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An efficient method for the diastereoselective synthesis of α-fluoro-β-hydroxy esters based on the radical reduction of α-bromo-α-fluoro-β-hydroxy esters

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Abstract—When α-bromo-α-fluoro-β-hydroxy esters were allowed to react successively with trimethylaluminum in toluene at −15°C for 0.5 h and with tributyltin hydride in the presence of a catalytic amount of triethylborane at −15°C for 4 h, the corresponding *threo*-α-fluoro-β-hydroxyalkanoates were obtained highly diastereoselectively in good yields. On the other hand, the α-bromo-β-hydroxy esters having an aromatic substituent were subjected to the reaction with tris(trimethylsilyl)silane in the presence of a catalytic amount of triethylborane in THF at −78°C for 10 h to give the corresponding *erythro*-α-fluoro-β-hydroxyalkanoates with high *erythro*-selectivity in good yields, but those carrying an aliphatic substituent being reduced in an almost nonstereoselective manner.

1. Introduction

α-Fluoro-β-hydroxy esters are one of the most important compounds for preparing a variety of fluorine-containing molecules, particularly of fluorinated counterparts of naturally occurring substances, which attract much attention in biological and physiological chemistry.[1] Usually, the most general and reliable method for the access to α-fluoro-β-hydroxy esters is either the aldol reaction of metal enolates of monofluoroacetates[2] or the Reformatsky reaction of bromofluoroacetate.[3] However, these reactions do not realize good stereoselection enough to apply to the stereoselective construction of such β-hydroxy ester frameworks. Therefore, it is of quite value to develop a stereocontrolled method for the synthesis of the α-fluoro-β-hydroxy ester derivatives.

In the recent literature are disclosed a number of stereocontrolled reactions involving acyclic α-ester radicals.[4] We recently succeeded in preparing α-bromo-α-fluoro-β-hydroxy esters **1** through the zinc-mediated coupling reaction of commercially available dibromofluoroacetate with aldehydes in the presence of diethylaluminum chloride.[5] Expecting that the combination of the ready access to such α-bromo esters **1** with the recent radical chemistry will provide us with a two-step, stereoselective route to the relevant α-fluoro-β-hydroxy esters starting from dibromofluoroacetate, we explored the reduction of **1** with radicalic reductants under various radical conditions. This paper describes the results of these reactions, demonstrating an efficient and simple approach to the diastereoselective synthesis of the *threo*- and *erythro*-isomers of α-fluoro-β-hydroxy esters based on the radical reduction with tributyltin hydride or tris(trimethylsilyl)silane.

2. Results and discussion

Taking into account that the use of a Lewis acid in the radical reaction[6,7] of β-alkoxy-α-halo esters is effective for achieving a high stereoselection, we first examined the radical reduction of *nonprotected* α-bromo-α-fluoro-β-hydroxy ester **1a** employing various organometallic reagents, which permit the in situ formation of the metal alkoxide of **1a** (Scheme 1). The results of these reactions are collected in Table 1. When the ester **1a** was allowed to react with tributyltin hydride in the absence of an organometallic reagent, the reduction product **2a** was obtained in good yield as a diastereomeric mixture of 49:51 (entry 1). The use of *n*-butyllithium and diethylzinc resulted in nonstereoselection of the reaction (entries 2 and 3), but some organoaluminum reagents were found to be effective for regulating the stereochemical course of the radical reduction of **1a** (entries 4–6). Thus, on the reaction of **1a** with diisobutylaluminum hydride (*i*-Bu_2AlH), triethylaluminum (Et_3Al), or trimethylaluminum (Me_3Al) at −78°C for 0.5 h, followed by treatment of tributyltin hydride and a catalytic amount of triethylborane (Et_3B) at the same temperature for 6 h, the *threo*-isomer[8] of **2a** was given

Keywords: α-fluoro-β-hydroxy esters; radical reaction; reduction; diastereoselection; chelation control; solvent effect.

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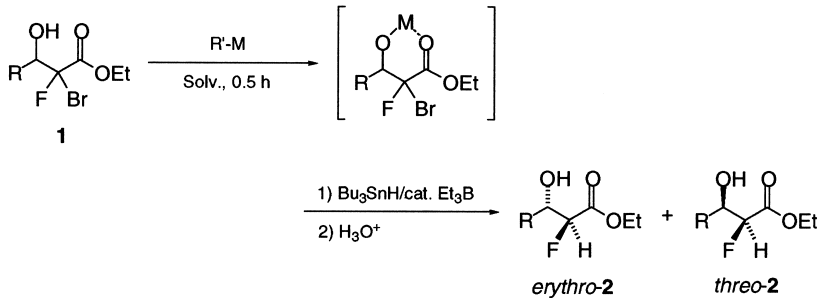


Scheme 1.

Table 1. Screening of reaction conditions in radical reduction of **1**

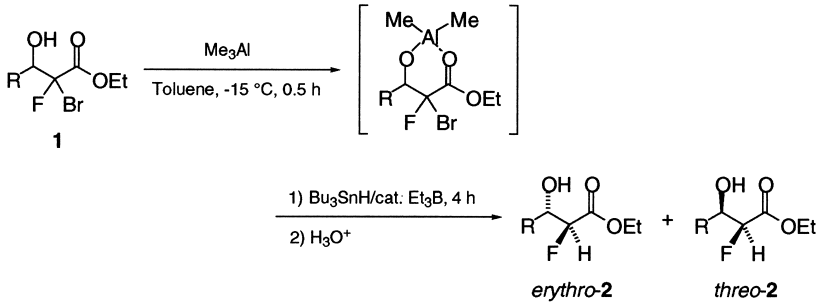
Entry	R		Isomer ratio[a] of **1** *erythro/threo*	R′M	Solvent	Temperature (°C)	Time (h)	Yield[b] of **2** (%)	Isomer ratio[a] of **2** *erythro/threo*
1	Ph	(**a**)	59:41	None	Toluene	−78	6	85	49:51
2	Ph	(**a**)	59:41	BuLi	Toluene	−78	6	57	42:58
3	Ph	(**a**)	59:41	Et_2Zn	Toluene	−78	6	80	43:57
4	Ph	(**a**)	59:41	*i*-Bu_2A1H	Toluene	−78	6	69	24:76
5	Ph	(**a**)	61:39	ET_3Al	Toluene	−78	6	77	11:89
6	Ph	(**a**)	61:39	Me_3Al	Toluene	−78	6	80	5:95
7	Ph	(**a**)	61:39	Me_3Al	Toluene	−15	4	84	5:95
9	Ph	(**a**)	57:43	Me_3Al	THF	−15	4	80	47:53
10	Ph	(**a**)	57:43	Me_3Al	CH_2Cl_2	−15	4	80	5:95
11	*n*-Pr	(**f**)	60:40	Me_3Al	Toluene	−15	4	75	9:91
12	*n*-Pr	(**f**)	100:0	Me_3Al	Toluene	−15	4	73	10:90
13	*n*-Pr	(**f**)	100:0	Me_3Al	Toluene	−78	6	81	11:89
14	*n*-Pr	(**f**)	0:100	Me_3Al	Toluene	−15	4	86	9:91
15	*n*-Pr	(**f**)	0:100	Me_3Al	Toluene	−78	6	75	5:95

[a] Determined by ^{19}F NMR.
[b] Isolated yields.

preferentially. The degrees of *threo*-selectivities were increased in the order of *i*-Bu_2AlH<Et_3Al<Me_3Al, Me_3Al leading to the best result.[9] These results are remarkable to suggest that the bulkiness of an alkyl group on aluminum plays an important role in determining the level of stereoselection. Moreover, it should be noted that the excellent stereoselectivity was realized even in the reaction at a higher reaction temperature, −15°C (entry 7).

Next, the reaction of **1a** was carried out by using THF or dichloromethane as a solvent, instead of toluene (entries 9 and 10). The reaction in dichloromethane at −15°C gave the result comparable to that in toluene (entry 7), but the reaction in THF at −15°C proceeded in a nearly nonstereoselective manner. As shown in entries 12–15, it was observed that the degree of *threo*-selectivity of the reaction was slightly affected with the relative configurations of the starting β-hydroxy esters. Thus, the *erythro*- and *threo*-isomers of **1f** were separately subjected to the radical reduction using Me_3Al at −15°C for 4 h or at −78°C for 6 h, producing the reduction product **2f** whose *erythro/threo* ratios were 10–11:90–89 and 9–5:91–95, respectively. This may be ascribed to difference in the relative stabilities for the chelated intermediates[7a,e,9b] of diastereomeric β-aluminum alkoxides.

With the optimized conditions in hand, we conducted the radical reductions of **1** bearing various substituents R (Scheme 2). The results of the reactions are summarized in Table 2. The reactions of the α-bromo-β-hydroxy esters **1** carrying an aromatic or aliphatic group, such as phenyl, *p*-tolyl, *p*-anisyl, propyl, hexyl, isopropyl, or *t*-butyl, at



Scheme 2.

Table 2. Radical reduction of hydroxy esters **1** using Me_3Al

Entry	R		Isomer ratio[a] of **1** *erythro/threo*	Yield[b] of **2** (%)	Isomer ratio[a] of **2** *erythro/threo*
1	Ph	(**a**)	61:39	77	4:6
2	*p*-MeC_6H_4	(**b**)	60:40	95	7:93
3	*p*-MeC_6H_4	(**c**)	51:49	86	6:94
4	MeCH=CH	(**e**)	57:43	73	14:86
5	*n*-Pr	(**f**)	60:40	75	9:91
6	*n*-Hex	(**g**)	46:54	72	10:90
7	*i*-Pr	(**h**)	63:37	68	7:93
8	*t*-Bu	(**i**)	46:54	66	4:96

[a] Determined by ^{19}F NMR.
[b] Isolated yields.

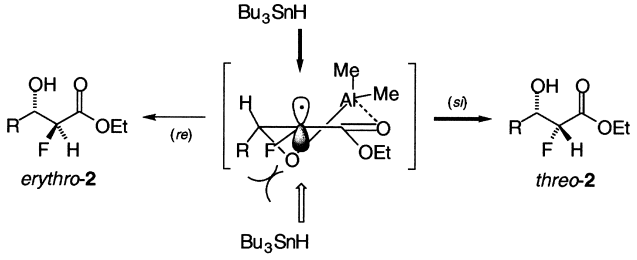


Figure 1. Possible stereochemical course in the *threo*-selective reduction of **1**.

−15°C for 4 h led to good yields of the corresponding reduction products **2** with high *threo*-selectivities. However, the ester **1e** bearing 1-propenyl group gave somewhat lower stereoselectivity (entry 4).

The stereochemical outcomes in the reduction of **1** may be explained in the following way. An intramolecularly chelated β-aluminum alkoxy ester,[9] formed in situ by the reaction of **1** with Me_3Al, undergoes a bromine abstraction with tributyltin radical to generate a chair-like chelated α-ester radical (Fig. 1). This radical will be preferentially attacked from the less hindered *si*-face by tributyltin hydride to give the product *threo*-**2**.

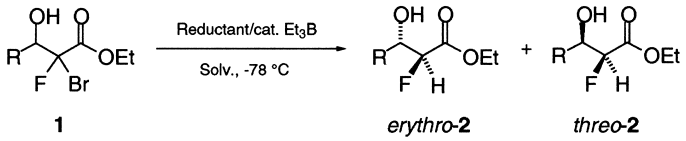
In view of the solvent effect of THF observed in the radical reduction of **1a** (Table 1, entry 9), we addressed our attention to a possible effect of solvents on the stereochemistry of the reaction,[10] with an expectation that a choice of solvent will be capable of realizing the *erythro*-selective radical reduction of **1**. Thus, the radical reduction of **1a** with tributyltin hydride without Me_3Al was examined at −78°C in various solvents, especially the coordinating solvents, such as THF, 2-propanol, and methanol, as shown in Table 3. But a dramatic change was not observed in the stereochemical outcomes of these reactions (entries 2–4). Tris(trimethylsilyl)silane (TTMSS)[11,12] is known to act as a radical reductant efficiently as tributyltin hydride. Surprisingly, the reaction of **1a** with TTMSS in the presence of a catalytic amount of Et_3B in THF at −78°C was found to occur with an excellent *erythro*-selectivity to give the reduction product **2a** in 73% yield, though the starting ester **1a** was recovered unchanged in 7% yield (entry 5). The use of 3 equiv. of the reductant was required for completion of the reaction (entry 6). Upon treatment of **1** carrying various aromatic substituents R with TTMSS and a catalytic amount of Et_3B in THF at −78°C for 10 h, the corresponding *erythro*-isomers of **2** were exclusively obtained as a sole isomer in good yields (entries 7–9). It is likely that THF may coordinate with the hydroxyl group of **1**, to disrupt an intramolecular hydrogen bonding in **1**. The intramolecular hydrogen bonding in the substrate is reported to favor the *threo*-selective course of the reaction (Scheme 3).[10]

Unfortunately, the reaction of the esters **1f** carrying an aliphatic substituent R took place in a nonstereoselective

Table 3. Radical reduction of hydroxy esters **1**

Entry	R		Isomer ratio[a] of **1** *erythro/threo*	Reductant	Solvent	Time (h)	Yield[b] of **2** (%)	Isomer ratio[a] of **2** *erythro/threo*
1	Ph	(**a**)	59:41	Bu_3SnH[c]	Toluene	6	85	49:51
2	Ph	(**a**)	63:37	Bu_3SnH[c]	THF	6	85	69:31
3	Ph	(**a**)	43:57	Bu_3SnH[c]	2-Propanol	6	84	43:57
4	Ph	(**a**)	43:57	Bu_3SnH[c]	Methanol	6	72	51:49
5	Ph	(**a**)	43:57	TTMSS[c]	THF	10	73[d]	100:0
6	Ph	(**a**)	43:57	TTMSS	THF	10	76	100:0
7	*p*-MeC_6H_4	(**b**)	53:47	TTMSS	THF	10	92	100:0
8	*p*-MeC_6H_4	(**c**)	56:44	TTMSS	THF	10	80	100:0
9	*p*-ClC_6H_4	(**d**)	43:57	TTMSS	THF	10	92	100:0
10	*n*-Pr	(**f**)	63:37	TTMSS	THF	10	80	51:49

[a] Determined by ^{19}F NMR.
[b] Isolated yields.
[c] Two equivalents of the reductant were used.
[d] The starting ester **1a** was recovered in 7% yield.



Scheme 3.

fashion (entry 10). All attempts to improve the degree of stereoselectivity were in failure.

A possible explanation for the stereochemistry of the *erythro*-selective reduction of **1** is made according to Fig. 2. The reaction is expected to proceed through an open-chain α-ester radical intermediate, free from the intramolecular hydrogen bonding[10] by a coordinating solvent THF. This open-chain α-ester radical may be attacked by TTMSS, extremely bulkier than tributyltin hydride, from the less hindered re-face of the most favored conformation,[13] to give rise to the product *erythro*-**2** preferentially. Since the aliphatic group R like *n*-Pr is not so bulky as the aromatic groups, it could not exert a sufficient steric effect to direct the stereoselective course of the reduction.

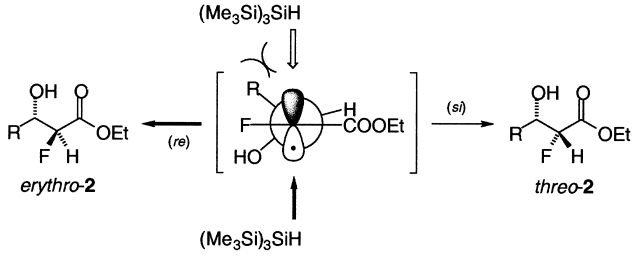


Figure 2. Possible stereochemical course in the *erythro*-selective reduction of **1**.

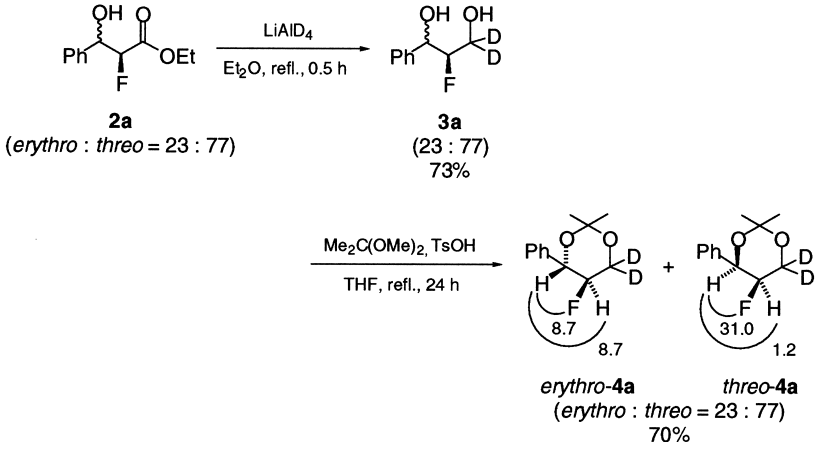
The stereochemical assignment of the reduction products **2** was made according to the procedure, as shown in Scheme 4. Thus, **2a** (isomer ratio, 23:77) was reduced with lithium aluminum deuteride in Et_2O at reflux temperature to give the diol **3a** (isomer ratio, 23:77), which was successively reacted with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid hydrate to give the corresponding acetonide **4a** (isomer ratio, 23:77). The ^1H and ^{19}F NMR analysis of **4a** indicated that the major isomer has the vicinal coupling constants, J_{H-H}=8.7 Hz and J_{H-F}=8.7 Hz, and the minor isomer has J_{H-H}=1.2 Hz and J_{H-F}=31.0 Hz, as shown in Scheme 4. Based on comparing the magnitudes of these vicinal couplings,[14] the acetonide **4a** with smaller vicinal coupling constant J_{H-F}=8.7 Hz was assigned as the *erythro*-isomer and the acetonide **4a** with larger vicinal coupling constant J_{H-F}=31.0 Hz as the *threo*-isomer.

3. Conclusions

In summary, we have developed a convenient and effective method for the stereoselective synthesis of the *threo*- and *erythro*-isomers of α-fluoro-β-hydroxyalkanoates **2** based on the radical reduction of α-bromo esters **1** which are readily available by the Reformatsky reaction of dibromofluoroacetate. The radical reduction of **1** was found to combine high *threo*- and *erythro*-stereoselectivities, depending on a choice of reaction conditions, particularly the use of organoaluminum reagent (Me_3Al) and a coordinating solvent (THF), together with reproducibility and simplicity of the manipulations.

4. Experimental

Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. ^1H NMR spectra were measured with a General Electric QE-300 (300.65 MHz) and/or Bruker DRX 500 (500.13 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker DRX (125.75 MHz) spectrometer in a chloroform-*d* ($CDCl_3$)



Scheme 4.

solution with tetramethylsilane (Me_4Si) as an internal reference. A JEOL JNM-EX90A (84.21 MHz, FT) spectrometer or Hitachi R-24F (56.46 MHz) was used for determining ^{19}F NMR spectra in a $CDCl_3$ solution with $CFCl_3$ as an internal standard. Mass spectra (MS) and high resolution mass spectra (HRMS) were taken on a Hitachi M-80B and/or JEOL JMS-700 mass spectrometer by electron impact (EI), chemical ionization (CI), or FAB (Cs^+) method using *m*-nitrobenzyl alcohol as a matrix. Elemental analyses were conducted with a Yanaco CHN CORDER MT-5.

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Toluene was distilled over calcium hydride and stored under argon. Trimethylaluminum (a 0.97 M hexane solution) and triethylborane (a 1.04 M hexane solution) were commercially available from Kanto Chemical Co. 2,6-Di-*tert*-butyl-*p*-cresol (BHT) was commercially available from Tokyo Kasei Chemical Co. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin layer chromatography (TLC) was done with Merck silica gel 60 F_{254} plates and column chromatography was carried out with Wakogel C-200. All reactions were conducted under an atmosphere of argon.

4.1. A general procedure for the *threo*-selective reduction of the hydroxy esters 1

The reaction of ethyl 2-bromo-2-fluoro-3-hydroxy-3-phenylpropanoate (**1a**) is representative. To a solution of **1a** (0.289 g, 1.0 mmol) in toluene (5.0 mL) was gradually added trimethylaluminum (0.97 M in hexane) (1.1 mL, 1.1 mmol) at −15°C under an argon atmosphere. After stirring at −15°C for 0.5 h, a solution of tributyltin hydride (0.582 g, 2.0 mmol) in toluene (5.0 mL) and triethylborane (1.04 M in hexane) (0.1 mL, 0.1 mmol) were added to the reaction mixture at −15°C. After being stirred at the same temperature for 4 h, the mixture was treated with a solution of BHT (0.022 g, 0.1 mmol) in toluene (0.5 mL) as a radical terminator and then was quenched with aqueous 10% HCl (20 mL). The resultant mixture was extracted with Et_2O (20 mL×5) and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate, 3:1) to afford analytically pure product **2a** (0.163 g, 0.769 mmol, 77% yield).

4.1.1. Ethyl *threo*-2-fluoro-3-hydroxy-3-phenylpropanoate (*threo*-2a). Yield 77%; needles from hexane; mp 46–47°C; ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.22 (t, J=7.3 Hz, 3H), 2.68 (br s, 1H), 4.17–4.28 (m, 2H), 5.02 (dd, J=48.0, 3.8 Hz, 1H), 5.14 (dd, J=22.0, 3.8 Hz, 1H), 7.30–7.42 (m, 5H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.95, 61.88, 73.93 (d, J=20.4 Hz), 91.46 (d, J=192.1 Hz), 126.50, 128.60, 128.61, 137.89 (d, J=2.5 Hz), 167.68 (d, J=24.2 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −203.23 (dd, J=48.0, 22.0 Hz, 1F); IR (KBr) 3456 (m), 2959 (w), 1759 (vs), 1458 (s), 1300 (s), 1273 (s), 1215 (s), 1103 (s), 1080 (s), 1045 (s), 1026 (s), 710 (s), 644 (m) cm^{-1}; MS (EI) *m/z* (rel. intensity) 212 (M^+, 2), 192 (21), 146 (4), 122 (15), 107 (100), 101 (4), 91 (25), 79 (100); HRMS (EI) calcd for (M^+) $C_{11}H_{13}FO_3$: 212.0848, found 212.0839. Anal. calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17. Found: C, 62.25; H, 6.01.

4.1.2. Ethyl *threo*-2-fluoro-3-hydroxy-3-(4-methylphenyl)-propanoate (*threo*-2b). Yield 95%; ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.20 (t, J=7.1 Hz, 3H), 2.53 (s, 3H), 2.65 (br s, 1H), 4.17–4.28 (m, 2H), 4.99 (dd, J=48.0, 3.8 Hz, 1H), 5.10 (dd, J=22.0, 3.8 Hz, 1H), 7.17–7.20 (m, 2H), 7.26–7.30 (m, 2H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.96, 21.13, 61.84, 73.77 (d, J=19.7 Hz), 91.53 (d, J=191.8 Hz), 126.41, 129.26, 134.93 (d, J=2.4 Hz), 138.41, 167.73 (d, J=24.2 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −203.28 (dd, J=48.0, 22.0 Hz, 1F); IR (neat) 3479 (m), 1747 (vs), 1060 (s) cm^{-1}; MS (EI) *m/z* (rel. intensity) 226 (M^+, 2), 206 (21), 160 (4), 136 (15), 121 (100), 105 (4); HRMS (EI) calcd for (M^+) $C_{12}H_{15}FO_3$: 226.1004, found 226.1017.

4.1.3. Ethyl *threo*-2-fluoro-3-hydroxy-3-(4-methoxyphenyl)propanoate (*threo*-2c). Yield 86%; needles from hexane; mp 45–46°C; ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.23 (t, J=7.2 Hz, 3H), 2.45 (br s, 1H), 3.81 (s, 3H), 4.17–4.27 (m, 2H), 4.97 (dd, J=48.3, 3.9 Hz, 1H), 5.08 (dd, J=22.0, 3.9 Hz, 1H), 6.89–6.92 (m, 2H), 7.31–7.34 (m, 2H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.96, 55.27, 61.81, 73.54 (d, J=20.2 Hz), 91.58 (d, J=191.6 Hz), 113.95, 127.87, 129.95 (d, J=3.4 Hz), 159.77, 167.71 (d, J=24.2 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −202.29 (dd, J=48.3, 22.0 Hz, 1F); IR (KBr) 3472 (m), 1767 (vs), 1300 (s), 1254 (s), 1204 (s), 1180 (s), 1103 (s), 1030 (s), 829 (s), 775 (s) cm^{-1}; MS (EI) *m/z* (rel. intensity) 242 (M^+, 11), 197 (5), 152 (11), 137 (100), 121 (10), 109 (35), 77 (18); HRMS (EI) calcd for (M^+) $C_{12}H_{15}FO_4$: 242.0953, found 242.0950.

4.1.4. Ethyl 2-fluoro-3-hydroxy-4-hexenoate (2e). Yield 73%; IR (neat) 3464 (s), 1747 (vs), 1377 (s), 1296 (s), 1211 (s), 1084 (s), 1033 (s), 968 (s) cm^{-1}; MS (CI) *m/z* (rel. intensity) 177 (M+H, 4), 159 (100), 147 (4), 117 (33), 87 (35), 74 (6); HRMS (CI) calcd for (M+H) $C_8H_{14}FO_3$: 177.0926, found 177.0925.

The erythro-isomer ***2e***. ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.29–1.35 (overlap with the *threo* isomer, 3H), 1.72–1.76 (overlap with the *threo* isomer, 3H), 2.00–2.30 (overlap with the *threo* isomer, 1H), 4.25–4.30 (overlap with the *threo* isomer, 2H), 4.45–4.53 (overlap with the *threo* isomer, 1H), 4.92 (dd, J=49.0, 3.5 Hz, 1H), 5.50–5.62 (overlap with the *threo* isomer, 1H), 5.82–5.91 (overlap with the *threo* isomer, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 14.09, 17.76, 61.68, 72.90 (d, J=21.7 Hz), 90.90 (d, J=190.1 Hz), 126.37 (d, J=5.8 Hz), 131.24; ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −202.04 (dd, J=49.0, 20.7 Hz, 1F).

The threo-isomer ***2e***. ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H), 1.75 (d, J=6.0 Hz, 3H), 2.12 (br s, 1H), 4.30 (q, J=7.1 Hz, 2H), 4.49 (ddd, J=22.5, 7.0, 3.5 Hz, 1H), 4.83 (dd, J=48.0, 3.5 Hz, 1H), 5.50–5.62 (m, 1H), 5.82–5.90 (m, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 14.09, 17.76, 61.77, 72.59 (d, J=20.6 Hz), 90.85 (d, J=190.1 Hz), 127.32 (d, J=4.3 Hz), 130.60, 167.80 (d,

J=24.0 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −205.48 (dd, J=48.0, 22.5 Hz, 1F).

4.1.5. Ethyl *threo*-2-fluoro-3-hydroxyhexanoate (*threo*-2f). Yield 75%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.97 (t, J=7.3 Hz, 3H), 1.33 (t, J=7.2 Hz, 3H), 1.40–1.65 (m, 4H), 2.06 (br s, 1H), 4.02 (dddd, J=24.4, 8.1, 5.3, 2.6 Hz, 1H), 4.30 (q, J=7.2 Hz, 2H), 4.83 (dd, J=48.0, 2.6 Hz, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.76, 14.07, 18.67, 34.71 (d, J=3.4 Hz), 61.73, 71.42 (d, J=20.5 Hz), 90.66 (d, J=188.0 Hz), 168.33 (d, J=24.2 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −208.60 (dd, J=48.0, 24.4 Hz, 1F); IR (neat) 3468 (m), 2963 (s), 2939 (s), 2874 (s), 1747 (vs), 1377 (s), 1300 (s), 1215 (s), 1138 (s), 1080 (s), 1026 (s) cm^{-1}; MS (CI) m/z (rel. intensity) 179 (M+H, 100), 161 (55), 133 (21), 106 (7), 85 (9), 78 (9), 73 (22); HRMS (CI) calcd for (M+H) $C_8H_{16}FO_3$: 179.1083, found 179.1074.

4.1.6. Ethyl *threo*-2-fluoro-3-hydroxynonanoate (*threo*-2g). Yield 72%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.89 (t, J=6.8 Hz, 3H), 1.33 (t, J=7.2 Hz, 3H), 1.30–1.66 (m, 10H), 1.85 (br s, 1H), 4.00 (dddd, J=24.2, 7.0, 6.9, 2.4 Hz, 1H), 4.31 (q, J=7.2 Hz, 2H), 4.83 (dd, J=48.0, 2.4 Hz, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 14.02, 14.12, 22.53, 25.42, 29.01, 31.64, 32.73 (d, J=3.5 Hz), 61.77, 71.78 (d, J=20.4 Hz), 90.62 (d, J=187.8 Hz), 168.32 (d, J=24.9 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −208.06 (dd, J=48.0, 24.2 Hz, 1F) (for the *threo* isomer), −200.04 (dd, J=49.2, 18.1 Hz, 1F) (for the *erythro* isomer); IR (neat) 3460 (m), 2932 (vs), 2858 (s), 1747 (vs), 1373 (s), 1300 (s), 1211 (s), 1138 (s), 1080 (s), 1030 (s) cm^{-1}; MS (CI) m/z (rel. intensity) 221 (M+H, 100), 203 (41), 147 (5); HRMS (CI) calcd for (M+H) $C_{11}H_{22}FO_3$: 221.1552, found 221.1549.

4.1.7. Ethyl *threo*-2-fluoro-3-hydroxy-4-methylpentanoate (*threo*-2h). Yield 68%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.01 (d, J=7.0 Hz, 3H), 1.08 (d, J=6.5 Hz, 3H), 1.33 (t, J=7.1 Hz, 3H), 1.86 (br s, 1H), 1.86–1.95 (m, 1H), 3.64 (ddd, J=27.5, 8.5, 2.0 Hz, 1H), 4.27–4.40 (m, 2H), 5.02 (dd, J=48.5, 2.0 Hz, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 14.11, 18.71, 18.93, 30.87 (d, J=3.1 Hz), 61.76, 77.09 (d, J=21.9 Hz), 89.33 (d, J=188.4 Hz), 168.60 (d, J=24.2 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −210.70 (dd, J=48.5, 27.5 Hz, 1F); IR (neat) 3479 (m), 2966 (s), 1763 (vs), 1300 (s), 1215 (s), 1142 (s), 1088 (s), 1053 (s), 1026 (s) cm^{-1}; MS (CI) m/z (rel. intensity) 179 (M+H, 100), 161 (49), 141 (77), 133 (9), 118 (4), 106 (5), 91 (4), 81 (4); HRMS (CI) calcd for (M+H) $C_8H_{16}FO_3$: 179.1083, found 179.1084.

4.1.8. Ethyl *threo*-2-fluoro-3-hydroxy-4,4-dimethylpentanoate (*threo*-2i). Yield 66%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.04 (d, J=1.0 Hz, 9H), 1.33 (t, J=7.3 Hz, 3H), 2.08 (br s, 1H), 3.67 (dd, J=30.0, 1.0 Hz, 1H), 4.25–4.34 (m, 2H), 5.13 (dd, J=48.5, 1.0 Hz, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 14.09, 26.27, 35.04, 61.83, 78.56 (d, J=18.0 Hz), 88.86 (d, J=189.5 Hz), 168.97 (d, J=25.3 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −208.62 (dd, J=48.5, 30.0 Hz, 1F); IR (neat) 3510 (m), 2963 (s), 1763 (vs), 1304 (s), 1211 (s), 1115 (s), 1065 (s), 1022 (s) cm^{-1}; MS (FAB) m/z (rel. intensity) 193 (M+H, 43); HRMS (FAB) calcd for (M+H) $C_9H_{18}FO_3$: 193.1240, found 193.1243.

4.2. A general procedure for the *erythro*-selective reduction of the hydroxy esters 1

The reaction of ethyl 2-bromo-2-fluoro-3-hydroxy-3-phenylpropanoate (**1a**) is representative. Under an argon atmosphere, to a solution of the hydroxy ester **1a** (0.289 g, 1.0 mmol) in THF (5.0 mL) was gradually added a solution of tris(trimrthylsilyl)silane (0.75 g, 3.0 mmol) in THF (5.0 mL) and triethylborane (1.04 M in hexane) (0.1 mL, 0.1 mmol) at −78°C. After stirring at the same temperature for 10 h, the mixture was quenched with a solution of BHT (0.022 g, 0.1 mmol) in toluene (0.5 mL) and then was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate, 3:1) to afford analytically pure product **2a** (0.161 g, 0.759 mmol, 76% yield).

4.2.1. Ethyl *erythro*-2-fluoro-3-hydroxy-3-phenylpropanoate (*erythro*-2a). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.19 (t, J=7.1 Hz, 3H), 2.69 (br s, 1H), 4.19 (q, J=7.1 Hz, 2H), 5.05 (dd, J=48.0, 5.0 Hz, 1H), 5.12 (dd, J=16.0, 5.0 Hz, 1H), 7.28–7.41 (m, 5H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.92, 61.77, 73.62 (d, J=21.9 Hz), 90.93 (d, J=191.2 Hz), 126.75, 128.45, 128.61, 137.51 (d, J=2.6 Hz), 167.69 (d, J=23.1 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −198.21 (dd, J=48.0, 16.0 Hz, 1F); IR (neat) 3479 (m), 1747 (vs), 1454 (s), 1377 (s), 1211 (s), 1026 (s), 718 (s) cm^{-1}; MS (FAB) m/z (rel. intensity) 213 (M+H, 57); HRMS (FAB) calcd for (M+H) $C_{11}H_{14}O_3F$: 213.0927, found 213.0924.

4.2.2. Ethyl *erythro*-2-fluoro-3-hydroxy-3-(4-methylphenyl)propanoate (*erythro*-2b). Yield 92%; needles from hexane; mp 50–51°C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.20 (t, J=7.2 Hz, 3H), 2.342 (s, 3H), 2.87 (br s, 1H), 4.19 (q, J=7.2 Hz, 2H), 5.02 (dd, J=47.5, 5.0 Hz, 1H), 5.07 (dd, J=17.0, 5.0 Hz, 1H), 7.15–7.18 (m, 2H), 7.20–7.28 (m, 2H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.94, 21.13, 61.73, 73.49 (d, J=21.9 Hz), 90.97 (d, J=191.0 Hz), 126.68, 129.12, 134.58 (d, J=2.7 Hz), 138.39, 167.77 (d, J=23.0 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −198.46 (dd, J=47.5, 17.0 Hz, 1F); IR (KBr) 3468 (s), 1755 (vs), 1215 (s), 1096 (s), 1045 (s), 1015 (s), 725 (s) cm^{-1}; MS (FAB) m/z (rel. intensity) 227 (M+H, 16); HRMS (FAB) calcd for (M+H) $C_{12}H_{16}O_3F$: 227.1083, found 227.1085.

4.2.3. Ethyl *erythro*-2-fluoro-3-hydroxy-3-(4-methoxyphenyl)propanoate (*erythro*-2c). Yield 80%; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.22 (t, J=7.2 Hz, 3H), 2.77 (br s, 1H), 3.81 (s, 3H), 4.20 (q, J=7.2 Hz, 2H), 5.01 (dd, J=34.0, 5.0 Hz, 1H), 5.07 (s, 1H), 6.80–6.91 (m, 2H), 7.30–7.33 (m, 2H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.99, 55.25, 61.76, 73.26 (d, J=22.2 Hz), 90.93 (d, J=190.4 Hz), 113.9, 128.12, 129.69, 159.80, 167.81 (d, J=23.5 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −198.86 (dd, J=49.2, 15.6 Hz, 1F); IR (neat) 3475 (m), 1747 (s), 1515 (s), 1251 (s), 1031 (s) cm^{-1}; MS (EI) m/z (rel. intensity) 242 (M^+, 11), 197 (5), 152 (11), 137 (100), 121 (10), 109 (35), 77 (18); HRMS (EI) calcd for (M^+) $C_{12}H_{15}O_4F$: 242.0953, found 242.0950.

4.2.4. Ethyl *erythro*-2-fluoro-3-hydroxy-3-(4-chlorophenyl)propanoate (*erythro*-2d). Yield 92%; needles from hexane; mp 60–61°C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.22 (t, J=7.1 Hz, 3H), 2.98 (br s, 1H), 4.21 (q, J=7.1 Hz, 2H), 5.00 (dd, J=48.0, 5.0 Hz, 1H), 5.10 (dd, J=15.5, 5.0 Hz, 1H), 7.30–7.35 (m, 4H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.96, 61.95, 72.95 (d, J=22.0 Hz), 90.72 (d, J=191.6 Hz), 128.17, 128.63, 134.45, 136.00 (d, J=3.3 Hz), 167.56 (d, J=23.0 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −198.12 (dd, J=48.0, 15.5 Hz, 1F); IR (KBr) 3464 (s), 1755 (vs), 1377 (s), 1354 (s), 1312 (s), 1215 (s), 1092 (s), 1045 (s), 1011 (s), 980 (s), 845 (s), 791 (s), 737 (s) cm^{-1}; MS (EI) *m/z* (rel. intensity) 242 (M^+, 11), 197 (5), 152 (11), 137 (100), 121 (10), 109 (35), 77 (18); HRMS (EI) calcd for (M^+) $C_{12}H_{15}O_4F$: 242.0953, found 242.0950. Anal. calcd for $C_{11}H_{12}ClFO_3$: C, 53.56; H, 4.90. Found: C, 53.47; H, 4.71.

4.2.5. Ethyl 2-fluoro-3-hydroxyhexanoate (2f). Yield 80%; IR (neat) 3468 (m), 2663 (s), 1747 (vs), 1300 (s), 1211 (s), 1138 (s), 1076 (s), 1030 (s) cm^{-1}; MS (FAB) *m/z* (rel. intensity) 179 (M+H, 49); HRMS (FAB) calcd for (M+H) $C_8H_{16}FO_3$: 179.1083, found 179.1093.

The erythro-isomer ***2f***. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.97 (t, J=7.3 Hz, 3H), 1.33 (t, J=7.3 Hz, 3H), 1.43–1.65 (m, 4H), 2.21 (br s, 1H), 3.97–4.08 (m, 1H), 4.27–4.33 (m, 2H), 4.86 (dd, J=48.5, 4.1 Hz, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.76, 14.06, 18.56, 33.43 (d, J=4.7 Hz), 61.70, 71.40 (d, J=21.8 Hz), 91.26 (d, J=187.3 Hz), 168.03 (d, J=22.8 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −200.07 (dd, J=48.5, 18.1 Hz, 1F).

The threo-isomer ***2f***. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.95 (t, J=7.3 Hz, 3H), 1.33 (t, J=7.3 Hz, 3H), 1.43–1.65 (overlap with the *erythro* isomer, 4H), 2.21 (br s, 1H), 3.97–4.08 (overlap with the *erythro* isomer, 1H), 4.27–4.33 (overlap with the *erythro* isomer, 2H), 4.83 (dd, J=48.0, 2.5 Hz, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 13.76, 14.06, 18.67, 34.70 (d, J=3.3 Hz), 61.73, 71.42 (d, J=20.4 Hz), 90.66 (d, J=188.0 Hz), 168.34 (d, J=24.2 Hz); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −208.60 (dd, J=48.0, 23.3 Hz, 1F).

4.3. Preparation of the acetonide 4a from 2a

Under an argon atmosphere, to a suspension of lithium aluminum deuteride (0.125 g, 3.0 mmol) and Et_2O (5.0 mL) was gradually added a solution of **2a** (0.698 g, 3.3 mmol) in Et_2O (2.0 mL) at reflux temperature. After stirring at the same temperature for 0.5 h, the mixture was quenched with ethyl acetate (0.3 mL) and aqueous 3N HCl (10 mL), and then was extracted with Et_2O (20 mL×5). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate) to give analytically pure diol **3** (0.507 g, 2.409 mmol, 73% yield). To a solution of the diol **3a** (0.260 g, 1.5 mmol) in THF (15.0 mL) was gradually added 2,2-dimethoxypropane (1.573 g, 15.0 mmol) and *p*-toluenesulfonic acid hydrate (0.029 g, 0.15 mmol). After being stirred at reflux temperature for 24 h, the mixture was quenched with a saturated aqueous $NaHCO_3$ solution and was extracted with Et_2O (30 mL×3). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant residue was chromatographed on silica gel using benzene to give analytically pure acetonide **4a** (0.224 g, 1.05 mmol, 70% yield).

4.3.1. 1,1-Dideuterio-2-fluoro-3-phenylpropane-1,3-diol (3a). Yield 73%; IR (neat) 3310 (vs), 2927 (m), 1454 (s), 1091 (s), 1073 (s), 1037 (s), 1024 (s), 998 (s), 967 (s), 754 (s), 715 (vs), 697 (s) cm^{-1}.

The erythro-isomer ***3a***. ^{1}H NMR (300.65 MHz, $CDCl_3$) δ 3.16 (br s, 1H), 3.78 (br s, 1H), 4.52 (dd, J=48.6, 6.0 Hz, 1H), 4.90 (dd, J=11.4, 6.0 Hz, 1H), 7.26–7.39 (m, 5H); ^{19}F NMR (60 MHz, $CDCl_3$) δ −116.40 (dd, J=46.6, 11.4 Hz, 1F).

The threo-isomer ***3a***. ^{1}H NMR (300.65 MHz, $CDCl_3$) δ 3.00 (br s, 1H), 3.55 (br s, 1H), 4.53 (dd, J=48.1, 6.0 Hz, 1H), 4.84 (dd, J=15.9, 6.0 Hz, 1H), 7.26–7.39 (m, 5H); ^{19}F NMR (60 MHz, $CDCl_3$) δ −120.30 (dd, J=48.1, 15.9 Hz, 1F).

4.3.2. 6,6-Dideuterio-5-fluoro-2,2-dimethyl-4-phenyl-1,3-dioxane (*erythro*-4a). Yield 16%; ^{1}H NMR (300.65 MHz, $CDCl_3$) δ 1.48 (s, 3H), 1.58 (s, 3H), 4.50 (dd, J=50.2, 8.7 Hz, 1H), 4.78 (dd, J=8.7, 8.7 Hz, 1H), 7.28–7.47 (m, 5H); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −194.70 (dd, J=50.2, 8.7 Hz, 1F); IR (neat) 2963 (s), 1261 (vs), 1101 (vs), 1026 (vs), 819 (s) cm^{-1}; MS (EI) *m/z* (rel. intensity) 212 (M^+, 1), 197 (9), 154 (91), 137 (83), 122 (62), 105 (100); HRMS (EI) calcd for (M^+) $C_{12}H_{13}FO_2$: 212.1181, found 212.1178.

4.3.3. 6,6-Dideuterio-5-fluoro-2,2-dimethyl-4-phenyl-1,3-dioxane (*threo*-4a). Yield 54%; ^{1}H NMR (300.65 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.56 (s, 3H), 4.38 (dd, J=47.2, 1.2 Hz, 1H), 4.96 (d, J=31.0 Hz, 1H), 7.25–7.46 (m, 5H); ^{19}F NMR (84.21 MHz, $CDCl_3$) δ −204.30 (ddm, J=47.2, 1.2 Hz, 1F); IR (neat) 2993 (m), 2941 (m), 1381 (s), 1258 (s), 1205 (s), 1194 (s), 1113 (s), 1086 (s), 1053 (s), 789 (vs), 772 (vs) cm^{-1}; MS (EI) *m/z* (rel. intensity) 212 (M^+, 2), 197 (14), 154 (100), 137 (100), 122 (61), 116 (4); HRMS (EI) calcd for (M^+) $C_{12}H_{13}FO_2$: 212.1181, found 212.1178.

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