkanols 8*-n

Schemes 2 and 3 show the synthetic procedures of the 5-fluoroalkanols **8**$^{(*)}$-n using the 5-alkyl-*δ*-valerolactones **1**$^{(*)}$-n as starting materials. As shown in Scheme 2, at first ring opening reaction of the lactone **1**-1 was carried out in good yield. However, the fluorination of the product, methyl 5-chlorohexanoate (**3**), with AgF gave methyl 5-fluorohexanoate (**4**) in 10% yield. As a result, the over all yield of this synthetic procedure was very low (<5%), and another route was investigated.

A key strategy for the new synthetic route was regio-selective protection of 1,5-alkanediol, **5***-n, obtained by reducing the optically active lactones **1***-n. After protection of a primary hydroxyl group of **5***-n, the secondary hydroxyl group should be substituted with fluorine. Benzoylation of the primary



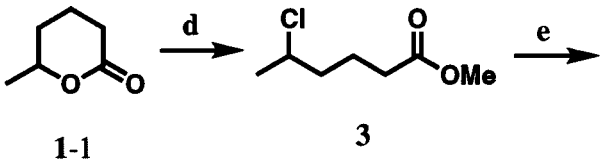
(a) (*R*)-(+)-NEA for n = 1 ~ 3 and (*S*)-(−)-PEA for n = 4 ~ 5 /benzene. (b) fractional crystallization. (c) 6 M HCl/MeOH.

SCHEME 1 Optical resolution of 5-alkyl-*δ*-valerolactones **1**-n.

TABLE 1 Fractional crystallizations of the diastereomeric amides **2**-n

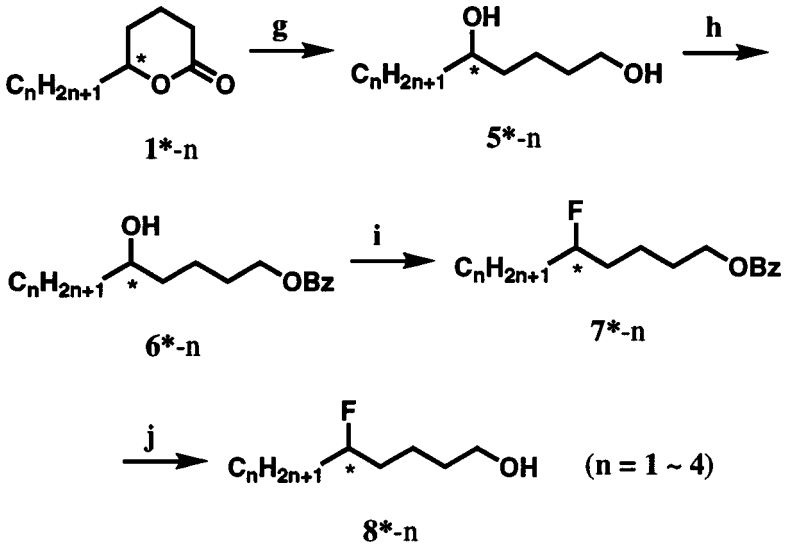
Recrystallized amide	*Amine*	*Solvent*	*Recryst. times*	*Yield/ %*[1]	*o.p./ % d.e.*[2]	*E/ %* [3]	*m.p./°C*	$[\alpha]_D$/ °[4]
(*R*,*R*)-(+)-**2***-1	(*R*)-(+)-NEA	EtOH/AcOEt = 1/5	4	18	97	17	133–134	+40
(*R*,*R*)-(+)-**2***-2	(*R*)-(+)-NEA	AcOEt	4	36	92	33	127–130	+31
(*R*,*R*)-(+)-**2***-3	(*R*)-(+)-NEA	AcOEt	4	39	94	37	124–126	+30
(*S*,*S*)-(−)-**2***-4	(*S*)-(−)-PEA	Hexane/AcOEt = 1/1	3	14	97	13	97–98	−79
(*S*,*S*)-(−)-**2***-5 [5]	(*S*)-(−)-PEA	Hexane/AcOEt = 1/1	3	36	99	35	105–107	−77

[1] Calculated based on half the amount of racemate.
[2] Determined by HPLC analysis (Wakosil 5SIL; Ø 4.6 mm × 250 mm; eluent, 70% (v/v) AcOEt in hexane; flow rate, 1.0 ml/min; detection wavelength, 254 nm).
[3] Yield × o.p./100.
[4] (*c* 1.0, MeOH).
[5] Ref. [9].



(d) HCl(g)/MeOH, 65%. (e) AgF/CH_3CN, 10%. (f) $LiAlH_4$/THF, 90%.

SCHEME 2 Synthesis of 5-fluorohexanol (**8**-1).



(g) $LiAlH_4$/THF. (h) BzCl/DABCO/CH_2Cl_2. (i) DAST/CH_2Cl_2.
(j) KOH/H_2O.

SCHEME 3 Synthesis of optically active 5-fluoroalkanols **8***-n.

alcohol was carried out in two ways: by the use of diethyl azodicarboxylate (DEAD) and triphenyl phosphine [10] or by the use of benzoylchloride and 1,4-diazabicyclo[2.2.2]octane (DABCO). It was found that the latter method gave the monobenzoylated diols **6***-n in higher yield, and its purification was easier than the former, Scheme 3. The fluorinated compounds **7***-n were synthesized by fluorination of **6***-n with a nucleophilic agent, diethylaminosulfur trifluoride (DAST), under mild conditions. The fluorination proceeded as S_N2 reaction with inversion of the absolute configuration [11]. Finally, the optically active **7***-n were hydrolyzed under weakly basic conditions and gave the optically active 5-fluoroalkanols **8***-n in good yield. No racemization occurred in this synthetic route, which was confirmed by determination of optical purity of the intermediate (5-fluoroalkyl benzoate **7***-n) using HPLC equipped with a chiral column (Daicel CHIRALCEL OB-H; Ø4.6 mm × 250 mm; 5% (v/v) 2-PrOH in Hexane; flowrate, 0.5 ml/min; detection wavelength, 254 nm).

CONCLUSION

The optical resolutions of the racemic 5-alkyl-*δ*-lactones were carried through diastereomeric amides derivatization method. The method gave the optically active lactones in high optical purity, which were used as starting materials to prepare the optically active 5-fluoroalkanols.

EXPERIMENTAL

The structures of the intermediates and products were confirmed by ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectroscopy (Bruker ARX400 and AM400), and infrared (IR) spectroscopy (Perkin-Elmer FT1640).

(*S,S*)-(−)-*N*-(1-Phenylethyl)-5-hydroxynonanamide (2*-4)

A typical synthetic procedure of diastereomeric amide is as follows: a mixture of 5-butyl-*δ*-valerolactone (2.81 g,18 mmol), (*S*)-(−)-1-phenylethylamine (2.18 g, 18 mmol) in dry benzene (4 ml) was stirred at 120°C for 3 hours. The solvent was evaporated off to obtain crystalline amide. Four times recrystallization from mixed solvent (AcOEt: Hexane = 1:1) gave diastereomerically pure amide [0.28 g, 1.0 mmol, 14% (calculated based on half the amount of racemate); $[\alpha]_D^{24}$ −78° (*c* 1.0, MeOH); m.p. 97–98°C; 97% d.e.]. Diastereomeric excess of the amide was determined by HPLC analysis (Wakosil 5SIL; Ø4.6 mm × 250 mm; eluent, 70% (v/v) AcOEt in hexane; flow rate, 1.0 ml/min; detection wavelength, 254 nm). The absolute configuration was determined from its derivatization product, (*S*)-(−)-5-butyl-*δ*-valerolactone (**1***-4). ^{1}H NMR ($CDCl_3$): 0.89–0.94 (t, 3H, CH_3), 1.43–1.48 (m, 10H, CH_2), 1.66–1.68 (d, 3H, CH_3), 1.82–1.85 (m, 1H, CHO), 2.30–2.59 (m, 2H, CH_2), 2.63 (m, 1H, OH), 3.55 (m, 1H, CHN), 5.90–5.94 (m, 1H, NH), 7.43–8.09 (m, 5H, Ar); IR (neat, cm^{-1}) 3286 (OH), 2931–2870 (CH_3, CH_2), 1645 (C=O); Elemental anal. calcd for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.84; H, 9.97: N, 5.05.

(*R,R*)-(+)-*N*-(1-(1-naphthyl)ethyl)-5-hydroxyhexanamide (2*-1)

Diastereomerically pure amide: $[\alpha]_D^{24}$ + 40° (*c*1.0, MeOH); m.p. 133–134°C; 97% d.e.; ^{1}H NMR ($CDCl_3$): 1.11–1.17 (d, 3H, CH_3), 1.36–1.80 (m, 4H, CH_2), 1.61–1.65 (d, 3H, CH_3), 2.14–2.24 (m, 2H, CH_2), 3.76 (m, 1H, CHN), 5.91–5.98 (m, 1H, NH), 7.40–8.11 (m, 7H, Ar); IR (neat, cm^{-1}) 3302 (OH), 1633 (C=O); Elemental anal. calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.84; H, 8.18; N, 4.89.

(*R,R*)-(+)-*N*-(1-(1-naphthyl)ethyl)-5-hydroxyheptanamide (2*-2)

Diastereomerically pure amide: $[\alpha]_D^{24}$ + 31° (*c*1.0, MeOH); m.p. 127–130°C; 92% d.e. ^{1}H NMR ($CDCl_3$): 0.85–0.91 (t, 3H, CH_3), 1.36–1.43 (m, 6H, CH_2), 1.66–1.69 (d, 3H, CH_3), 1.72–1.75 (m, 1H, CHO), 2.15–2.19 (m, 2H, CH_2), 3.46 (m, 1H, CHN), 5.92 (m, 1H, NH), 7.41–8.09 (m, 7H, Ar); IR (neat, cm^{-1}) 3296 (OH), 1636 (C=O).

(*R,R*)-(+)-*N*-(1-(1-naphthyl)ethyl)-5-hydroxyoctanamide (2*-3)

Diastereomerically pure amide: $[\alpha]_D^{24}$ + 30° (*c*1.0, MeOH); m.p. 124–126°C; 94% d.e. ^{1}H NMR ($CDCl_3$): 0.89–0.94 (t, 3H, CH_3), 1.43–1.48 (m, 8H, CH_2), 1.66–1.68 (d, 3H, CH_3), 1.82–1.85 (m, 1H,

CHO), 2.30–2.59 (m, 2H, CH_2), 2.63 (m, 1H, OH), 3.55 (m, 1H, CHN), 5.90–5.94 (m, 1H, NH), 7.43–8.09 (m, 7H, Ar); IR (neat, cm^{-1}) 3297 (OH), 1639 (C=O); Elemental anal. calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.45; H, 8.85; N, 4.28.

(*S*)-(−)-5-Butyl-*δ*-valerolactone (1*-4)

A typical synthetic procedure of lactonization is as follows: to a solution of amide **2***-4 (440 mg, 1.59 mmol) in 99% EtOH (10 ml), 6M hydrochloric acid (0.5 ml) was added. The mixture was stirred at 90°C for five hours and was extracted with Et_2O. The mixture of the crude product and 2M NaOH (3.0 ml) was stirred at 95°C for two hours, and 2M hydrochloric acid (5 ml) was added to the mixture. The mixture was extracted with Et_2O to yield a crude of 5-hydroxy acid. A solution of the acid, *p*-toluenesulfonic acid (∼0.5 mg), and dry benzene was stirred at 85°C for two hours and was extracted with Et_2O. The extract was washed with 5% Na_2CO_3 aqueous solution and was dried over Na_2SO_4. The crude product was distilled and gave the lactone (230 mg, 1.47 mmol, 92.5%). $[\alpha]_D^{26}$ − 35° (*c*1.0, MeOH); 97% e.e. Enantiomeric excess of the lactone was determined by HPLC analysis (Chiralcel OB-H; Ø4.6 mm × 250 mm; eluent, 5% (v/v) 2-PrOH in hexane; flow rate, 0.5 ml/min; detection wavelength, 220 nm). ^{1}H NMR ($CDCl_3$): 0.88–0.91 (t, 3H, CH_3), 1.30–1.92 (m, 10H, CH_2), 2.42–2.56 (dm, 2H, CH_2), 4.23–4.29 (m, 1H, CH); IR (neat, cm^{-1}) 2955, 2871 (CH_3, CH_2), 1740 (C=O). As reference, optical rotation of (*R*)-(+)-5-butyl-*δ*-valerolactone prepared by fermenting baker's yeast: $[\alpha]_D^{20}$ + 63° (*c*2.2, THF) [8].

(*R*)-(+)-5-Methyl-*δ*-valerolactone (1*-1): $[\alpha]_D^{27}$ + 15° (*c*1.0, MeOH); 97% e.e.; ^{1}H NMR ($CDCl_3$): 1.31–1.34 (d, 3H, CH_3), 1.75–1.91 (m, 4H, CH_2), 2.46 (t, 2H, CH_2), 4.35–4.43 (m, 1H, CH); ^{13}C NMR ($CDCl_3$): 18.4 (CH_3), 21.6, 29.1, 29.5 (CH_2), 76.4 (CH), 170.8 (C=O); IR (neat, cm^{-1}) 2977 (CH_3), 1736 (C=O). As reference, optical rotation of (*S*)-(−)-5-methyl-*δ*-valerolactone prepared by asymmetric synthesis: $[\alpha]_D^{22}$ − 46° (*c*2.0, EtOH) [7].

(*S*)-(−)-5-Ethyl-*δ*-valerolactone (1*-2): $[\alpha]_D^{25}$ − 14° (*c*1.0, MeOH); 92% e.e.; ^{1}H NMR ($CDCl_3$): 0.82–0.91 (t, 3H, CH_3), 1.38–1.63 (m, 6H, CH_2), 2.30–2.41 (m, 2H, CH_2), 4.01–4.12 (m, 1H, CH); IR (neat, cm^{-1}) 2939, 2877 (CH_3, CH_2), 1732 (C=O). As reference, optical rotation of (*S*)-(−)-5-ethyl-*δ*-valerolactone prepared by asymmetric synthesis: $[\alpha]_D^{23}$ − 48°(*c*1.6, THF) [7].

(*R*)-(+)-5-Propyl-*δ*-valerolactone (1*-3): $[\alpha]_D^{27}$+48° (*c*1.0, MeOH); 98% e.e.; ^{1}H NMR ($CDCl_3$): 0.84–0.92 (t, 3H, CH_3), 1.44–1.81 (m, 4H, CH_2), 2.41 (m, 2H, CH_2), 4.21 (m, 1H, CH); IR (neat, cm^{-1}) 2957, 2872 (CH_3, CH_2), 1734 (C=O). As reference, optical rotation of (*R*)-(+)-5-propyl-*δ*-valerolactone prepared by fermenting baker's yeast: $[\alpha]_D^{20}$ + 66° (*c*1.7, THF) [8].

(*S*)-(+)-5-Hydroxynonanol (5*-4): A typical preparation procedure of optically active alcohol is as follows: to a suspended solution of $LiAlH_4$ (0.87 g, 23 mmol), a solution of (*S*)-(−)-5-butyl-*δ*-valerolactone (2.3 g, 15 mmol) in dry THF (10 ml) was slowly added. The mixture was stirred for six hours at room temperature under N_2 atmosphere. Saturated Na_2SO_4 solution and 3M hydrochloric acid was added. The organic layer was extracted with Et_2O and dried over anhydrous $MgSO_4$. The condensed crude product was distilled (135–150°C, 30 mmHg) to yield a colorless liquid (2.26 g, 14.1 mmol, 94%). $[\alpha]_D^{24}$ +0.5° (*c*1.0, MeOH); ^{1}H NMR ($CDCl_3$): 0.89–0.92 (t, 3H, CH_3), 1.29–1.61 (m, 12H, CH_2), 2.63 (m, 1H, OH), 3.58–3.59 (m, 1H, CHO), 3.61–3.64 (t, 2H, CH_2O); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 21.7, 22.7, 27.8, 32.4, 36.8, 37.2 (CH_2), 62.3 (CH_2OH), 71.6 (CHOH); IR (neat, cm^{-1}) 3355 (OH), 2932–2862 (CH_3, CH_2).

(*R*)-(−)-5-Hydroxyhexanol (5*-1): $[\alpha]_D^{24}$ −6.3° (*c*1.0, MeOH); ^{1}H NMR ($CDCl_3$): 1.83–1.86 (m, 1H, CHO), 3.76 (q, 2H, CH_2O); ^{13}C NMR ($CDCl_3$): 62.2 (CH_2OH), 67.8 (CHOH); IR (neat, cm^{-1}) 3345 (OH).

(*S*)-(+)-5-Hydroxyheptanol (5*-2): $[\alpha]_D^{24}$ + 2.1° (*c*1.0, MeOH); ^{1}H NMR ($CDCl_3$): 2.52 (m, 1H, OH), 3.53–3.54 (m, 1H, CHO), 3.62–3.65 (t, 2H, CH_2O); ^{13}C NMR ($CDCl_3$): 62.4 (CH_2OH), 73.0 (CHOH); IR (neat, cm^{-1}) 3357 (OH).

(*R*)-(−)-5-Hydroxyoctanol (5*-3): $[\alpha]_D^{26}$ − 1.0° (*c*1.0, MeOH); ^{1}H NMR ($CDCl_3$): 3.55–3.57 (m, 1H, CHO), 3.60–3.62 (t, 2H, CH_2O); ^{13}C NMR ($CDCl_3$): 62.5 (CH_2OH), 71.5 (CHOH); IR (neat, cm^{-1}): 3372 (OH).

(*S*)-(+)-5-Hydroxynonyl benzoate (6*-4): A typical benzoylation is as follows: to a stirred solution of (*S*)-(+)-5-hydroxynonanol (**5***-4) (100 mg, 0.63 mmol) and benzoyl chloride (88 mg, 0.62 mmol) in dry CH_2Cl_2 (2 ml), 1,4-diazabicyclo[2.2.2]octane

(DABCO) (213 mg, 1.9 mmol) was added slowly. The solution was then stirred at room temperature for 3 hours under N_2 atmosphere. Dilute HCl solution was added. The organic layer was extracted with CH_2Cl_2. The extract was washed with distilled water and dried over anhydrous Na_2SO_4. The condensed mixture was purified by thin layer chromatography (AcOEt:Hexane = 1:5) to yield a light yellow liquid (126 mg, 0.48 mmol, 77%). $[\alpha]_D^{27}$ + 3.2° (*c*1.1, MeOH); ^{1}H NMR ($CDCl_3$): 0.88–0.92 (t, 3H, CH_3), 1.31–1.81 (m, 12H, CH_2), 3.62 (m, 1H, CHO), 4.32–4.35 (t, 2H, CH_2O), 7.41–8.05 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$): 14.0 (CH_3), 22.2, 22.7, 27.8, 28.8, 36.9, 37.2 (CH_2), 64.9 (CH_2OBzl), 71.7 (CHOH), 128.3–132.8 (Ar), 166.7 (C=O); IR (neat, cm^{-1}) 3411 (OH), 2932–2861 (CH_3, CH_2), 1720 (C=O).

(*R*)-(−)-5-Hydroxyhexyl benzoate (6*-1): $[\alpha]_D^{27}$ − 0.7° (*c*0.9, MeOH); ^{1}H NMR ($CDCl_3$): 1.19–1.21 (d, 3H, CH_3), 1.49–1.78 (m, 6H, CH_2), 3.81 (m, 1H, CHO), 4.11–4.34 (t, 2H, CH_2O), 7.41–8.05 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$): 22.1 (CH_3), 23.4, 28.6, 38.7 (CH_2), 64.8 (CH_2OBzl), 67.7 (CHOH), 128.3–132.7 (Ar), 166.6 (C=O); IR (neat, cm^{-1}) 3400 (OH), 2962–2866 (CH_3, CH_2), 1720 (C=O).

(*S*)-(+)-5-Hydroxyheptyl benzoate (6*-2): $[\alpha]_D^{27}$ + 1.5° (*c*1.0, MeOH); ^{1}H NMR ($CDCl_3$): 0.89–0.93 (t, 3H, CH_3), 1.32–1.83 (m, 8H, CH_2), 3.61 (m, 1H, CHO), 4.31 (t, 2H, CH_2O), 7.40–8.05 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$): 13.4 (CH_3), 22.2, 26.7, 36.2, 39.2 (CH_2), 64.9 (CH_2OBzl), 69.7 (CHOH), 128.3–132.8 (Ar), 166.7 (C=O); IR (neat, cm^{-1}) 3349 (OH), 2936–2873 (CH_3, CH_2), 1719 (C=O).

(*R*)-(−)-5-Hydroxyoctyl benzoate (6*-3): $[\alpha]_D^{25}$ − 2.6° (*c*1.1, MeOH); ^{1}H NMR ($CDCl_3$): 0.90–0.94 (t, 3H, CH_3), 1.33–1.81 (m, 10H, CH_2), 3.62 (m, 1H, CHO), 4.31–4.34 (t, 2H, CH_2O), 7.41–8.05 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$): 14.1 (CH_3), 18.7, 22.1, 28.7, 36.8, 39.6 (CH_2), 64.9 (CH_2OBzl), 71.5 (CHOH), 128.3–132.8 (Ar), 166.7 (C=O); IR (neat, cm^{-1}): 3427 (OH), 2956–2871 (CH_3, CH_2), 1720 (C=O).

(*R*)-(−)-5-Fluorononyl benzoate (7*-4): A typical fluorination is as follows: a solution of diethylamino sulfurtrifluoride (DAST) (320 mg, 2.0 mmol) in 5 ml of dry CH_2Cl_2 was added to a stirred solution of (*S*)-(+)-5-hydroxynonyl benzoate (**6***-4) (150 mg, 0.6 mmol) in dry CH_2Cl_2 (3 ml) at −78°C under N_2 atmosphere. The mixture was stirred for 30 minutes at the same temperature. Saturated Na_2SO_4 solution was added, and the organic layer was extracted with CH_2Cl_2. The extract was washed with distilled water and dried over anhydrous Na_2SO_4. The solvent was evaporated off, and remaining mixture was purified by thin layer chromatography (AcOEt:Hexane = 1:7) to yield a light yellow liquid (81 mg, 0.30 mmol, 54%). $[\alpha]_D^{26}$ − 0.7° (*c* 0.8, MeOH); 95% e.e. (determined by Chiralcel OB-H; Ø4.6 mm × 250 mm; eluent, 5% (v/v) 2-PrOH in hexane; flow rate, 0.5 ml/min; detection wavelength, 254 nm); ^{1}H NMR ($CDCl_3$): 0.88–0.92 (t, 3H, CH_3), 1.31–1.82 (m, 12H, CH_2), 4.32–4.35 (t, 2H, CH_2O), 4.40–4.57 (dm, 1H, CHF, $J_{H\text{-}F}$ = 49.45 Hz), 7.42–8.05 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 21.8, 22.5, 27.2, 28.6, 34.7, 34.9 (CH_2), 64.8 (CH_2OBzl), 93.4–95.1 (d, CHF, J = 166.8 Hz), 128.3–132.8 (Ar), 166.6 (C=O); ^{19}F NMR ($CDCl_3$): −181.2∼−181.0 (m, CHF); IR (neat, cm^{-1}) 3063 (Ar), 2954–2870 (CH_3, CH_2), 1720 (C=O).

(*S*)-(+)-5-Fluorohexyl benzoate (7*-1): $[\alpha]_D^{26}$ + 2.7° (*c* 1.0, MeOH); 96% e.e.; ^{1}H NMR ($CDCl_3$): 1.22–1.24 (d, 3H, CH_3), 1.27–1.78 (m, 6H, CH_2), 4.03 (t, 2H, CH_2O), 4.40–4.58 (dm, 1H, CHF, $J_{H\text{-}F}$ = 49.5 Hz), 7.40–8.03 (m, 5H, Ar); ^{19}F NMR ($CDCl_3$): −182.2∼−181.9 (m, CHF); IR (neat, cm^{-1}) 3063 (Ar), 2944–2870 (CH_3, CH_2), 1720 (C=O).

(*R*)-(−)-5-Fluoroheptyl benzoate (7*-2): $[\alpha]_D^{26}$ −5.3° (*c*0.9, MeOH); 90% e.e.; ^{1}H NMR ($CDCl_3$): 0.95–0.99 (t, 3H, CH_3), 1.50–1.85 (m, 8H, CH_2), 4.32 (t, 2H, CH_2O), 4.32–4.49 (dm, 1H, CHF, $J_{H\text{-}F}$ = 49.5 Hz), 7.42–8.05 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$): 9.3 (CH_3), 21.8, 27.9, 28.6, 34.4 (CH_2), 64.8 (CH_2OBzl), 94.5–96.2 (d, CHF, J = 170.0 Hz), 128.3–132.8 (Ar), 166.6 (C=O); ^{19}F NMR ($CDCl_3$): −182.5∼−182.2 (m, CHF); IR (neat, cm^{-1}) 3063 (Ar), 2940–2871 (CH_3, CH_2), 1720 (C=O).

(*S*)-(+)-5-Fluorooctyl benzoate (7*-3): $[\alpha]_D^{24}$ + 0.9° (*c* 0.95, MeOH); 92% e.e.; ^{1}H NMR ($CDCl_3$): 0.92–0.95 (t, 3H, CH_3), 1.48–1.82 (m, 10H, CH_2), 4.32–4.35 (t, 2H, CH_2O), 4.41–4.58 (dm, 1H, CHF, $J_{H\text{-}F}$ = 49.5 Hz), 7.41–8.05 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$): 13.8 (CH_3), 18.2, 21.7, 28.5, 34.8, 37.3 (CH_2), 64.7 (CH_2OBzl), 93.0–94.7 (d, CHF, J = 170.0 Hz), 128.3–132.8 (Ar), 166.5 (C=O); ^{19}F NMR ($CDCl_3$): −181.7∼−181.4 (m, CHF); IR (neat, cm^{-1}) 3063 (Ar), 2940–2871 (CH_3, CH_2), 1720 (C=O).

(*R*)-(+)-5-Fluorononanol (8*-4): A typical procedure to obtain optically active 5-fluoroalkanol is as follows: to a stirred solution of (*R*)-(−)-5-fluorononyl benzoate (**5***-4) (75 mg, 0.3 mmol) in MeOH (2 ml), 1M KOH (1 ml) was added. The mixture was stirred

at room temperature for overnight. The mixture was extracted with Et_2O, and washed with a 5 wt% Na_2CO_3 solution. The extract was dried over anhydrous $MgSO_4$. The solvent was evaporated off to yield a colorless liquid (38 mg, 0.23 mmol, 84%). $[\alpha]_D^{27} + 0.2^\circ$ (*c* 1.8, Et_2O); ^1H NMR ($CDCl_3$): 0.89–0.93 (t, 3H, CH_3), 1.32–1.62 (m, 12H, CH_2), 3.64–3.67 (t, 2H, CH_2O), 4.40–4.54 (dm, 1H, CHF, $J_{H\text{-}F} = 49$ Hz); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 21.4, 22.5, 27.2, 32.5, 34.7, 34.9 (CH_2), 62.7 (CH_2OH), 93.6–95.2 (d, CHF, $J = 166.9$ Hz); ^{19}F NMR ($CDCl_3$): −181.1∼−180.7 (m, CHF). Elementary analysis of this compound was determined as its derivative, 2-*p*-decyloxyphenyl-5-(5-fluorononyloxy)pyrimidine [12]: ^1H NMR ($CDCl_3$): 0.80–0.87 (dt, 6H, CH_3), 1.21–1.76 (m, 28H, CH_2), 3.93–4.04 (dt, 4H, CH_2O), 4.37–4.50 (dm, 1H, CHF, $J = 49.6$ Hz), 6.88–6.92 (d, 2H, Ar, $J = 9.9$ Hz), 8.19–8.21 (d, 2H, Ar, $J = 8.8$ Hz), 8.35 (s, 2H, Ar); ^{13}C NMR ($CDCl_3$): 13.9, 14.1 (CH_3), 21.6–34.9 (CH_2), 68.1, 68.6 (CH_2O), 93.4–95.0 (d, CHF, $J = 167.5$ Hz), 114.4–160.78 (Ar); Elemental analysis calculated for $C_{29}H_{45}FN_2O_2$: C, 73.69; H, 9.60; N, 5.93. Found: C, 73.79; H, 9.75; N, 5.91.

(*S*)-(+)-5-Fluorohexanol (8*-1): $[\alpha]_D^{25} + 15.8^\circ$ (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$): 1.27 (d, 3H, CH_3), 1.35–1.88 (m, 6H, CH_2), 3.66 (t, 2H, CH_2O), 4.50–4.81 (dm, 1H, CHF, $J_{H\text{-}F} = 62$ Hz); ^{13}C NMR ($CDCl_3$): 21.2 (CH_3), 21.4, 32.4, 36.6 (CH_2), 62.7 (CH_2OH), 90.9 (d, CHF, $J = 164.2$ Hz).

(*R*)-(−)-5-Fluoroheptanol (8*-2): $[\alpha]_D^{25} - 6.7^\circ$ (*c* 0.7, MeOH); ^1H NMR ($CDCl_3$): 0.95–0.99 (t, 3H, CH_3), 1.43–1.67 (m, 8H, CH_2), 3.64–3.67 (t, 2H, CH_2O), 4.33–4.49 (dm, 1H, CHF, $J_{H\text{-}F} = 48$ Hz); ^{13}C NMR ($CDCl_3$): 9.3 (CH_3), 21.4, 28.1, 32.5, 34.5 (CH_2), 62.7 (CH_2OH), 94.7–96.3 (d, CHF, $J = 166.9$ Hz); ^{19}F NMR ($CDCl_3$): −182.3∼−181.9 (m, CHF). Elementary analysis of this compound was determined as its derivative, 2-(*p*-decyloxyphenyl)-5-(5-fluoroheptyloxy)pyrimidine [12]: ^1H NMR ($CDCl_3$): 0.86–1.00 (dt, 6H, CH_3), 1.27–1.87 (m, 24H, CH_2), 3.93–4.10 (dt, 4H, CH_2O), 4.38–4.51 (dm, 1H, CHF, $J = 49.6$ Hz), 6.95–6.98 (d, 2H, Ar, $J = 8.8$ Hz), 8.25–8.27 (d, 2H, Ar, $J = 8.8$ Hz), 8.41 (s, 2H, Ar); ^{13}C NMR ($CDCl_3$): 14.1 ($2CH_3$), 21.4–34.4 (CH_2), 68.1, 68.6 (CH_2O), 94.5–96.2 (d, CHF, $J = 167.6$ Hz), 114.4–160.7 (Ar); Elemental analysis calculated for $C_{27}H_{41}FN_2O_2$: C, 72.94; H, 9.29; N, 6.30. Found: C, 72.62; H, 9.40; N, 6.21.

(*S*)-(−)-5-Fluorooctanol (8*-3): $[\alpha]_D^{27} - 1.8^\circ$ (*c* 2.2, Et_2O); ^1H NMR ($CDCl_3$): 0.92–0.95 (t, 3H, CH_3), 1.33–1.71 (m, 10H, CH_2), 3.63–3.66 (t, 2H, CH_2O), 4.39–4.57 (dm, 1H, CHF, $J_{H\text{-}F} = 50$ Hz); ^{13}C NMR ($CDCl_3$): 13.8 (CH_3), 18.3, 21.3, 32.4, 34.9, 37.3 (CH_2), 62.6 (CH_2OH), 93.3–94.9 (d, CHF, $J = 166.9$ Hz); ^{19}F NMR ($CDCl_3$): −180.9 (dm, CHF). Elementary analysis of this compound was determined as its derivative, 2-(*p*-(5-fluorooctyloxy) phenyl)-5-decyloxypyrimidine [12]: ^1H NMR ($CDCl_3$): 0.87–0.96 (dt, 6H, CH_3), 1.27–1.84 (m, 26H, CH_2), 4.02–4.09 (dt, 4H, CH_2O), 4.44–4.58 (dm, 1H, CHF, $J = 49.5$ Hz), 6.95–6.97 (d, 2H, Ar, $J = 8.8$ Hz), 8.25–8.27 (d, 2H, Ar, $J = 8.8$ Hz), 8.41 (s, 2H, Ar); ^{13}C NMR ($CDCl_3$): 13.9, 14.1 (CH_3), 18.3–31.8 (CH_2), 67.7, 68.9 (CH_2O), 93.2–94.9 (d, CHF, $J = 166.9$ Hz), 114.4–160.5 (Ar); Elemental analysis calculated for $C_{28}H_{43}FN_2O_2$: C, 73.32; H, 9.45; N, 6.11. Found: C, 73.34; H, 9.59; N, 6.09.

As reference, we have reported a synthesis of (*S*)-(−)-5-fluorodecanol from (*R*)-(+)-1,2-epoxyheptane [5]: $[\alpha]_D^{24} - 1.2^\circ$ (*c* 2.0, Et_2O); ^1H NMR ($CDCl_3$): 0.90 (t, 3H, CH_3), 1.24–1.68 (m, 14H, CH_2), 1.89 (s, 1H, OH), 3.64 (t, 2H, CH_2O), 4.38–4.56 (dm, 1H, CHF, $J_{H\text{-}F} = 49$ Hz); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 21.4, 22.5, 24.7, 31.6, 32.5, 34.8, 35.1 (CH_2), 62.6 (CH_2OH), 94.4 (d, CHF, $J = 166.9$ Hz); ^{19}F NMR ($CDCl_3$): −180.9 (dm, CHF).

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