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Enantioselective Aldol Reaction with Bromofluoroketene Silyl Acetals

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Abstract: The aldol reaction of aldehydes with bromofluoroketene ethyl trimethylsilyl acetal in the presence of a catalytic amount of a chiral Lewis acid at -78°C provides a mixture of the corresponding syn- and anti- α -bromo- α -fluoro- β -hydroxy esters with high enantioselectivities (up to 99% ee). Reaction temperature has a great influence on the stereoselectivity. The aldol reaction at -20°C proceeds with high enantio- and diastereoselectivities to preferentially afford the anti-aldols having opposite signs of optical rotation to those at -78°C. © 1999 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

The synthesis of chiral fluoroorganic compounds, which play an important role in the research on biological chemistry and in the development of medicines, is one of the most important aspects of modern organofluorine chemistry in view of fluorine's unique influence on biological activity.¹⁻⁵ However, fluorine-containing molecules with generally unusual reactivity, due to the strongly electronegative nature of fluorine, frequently prevent asymmetric reactions developed for nonfluorinated compounds from working. Thus, fluoroorganic compounds remain as extremely difficult but challenging problems to be solved for enantiocontrolled synthesis.

We previously described an efficient catalytic asymmetric aldol reaction of a difluoroketene silyl acetal for the synthesis of optically active α, α -difluoro- β -hydroxy esters.^{6,7} Furthermore, we have recently succeeded in a highly enantioselective aldol reaction with bromofluoroketene ethyl trimethylsilyl acetal (1) mediated by a chiral Lewis acid,^{8,9} and the details are described in this paper.

RESULTS AND DISCUSSION

Preparation of bromofluoroketene ethyl trimethylsilyl acetal (1) and its reactivity in the absence of Lewis acids. The bromofluoroketene acetal solution, generated by adding ethyl dibromofluoroacetate to a mixture of chlorotrimethylsilane and activated zinc powder in tetrahydrofuran at -20°C and stirring for an additional hour, was diluted with *n*-pentane and filtered to remove zinc salts, and the filtrate was concentrated *in vacuo*. After the dilution-filtration-concentration sequence was repeated once more, distillation of the residue under reduced pressure isolated the pure acetal 1 as a mixture of *E*- and *Z*-isomers. The E/Z ratio was determined to

be 62/38 by 19 F NMR, and the minor isomer was confirmed to be the (Z)-acetal by the NOE between the fluorine atom and the methylene proton of the ethoxy group (Scheme 1).



Interestingly, the bromofluoroketene acetal 1 as well as the reported difluoroketene silyl acetal⁷ reacted with benzaldehyde in the absence of a Lewis acid in dichloromethane even at -78°C to afford a mixture of *syn-* and *anti-*aldols 2 in 23% yield. On the contrary, the reaction of benzaldehyde with fluorine-free ketene acetal 3 gave the corresponding aldol 4 in a trace amount at -78°C and in 21% yield even at 40°C (Scheme 2). The *syn/anti* ratio (60/40) of the product 2 at 40°C is considered to correspond to the *E/Z* ratio (62/38) of the substrate 1, suggesting that the uncatalyzed aldol reaction proceeds through the boat-like transition state A shown in Figure 1.¹⁰ As previously mentioned in the case of the difluoroketene acetal,⁷ the high reactivity of the bromofluoroketene acetal 1 may be explained by the model structure **B** in which the silicon-oxygen bond is out of the carbon-carbon double bond plane and which bears a geometrical similarity to the acetal 1 in the cyclic transition state A (Figure 1). The silicon-oxygen bond in the optimized structure of the fluorine-free acetal 3 is on the same plane with the carbon-carbon double bond.⁷





Fig. 1. Possible transition states for the uncatalyzed aldol reaction of bromofluoroketene acetal 1

Asymmetric aldol reaction of the bromofluoroketene acetal 1 mediated by Masamune's catalyst 5 at -78 °C. We next examined the aldol reaction of aldehydes with the bromofluoroketene acetal 1 in the presence of Masamune's catalyst 5.^{11,12} The reaction was carried out by adding an aldehyde to 20 mol% of the catalyst and 1.2 equivalents of 1 in nitroethane at -78 °C over 3 h and stirring at the same temperature for an additional hour.¹³ After the obtained silyl ether was hydrolyzed with 2 N aqueous HCl, the corresponding aldols, 2 and 6-12, were isolated by flash chromatography, and their optical yields were determined by HPLC analysis using chiral columns. These results are summarized in Table 1.

Table 1. Enantioselective aldol reaction of various aldehydes with the bromofluoroketene silyl acetal 1 in the presence of Masamune's catalyst 5

RCHO + F ₂ OSiMe ₃ <u>catalyst 5 (20 mol%)</u> Br [*] OR ¹ EtNO ₂ , -78°C	$\begin{array}{ccc} OH & OH \\ R^{3} & 2 CO_{2}R^{1} + R^{3} & 2 CO_{2}R^{1} \\ Br & F & F & Br \end{array}$	O O2S H
(1.2 equiv)	syn anti	
1: R' = Et (<i>E/Z</i> = 62/38) 13: R ¹ = <i>i</i> -Pr (<i>E/Z</i> = 62/38)	2, 6-12: R ¹ = Et, 14: R ¹ = <i>i</i> -Pr	5

Entry	RCHO	Yield ^a	syn/anti ^b	Ee $(syn)^c$	Ee (anti) ^c	Product
1	РһСНО	90	69/31	98 (2 <i>S</i> ,3 <i>R</i>) ^d	90 (2 <i>R</i> ,3 <i>R</i>)	2
2	(E)-PhCH=CHCHO	96	57/43	83 (+)	83 (+)	6
3	PhCH ₂ CH ₂ CHO	89	46/54	98 (+)	98 (+)	7
4	PhCH ₂ OCH ₂ CHO	81	57/43 ^e	97 (-) ^e	97 (+) ^e	8
5	<i>с</i> -С ₆ Н ₁₁ СНО	74	52/48	94 (+)	89 (+)	9
6	CH ₃ CH ₂ CH ₂ CHO	90	46/54	97 (+) ^f	98 (+)	10
7	(CH ₃) ₂ CHCH ₂ CHO	96	48/52	98 (+)	98 (+)	11
8	(C ₂ H ₅) ₂ CHCHO	70	54/46	99 (+)	98 (+)	12
9g	(E)-PhCH=CHCHO	89	39/61e	95 (-) ^h	95 (-) ^e	14

a) Isolated yield; b) Based on isolated yields of syn- and anti-aldols; c) HPLC analysis using a Daicel Chiralcel OD-H, OB-H or AD column; d) Stereochemistry was determined by X-ray analysis of the camphanate obtained from syn-2 and (-)-camphanic chloride; e) Determined using the corresponding acetate; f) Enantiomeric excess was determined using the corresponding 3,5dinitrobenzoate; g) The isopropyl acetal 13 was used in place of 1; h) The acetate of syn-14 was converted to an acetonide whose enantiomeric excess was determined by HPLC analysis.

In all cases, the aldol reactions smoothly proceeded to provide a mixture of syn- and anti-aldols in excellent-to-good chemical yields. Although the reactions were not diastereoselective (syn/anti = 69/31 to 39/61), all syn- and anti-aldol products were obtained with excellent enantiomeric excesses. For example, 2-ethylbutanal afforded the (+)-syn- and anti-aldols 12 with 99% ee and 98% ee, respectively, in 70% yield (entry 8). The syn-aldol obtained from benzaldehyde (syn-2) was shown to have the (2S,3R)-configuration by X-ray analysis of the corresponding camphanate (entry 1).¹⁴ Although (E)-cinnamaldehyde afforded the lowest enantiomeric excess (entry 2), use of bromofluoroketene isopropyl trimethylsilyl acetal (13) greatly improved the enantioselectivity (entry 9).

Effects of reaction temperature on the enantiofacial selection of aldehydes with the bromofluoroketene acetal 1. Interestingly, the enantiofacial selection in the aldol reaction was found to depend on reaction temperature. Reaction of 3-methylbutanal with the bromofluoroketene acetal 1 was carried out by the addition of the aldehyde to a solution of the acetal and the catalyst over 3 h at the specified temperature, followed by stirring at the same temperature for an additional hour, prior to quenching (Table 2, entries 1-4). While the *syn*- and *anti*-products at -78°C show dextrorotation (entry 1), those at higher temperatures (-45, -20 and -10°C) are levorotatory (entries 2-4). It is noteworthy that the reactions at -78 and -20°C afforded the (+)- and (-)-*anti*- aldols 11, respectively, with significant enantiomeric excesses (98% ee and 91% ee, entries 1 and 3). The *syn*-isomers at -45, -20 and -10°C also showed opposite signs of optical rotation to that at -78°C, although the degrees of enantioselectivity were modest (entries 2-4). Furthermore, *anti* diastereoselection was observed at -20 and -10°C (entries 3 and 4), while the reactions at -78 and -45°C resulted in a nearly 1:1 mixture of the *syn*- and *anti*-aldols.

	сно + 1 (E	(1.2 equiv) 7/Z = 62/38)	catalyst 5 (20 mol%) EtNO ₂	syn-11 + anti-11	
Entry	Temp.	Yield ^a (%)	syn/anti ^b	Ee (syn) ^c (%)	Ee (anti) ^c (%)
1	-78°C	96	48/52	98 (+)	98 (+)
2	-45°C	94	51/49	14 (-)	24 (-)
3	-20°C	87	11/89	31 (-)	91 (-)
4	-10°C	80	16/84	31 (-)	86 (-)
5	-78°C, then -20°C (2 h)	91	47/53	99 (+)	99 (+)
6 ^d	-78°C	81	50/50	97 (+)	99 (+)
7 ^d	-20°C	14	61/39	30 (+)	36 (+)

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a) Isolated yield; b) Based on isolated yields of syn- and anti-aldols; c) HPLC analysis using a Daicel Chiralcel OD-H column; d) A solution of the acetal 1 was to a solution of 3-methylbutanal and the catalyst 5 in nitroethane over 3 h. The reaction was stirred for an additional hour prior to quenching.

After an additional hour at -78°C, elevating the reaction temperature to -20°C and stirring for 2 h did not affect the stereoselectivity [*syn/anti* = 47/53; *syn*-11: 99% ee; *anti*-11: 99% ee, Table 2, entry 5]. Although the aldehyde was added to the acetal 1 and the catalyst 5 in entries 1-5, the addition of 1 to the aldehyde and 5 over 3 h at -20°C did not cause any reversal in the enantiofacial selection (entry 7).

As shown in Table 3, the aldol reactions at -20°C were examined using other several other aldehydes. The reaction was carried out by adding an aldehyde to a solution of the catalyst 5 and the acetal 1 over 3 h and stirring for an additional hour prior to quenching. The reactions were *anti* selective except for benzaldehyde and their *syn/anti* ratios ranged from 11:89 to 26:74 (entries 2-6). All *syn-* and *anti-*aldols but *syn-*2 show opposite signs of optical rotation to those obtained at -78°C. More interestingly, (-)-*anti-*aldols **7-10** and **12** except for *anti-*2 were obtained with significant degrees of enantioselectivity (72-93% ee's, entries 2-6).

Table 3. Enantioselective aldol reaction of various aldehydes with the bromofluoroketene acetal 1 in the presence of the catalyst 5 at $-20^{\circ}C^{a}$

				OH	OH 3 OO F
RCHO	+	1 (1.2 equiv) (<i>E/Z</i> = 62/38)	EtNO ₂ , -20°C	R 2 CO ₂ Et F Br	+ R 2 CO ₂ Et Br F
				syn	anti

Entry	RCHO	Yield ^b (%)	syn/anti ^c	Ee (syn) ^d (%)	Ee (anti) ^d (%)	Product
1	PhCHO	89	49/51	13 (2S,3R) ^e	13 (25,35)	2
2	PhCH ₂ CH ₂ CHO	85	13/87	48 (-)	92 (-)	7
3	PhCH ₂ OCH ₂ CHO	80	26/74 ^f	29 (+) ^f	72 (-) ^f	8
4	<i>с</i> -С ₆ Н ₁₁ СНО	90	20/80	18 (-)	81 (-)	9
5	CH ₃ CH ₂ CH ₂ CHO	87	11/89	49 (-) ^g	93 (-)	10
6	(C ₂ H ₅) ₂ CHCHO	85	23/77	21 (-)	74 (-)	12

a) All reactions were carried out by adding an aldehyde to a solution of the acetal 1 and the catalyst 5 at -20°C over 3 h and stirring at the same temperature for 1 h; b) Isolated yield; c) Based on isolated yields of *syn-* and *anti*-aldols; d) HPLC analysis using a Daicel Chiralcel OD-H, OB-H or AD column; e) Stereochemistry was determined by X-ray analysis of the camphanate obtained from *syn-*2 and (-)-camphanic chloride; f) Determined using the corresponding acetate; g) Enantiomeric excess was determined using the corresponding 3,5-dinitrobenzoate.

As previously reported, such a reversal of enantiofacial selection was not observed with a fluorine-free acetal, the dimethylketene silyl acetal 3, although elevating the reaction temperature to -20°C decreased the degree of enantioselectivity.⁷ The temperature-dependent reversal of the enantioselectivity may be specific to fluorine-substituted ketene silyl acetals.

The aldol reaction of 3-methylbutanal was also examined using the isopropyl acetal 13 and bromofluoroketene methyl trimethylsilyl acetal (16) at -20°C. As shown in Scheme 3, both the acetals also showed *anti* stereoselectivity and provided the corresponding *anti*-aldols having levorotation as well as the ethyl acetal 1. However, the degrees of enantioselectivity except for that of *syn*-15 could not be improved.



Reaction mechanism. The reason remains unclear why elevating the reaction temperature causes the reversal of the enantiofacial selection and the *anti* stereoselectivity is obtained at -20°C. However, the ¹⁹F NMR spectra of a 1:1 mixture of acetal 1 and catalyst 5 in $C_2D_5NO_2$ at -78 and -20°C gave a hint for the reaction mechanisms: the former (-78°C) showed two singlet peaks originating from the bromofluoroketene acetal 1 [-132.88 ppm (*E*-1) and -134.13 ppm (*Z*-1)], while four new peaks (-128.73, -129.65, -137.30, and -137.70 ppm) appeared in the latter (-20°C) as shown in Figure 2. The appearance of these new peaks at -20°C may suggest transmetallation from the silyl acetal 1 to a boron acetal. On the other hand, the ¹³C NMR of a 1:1

mixture of the ¹³C-labelled fluorine-free acetal 3 [¹³Me·MeC=C(OMe)OSiMe₃] and the catalyst 5 in $C_2D_5NO_2$ at -20°C showed almost the same spectrum as that at -78°C.



Fig. 2. ¹⁹F NMR of a 1:1 mixture of acetal 1 and catalyst 5 in C₂D₅NO₂ at -20°C

In the aldol reaction mediated by the catalyst 5, the bromofluoroketene acetal 1 preferentially reacts on the *si* face of aldehydes at -78°C and the fluorine-free dimethylketene acetal 3 also shows the same enantiofacial selection.^{11,12} We propose extended open transition states C and D for the reaction at -78°C (Figure 3). The *syn*- and *anti*-aldols are given through transition states C and D, respectively.



Fig. 3. Possible transition states for the aldol reaction at -78°C

On the contrary, the aldol reaction at -20°C preferentially proceeds with *re* facial enantioselection and is *anti* stereoselective. We propose chair-like closed transition states G and H, derived from boron acetal E or F and an aldehyde (RCHO), for the reaction at -20°C (Figure 4). These transition states lead to the reversal of the enantioselectivity when transmetallation to the boron acetals E and F rapidly occurs.¹⁵ The *anti* selectivity may be caused by the predominant formation of the (Z)-boron acetal E and/or its higher reactivity than the (E)-isomer F. From the (Z)-boron acetal E, the corresponding (2S,3S)-*anti*-aldol should be obtained through the cyclic transition state G. However, a cyclic transition state I coordinated by the catalyst 5 is also a probable model leading to the *anti* product.^{16,17}



Fig. 4. Possible transition states for the aldol reaction at -20°C

CONCLUSION

Aldol reaction of aldehydes with bromofluoroketene ethyl trimethylsilyl acetal (1) catalyzed by chiral Lewis acid 5 at -78°C provides the corresponding syn- and anti- α -bromo- α -fluoro- β -hydroxy esters with high enantiomeric excesses although the reaction is not diastereoselective. Elevating the reaction temperature to -20°C predominantly affords the anti-aldols showing the opposite signs of optical rotation to those obtained at -78°C in excellent-to-good optical yields.

EXPERIMENTAL

General. All reactions were carried out under an argon atmosphere with magnetic stirring in oven-dried glassware. Nitroethane was distilled from phosphorus pentoxide in the presence of hydroquinone immediately before use. Other solvents and reagents were used as supplied or purified. Anhydrous MgSO4 and Na₂SO₄ were used as the drying agents. TLC was carried out with pre-coated Kieselgel 60F₂₅₄ plates (Merck). Silica gel 60 (Merck, 230-400 mesh) was used for column chromatography. Liquid chromatographic analysis was performed on a Shimadzu LC-10A at 254 nm or 230 nm using a chiral column (Daicel Chiralcel OD-H, OB-H and AD columns). Optical rotations were measured at 589 nm using a 1.0-dm cell with a total volume of 1 mL on a JASCO DIP-370 polarimeter. Infrared spectra were taken on a Perkin-Elmer 1600 FT-IR. Absorption was expressed in reciprocal centimeters (cm⁻¹). ¹H NMR and ¹⁹F NMR spectra were recorded at 200 MHz and 188 MHz, respectively, on a Varian Gemini-200 instrument. ¹H NMR signals were expressed in parts per million (ppm) downfield from TMS as the internal standard. ¹⁹F NMR spectra were given upfield from CCl₃F as the internal standard. Coupling constants are in hertz. CDCl₃ served as solvent for ¹H and ¹⁹F NMR. Low- and high-resolution mass spectral analyses were performed at 70 eV electron-impact (EI) using a Kratos CONCEPT-1H double-focusing magnetic sector spectrometer. Elemental and X-ray structure analyses were carried out at the Toray Research Center, Inc., Tokyo.

Preparation of bromofluoroketene ethyl trimethylsilyl acetal (1). To a suspension of activated zinc powder (4.5 g, 61.95 mmol) in anhydrous THF (120 mL) were added 1,2-dibromoethane (375 μ L, 4.35 mmol) and chlorotrimethylsilane (450 μ L, 3.55 mmol) at 40°C. This mixture was stirred at the same temperature for 20 min and then cooled to -20°C. Chlorotrimethylsilane (7.57 mL, 59.68 mmol) was added. Ethyl

dibromofluoroacetate (7.92 mL, 56.84 mmol) was then added over 10 min at -20°C, and the reaction mixture was stirred at the same temperature for an additional hour. After warming to room temperature, the mixture was diluted with *n*-pentane (200 mL), stirred vigorously for 5 min and then filtered through a pad of Celite to remove some salts. The filtrate was concentrated *in vacuo* (<25°C/20-30 mmHg). The dilution-filtration-concentration sequence was repeated once more, and the residue was distilled under reduced pressure to give 1 (9.37 g, 64%) as a colorless oil: bp 37.0-38.5°C/1.2 mmHg; ¹H NMR 0.25 (s, 5.54H), 0.25 (s, 3.46H), 1.26 (t, *J* = 7.1 Hz, 1.85H), 1.28 (t, *J* = 7.1 Hz, 1.15H), 3.88 (q, *J* = 7.1 Hz, 1.23H), 3.95 (q, *J* = 7.1 Hz, 0.77H); ¹⁹F NMR -133.14 (s, 0.62F), -134.52 (s, 0.38F); IR (neat): 2964, 1703, 1255, 1149, 1060, 851 cm⁻¹; MS: *m/z* 258 [M+], 256 [M+], 230, 228, 143, 141; HRMS calcd for C₇H₁₄BrFO₂Si [M+]: 255.9931. Found: 255.9921.

Bromofluoroketene isopropyl trimethylsilyl acetal (13). Compound 13 was obtained in 48% yield from isopropyl dibromofluoroacetate using the same procedure as 1: a colorless oil; bp 55-62°C/7 mmHg; ¹H NMR 0.21-0.23 (m, 5.58H), 0.24-0.26 (s, 3.42H), 1.20-1.27 (m, 6H), 4.20-4.36 (m, 1H); ¹⁹F NMR -131.82 (s, 0.62F), -138.08 (s, 0.38F); IR (neat): 2981, 1702, 1255, 1146, 1052, 851 cm⁻¹; MS: m/z 272 [M⁺], 270 [M⁺], 230, 228, 143, 141; HRMS calcd for C₈H₁₆BrFO₂Si [M⁺]: 270.0087. Found: 270.0075.

Bromofluoroketene methyl trimethylsilyl acetal (16). Compound 16 was obtained in 37% yield from methyl dibromofluoroacetate using the same procedure as 1: a colorless oil; bp 42-49°C/5 mmHg; ¹H NMR 0.26 (s, 5.47H), 0.28 (s, 3.53H), 3.58 (s, 1.83H), 3.69 (s, 1.17H); ¹⁹F NMR -135.00 (s, 0.61F), -135.58 (s, 0.39F); IR (neat): 2960, 1706, 1256, 1149, 1066, 851 cm⁻¹; MS: m/z 244 [M⁺], 242 [M⁺], 229, 227, 201, 199; HRMS calcd for C₆H₁₂BrFO₂Si [M⁺]: 241.9774. Found: 241.9777.

Typical procedure for the aldol reaction with bromofluoroketene ethyl trimethylsilyl acetal (1) mediated by catalyst 5. Ethyl 2-bromo-2-fluoro-3-hydroxy-3-phenylpropanoate (2). To (15,25,5R)-2-isopropyl-5-methyl-1-(N-4'-toluenesulfonamido)cyclohexanecarboxylic acid (71 mg, 0.20 mmol) in nitroethane (3 mL) was added dropwise a 1 M THF solution of BH₃·THF complex (200 µL, 0.20 mmol) at room temperature. The solution was allowed to warm to 45°C, stirred for 1 h and cooled to -78°C. The bromofluoroketene acetal 1 (309 mg, 1.2 mmol) was added. A solution of benzaldehyde (106 mg, 1.0 mmol) in nitroethane (2 mL) was then added using a syringe pump over 3 h at -78°C, and the reaction mixture was stirred at the same temperature for an additional hour, quenched with saturated NaHCO3 and extracted with ether. The combined extracts were washed with brine, dried and filtered. Concentration in vacuo gave an oily residue which was redissolved in 2 N HCl (2 mL) and THF (10 mL). After stirring at room temperature for 1 h, the reaction mixture was extracted with ether. The combined extracts were washed with saturated NaHCO3 and brine, dried and filtered. After evaporation of the solvent, the oily residue was purified by flash chromatography (n-hexane-EtOAc) to afford syn-2 (180 mg, 62%) and anti-2 (82 mg, 28%): syn-2: a colorless oil; $[\alpha]_D^{21} + 1.6^{\circ}$ (c 1.23, CHCl₃) (98% ee); ¹H NMR 1.24 (t, J = 7.1 Hz, 3H), 3.03-3.28 (brs, 1H), 4.25 (q, J = 7.1 Hz, 2H), 5.24 (d, J 17.8 Hz, 1H), 7.30-7.52 (m, 5H); ¹⁹F NMR -131.65 (d, J = 17.8 Hz); IR (neat): 3496, 1748, 1301, 1274, 701 cm⁻¹; MS: m/z 292 [M+], 290 [M+], 186, 184, 107, 79; HRMS calcd for C₁₁H₁₂BrFO₃ [M+]: 289.9954. Found: 289.9940. HPLC analysis: t_R (minor), 12.6 min (1.1%); t_R (major), 14.3 min (98.7%) (Chiralcel OB-H, n-hexane/EtOH 20/1, 1.0 mL/min); anti-2: a colorless oil; [α]_D²³ -57.8° (c 0.93, CHCl₃) (90% ee); ¹H NMR 1.37 (t, J = 7.1 Hz, 3H), 2.80-3.00 (brs, 1H), 4.40 (q, J = 7.1 Hz, 2H), 5.30 (d, J = 20.7 Hz, 1H), 7.33-7.58 (m, 5H); 19 F NMR -137.23 (d, J = 20.7 Hz); IR (neat): 3480, 1749, 1298, 1266, 700 cm⁻¹; MS: m/z 292 [M⁺], 290 [M⁺], 186, 184, 107, 79; HRMS calcd for C₁₁H₁₂BrFO₃ [M⁺]: 289.9954. Found: 289.9950. HPLC analysis: t_R (major), 20.0 min (95.1%); t_R (minor), 21.7 min (4.9%) (Chiralcel OD-H, n-hexane/EtOH 20/1, 0.5 mL/min).

Ethyl 2-bromo-2-fluoro-3-hydroxy-5-phenyl-4-pentenoate (6). Compound 6 (*syn/anti* = 57/43) was obtained in 96% yield from cinnamaldehyde using the same procedure as 2: *syn-*6: a colorless oil; $[\alpha]_D^{28}$ +22.9° (*c* 0.82, CHCl₃) (83% ee); ¹H NMR 1.34 (t, *J* = 7.2 Hz, 3H), 1.58 (brs, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.75-4.89 (m, 1H), 6.24 (ddd, *J* = 15.9, 7.0, 1.0 Hz, 1H), 6.80 (d, *J* = 6.8 Hz, 1H), 7.25-7.43 (m, 5H); ¹⁹F NMR -130.10

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(d, J = 15.9 Hz); IR (neat): 3481, 1760, 1272, 1029, 755 cm⁻¹; MS: m/z 318 [M⁺], 316 [M⁺], 237, 147, 133, 105; HRMS calcd for C₁₃H₁₄BrFO₃ [M⁺]: 316.0110. Found: 316.0089. HPLC analysis: t_R (minor), 27.7 min (8.5%); t_R (major), 30.7 min (91.5%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 1.0 mL/min); *anti-6*: a colorless oil; $[\alpha]_D^{28} + 27.4^\circ$ (c 0.85, CHCl₃) (83% ee); ¹H NMR 1.39 (t, J = 7.1 Hz, 3H), 2.60 (m, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.80-5.00 (m, 1H), 6.39 (dd, J = 15.6, 6.7 Hz, 1H), 6.87 (d, J = 15.6 Hz, 1H), 7.27-7.50 (m, 5H); ¹⁹F NMR -137.02 (d, J = 19.4 Hz); IR (neat): 3446, 1749, 1278, 1040, 758 cm⁻¹; MS: m/z 318 [M⁺], 316 [M⁺], 237, 147, 133, 105; HRMS calcd for C₁₃H₁₄BrFO₃ [M⁺]: 316.0110. Found: 316.0089. HPLC analysis: t_R (minor), 10.9 min (8.7%); t_R (major), 12.4 min (91.3%) (Chiralcel OD-H, *n*-hexane/EtOH 20/1, 1.0 mL/min).

Ethyl 2-bromo-2-fluoro-3-hydroxy-5-phenylpentanoate (7). Compound 7 (*syn/anti* = 46/54) was obtained in 89% yield from hydrocinnamaldehyde using the same procedure as **2**: *syn-7*: a colorless oil; $[\alpha]_D^{25}$ +32.7° (*c* 0.82, CHCl₃) (98% ee); ¹H NMR 1.32 (t, *J* = 7.1 Hz, 3H), 1.80-2.12 (m, 2H), 2.63-3.06 (m, 3H), 3.91-4.09 (m, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 7.13-7.40 (m, 5H); ¹⁹F NMR -129.13 (d, *J* = 12.3 Hz); IR (neat): 3501, 1748, 1271, 1033, 701 cm⁻¹; MS: *m/z* 320 [M⁺], 318 [M⁺], 239, 221, 129, 91; HRMS calcd for C₁₃H₁₆BrFO₃ [M⁺]: 318.0267. Found: 318.0260. HPLC analysis: *t*_R (minor), 9.9 min (0.8%); *t*_R (major), 12.5 min (99.2%) (Chiralcel OD-H, *n*-hexane/EtOH 20/1, 1.0 mL/min); *anti-7*: a colorless oil; $[\alpha]_D^{26}$ +33.2° (*c* 1.01, CHCl₃) (98% ee); ¹H NMR 1.36 (t, *J* = 7.1 Hz, 3H), 1.80-2.03 (m, 1H), 2.30-2.50 (m, 2H), 2.67-3.08 (m, 2H), 4.06-4.29 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 7.12-7.38 (m, 5H); ¹⁹F NMR -136.85 (d, *J* = 19.9 Hz); IR (neat): 3468, 1749, 1298, 1053, 700 cm⁻¹; MS: *m/z* 320 [M⁺], 318 [M⁺], 318 [M⁺], 239, 221, 129, 91; HRMS calcd for C₁₃H₁₆BrFO₃ [M⁺]: 318.0267. Found: 318.0262. HPLC analysis: *t*_R (minor), 8.1 min (1.2%); *t*_R (major), 10.9 min (98.8%) (Chiralcel OD-H, *n*-hexane/EtOH 20/1, 1.0 mL/min).

Ethyl 4-benzyloxy-2-bromo-2-fluoro-3-hydroxybutanoate (8). Compound 8 (syn/anti = 57/43) was obtained in 81% yield from benzyloxyacetaldehyde using the same procedure as 2. A mixture of syn- and anti-8, which could not separated, was acetylated with acetic anhydride (2 equiv) in the presence of 4-(dimethylamino)pyridine in pyridine at room temperature for 14 h and pyrified by flash chromatography: the acetate of syn-8: a colorless oil; $[\alpha]_D^{27}$ -0.2° (c 0.89, CHCl₃) (97% ee); ¹H NMR 1.24 (t, J = 7.1 Hz, 3H), 2.20 (s, 3H), 3.67 (dd, J = 7.0, 1.0 Hz, 2H), 4.05-4.28 (m, 2H), 4.41-4.55 (m, 2H), 5.80 (dt, J = 22.4, 7.0 Hz, 1H), 7.21-7.45 (m, 5H); ¹⁹F NMR -131.41 (d, J = 22.4 Hz); IR (neat): 1765, 1371, 1219, 1041, 913 cm⁻¹; MS: m/z 378 [M+], 376 [M+], 229, 227, 131, 103, 91; HRMS calcd for C15H18BrFO5 [M+]: 376.0322. Found: 376.0312. HPLC analysis: t_R (major), 6.8 min (98.5%); t_R (minor), 7.6 min (1.5%) (Chiralcel OD-H, nhexane/EtOH 50/1, 1.0 mL/min); the acetate of anti-8: a colorless oil; $[\alpha]_D^{26}$ +15.3° (c 0.83, CHCl₃) (97% ee); ¹H NMR 1.32 (t, J = 7.1 Hz, 3H), 2.10 (s, 3H), 3.84 (ddd, J = 11.4, 7.8, 1.0 Hz, 1H), 4.16 (dd, J = 11.4, 7.8, 1H), 7.8 (dd, J = 11.4, 7.8 3.1 Hz, 1H), 4.26-4.38 (m, 2H), 4.49-4.69 (m, 2H), 5.86 (ddd, J = 22.1, 7.8, 3.1 Hz, 1H), 7.25-7.40 (m, 5H); ¹⁹F NMR -131.40 (d, J = 22.2 Hz); IR (neat): 1768, 1371, 1215, 1037, 944 cm⁻¹; MS: m/z 378 [M⁺], 376 [M⁺], 229, 227, 131, 103, 91; HRMS calcd for C₁₅H₁₈BrFO₅ [M⁺]: 376.0322. Found: 376.0314. HPLC analysis: t_R (minor), 7.3 min (1.7%); t_R (major), 8.3 min (98.3%) (Chiralcel OD-H, n-hexane/EtOH 9/1, 1.0 mL/min).

Ethyl 2-bromo-3-cyclohexyl-2-fluoro-3-hydroxypropanoate (9). Compound 9 (*syn/anti* = 52/48) was obtained in 74% yield from cyclohexanecarboxaldehyde using the same procedure as 2: *syn-*9: a colorless oil; $[\alpha]_D^{25}$ +5.5° (*c* 0.76, CHCl₃) (94% ee); ¹H NMR 1.12-2.03 (m, 11H), 1.37 (t, *J* = 7.1 Hz, 3H), 2.45 (brs, 1H), 3.84-4.03 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H); ¹⁹F NMR -128.70 (d, *J* = 21.8 Hz); IR (neat): 3502, 1761, 1269, 1043, 896 cm⁻¹; MS (FAB): *m/z* 299 [MH⁺], 297 [MH⁺]; HRMS (FAB) calcd for C₁₁H₁₉BrFO₃ [MH⁺]: 297.0502. Found: 297.0499. HPLC analysis: *t*_R (minor), 6.7 min (3.0%); *t*_R (major), 7.1 min (97.0%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 1.0 mL/min); *anti-*9: a colorless oil; $[\alpha]_D^{27}$ +11.4° (*c* 0.88, CHCl₃) (89% ee); ¹H NMR 1.07-2.41 (m, 12H), 1.37 (t, *J* = 7.2 Hz, 3H), 3.91-4.13 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H); ¹⁹F NMR -133.98 (dd, *J* = 23.1, 2.4 Hz); IR (neat): 3501, 1750, 1271, 1035, 890 cm⁻¹; MS (FAB): *m/z* 299 [MH⁺], 297 [MH⁺]; HRMS (FAB) calcd for C₁₁H₁₉BrFO₃ [MH⁺]: 297.0516. Found: 297.0495. HPLC analysis: t_R (minor), 6.4 min (5.6%); t_R (major), 7.0 min (94.4%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 1.0 mL/min).

Ethyl 2-bromo-2-fluoro-3-hydroxyhexanoate (10). Compound **10** (*syn/anti* = 46/54) was obtained in 90% yield from butanal using the same procedure as **2**: *syn-***10**: a colorless oil; $[\alpha]_D^{25}$ +16.4° (*c* 1.02, CHCl₃) (97% ee); ¹H NMR 0.96 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.32-1.78 (m, 4H), 2.64 (brs, 1H), 3.98-4.13 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H); ¹⁹F NMR -129.63 (d, *J* = 13.0 Hz); IR (neat): 3469, 1749, 1281, 1044, 670 cm⁻¹; MS (FAB): *m/z* 259 [MH⁺], 257 [MH⁺]; HRMS (FAB) calcd for C₈H₁₅BrFO₃ [MH⁺]: 257.0189. Found: 257.0194. The corresponding 3,5-dinitrobenzoate was prepared according to the literature.¹⁸ HPLC analysis of the 3,5-dinitrobenzoate: *t*_R (minor), 13.3 min (1.7%); *t*_R (major), 15.2 min (98.3%) (Chiralcel AD, *n*-hexane/EtOH 20/1, 1.0 mL/min); *anti*-10: a colorless oil; $[\alpha]_D^{25}$ +20.6° (*c* 1.01, CHCl₃) (98% ee); ¹H NMR 0.99 (t, *J* = 7.4 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.42-2.23 (m, 5H), 4.06-4.29 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H); ¹⁹F NMR -137.39 (d, *J* = 20.5 Hz); IR (neat): 3466, 1750, 1299, 1167, 672 cm⁻¹; MS (FAB): *m/z* 259 [MH⁺], 257 [MH⁺]; HRMS (FAB) calcd for C₈H₁₅BrFO₃ [MH⁺]: 257.0192. HPLC analysis: *t*_R (minor), 5.0 min (1.1%); *t*_R (major), 5.9 min (98.9%) (Chiralcel OD-H, *n*-hexane/EtOH 20/1, 1.0 mL/min); *t*_R (major), 5.9 min (98.9%) (Chiralcel OD-H, *n*-hexane/EtOH 20/1, 1.0 mI/min); *t*_R (major), 5.9 min (98.9%) (Chiralcel OD-H, *n*-hexane/EtOH 20/1, 1.0 mI/min); *t*_R (major), 5.9 min (98.9%) (Chiralcel OD-H, *n*-hexane/EtOH 20/1, 1.0 mI/min); *t*_R (major), 5.9 min (98.9%) (Chiralcel OD-H, *n*-hexane/EtOH 20/1, 1.0 mI/min).

Ethyl 2-bromo-2-fluoro-3-hydroxy-5-methylhexanoate (11). Compound 11 (*syn/anti* = 48/52) was obtained in 96% yield from 3-methylbutanal using the same procedure as 2: *syn-*11: a colorless oil; $[\alpha]_D^{26} + 24.4^{\circ}$ (*c* 0.66, CHCl₃) (98% ee); ¹H NMR 0.92 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.19-1.30 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.58-2.02 (m, 2H), 2.55-2.62 (m, 1H), 4.02-4.20 (m, 1H), 4.29-4.43 (m, 2H); ¹⁹F NMR -129.86 (d, *J* = 15.2 Hz); IR (neat): 3467, 1749, 1265, 1046, 899 cm⁻¹; MS (FAB): *m/z* 273 [MH⁺], 271 [MH⁺]; HRMS (FAB) calcd for C9H₁₇BrFO₃ [MH⁺]: 271.0345. Found: 271.0356. HPLC analysis: *t*_R (minor), 13.1 min (0.8%); *t*_R (major), 13.9 min (99.2%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 0.5 mL/min); *anti-*11: a colorless oil; $[\alpha]_D^{26} + 28.2^{\circ}$ (*c* 0.91, CHCl₃) (98% ee); ¹H NMR 0.99 (d, *J* = 6.2 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.48-2.25 (m, 4H), 4.12-4.32 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H); ¹⁹F NMR -137.67 (d, *J* = 20.5 Hz); IR (neat): 3468, 1751, 1262, 1047, 855 cm⁻¹; MS (FAB): *m/z* 273 [MH⁺], 271 [MH⁺]; HRMS (FAB) calcd for C9H₁₇BrFO₃ [MH⁺]: 271.0345. Found: 271.0336. HPLC analysis: *t*_R (minor), 12.7 min (0.9%); *t*_R (major), 14.7 min (99.1%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 0.5 mL/min);

Ethyl 2-bromo-4-ethyl-2-fluoro-3-hydroxyhexanoate (12). Compound 12 (*syn/anti* = 54/46) was obtained in 70% yield from 2-ethylbutanal using the same procedure as 2: *syn-12*: a colorless oil; $[\alpha]_D^{26}$ +19.2° (*c* 0.67, CHCl₃) (99% ee); ¹H NMR 0.80-0.98 (m, 6H), 1.20-1.73 (m, 5H), 1.36 (t, *J* = 7.2 Hz, 3H), 2.38 (brs, 1H), 4.06-4.25 (m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H); ¹⁹F NMR -128.79 (d, *J* = 23.7 Hz); IR (neat): 3523, 1750, 1271, 1045, 891 cm⁻¹; MS (FAB): *m/z* 287 [MH⁺], 285 [MH⁺]; HRMS (FAB) calcd for C₁₀H₁₉BrFO₃ [MH⁺]: 285.0502. Found: 285.0500. HPLC analysis: t_R (minor), 14.5 min (0.5%); t_R (major), 16.2 min (99.5%) (Chiralcel AD, *n*-hexane/EtOH 50/1, 0.5 mL/min); *anti-12*: a colorless oil; $[\alpha]_D^{26}$ +15.6° (*c* 0.97, CHCl₃) (98% ee); ¹H NMR 0.97 (t, *J* = 7.7 Hz, 6H), 1.02-2.35 (m, 6H), 1.37 (t, *J* = 7.1 Hz, 3H), 4.17-4.30 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H); ¹⁹F NMR -136.05 (d, *J* = 25.0 Hz); IR (neat): 3512, 1751, 1270, 1038, 890 cm⁻¹; MS (FAB): *m/z* 287 [MH⁺], 285 [MH⁺]; HRMS (FAB) calcd for C₁₀H₁₉BrFO₃ [MH⁺]: 285.0502. Found: 285.0502. HPLC analysis: t_R (minor), 17.2 min (0.8%); t_R (major), 21.8 min (99.2%) (Chiralcel AD, *n*-hexane/EtOH 50/1, 0.5 mL/min).

Isopropyl 2-bromo-2-fluoro-3-hydroxy-5-phenyl-4-pentenoate (14). Compound 14 (syn/anti = 39/61) was obtained in 89% yield from cinnamaldehyde using the same procedure as 2. A mixture of syn- and anti-14, which could not separated, was acetylated with acetic anhydride (2 equiv) in the presence of 4- (dimethylamino)pyridine in pyridine at room temperature for 14 h and purified by flash chromatography: the acetate of syn-14: a colorless oil; $[\alpha]_D^{22}$ -15.8° (c 0.61, CHCl₃) (95% ee); ¹H NMR 1.29 (d, J = 6.3 Hz, 3H), 1.30 (d, J = 6.3 Hz, 3H), 2.20 (s, 3H), 5.15 (qq, J = 6.3, 6.3 Hz, 1H), 6.05 (dd, J = 23.1, 8.6 Hz, 1H), 6.12 (dd,

J = 15.5, 8.6 Hz, 1H), 6.80 (d, J = 15.5 Hz, 1H), 7.22-7.42 (m, 5H); ¹⁹F NMR -130.14 (d, J = 23.1 Hz); IR (neat): 2985, 1761, 1221, 1104, 1028 cm⁻¹; MS: m/z 374 [M⁺], 372 [M⁺], 293, 251, 209, 133; HRMS calcd for C₁₆H₁₈BrFO₄ [M⁺]: 372.0373. Found: 372.0360. The acetate of syn-14 (50 mg, 0.13 mmol) was reduced with NaBH₄ (10 mg, 0.26 mmol) in EtOH (2 mL) at room temperature for 1 h. The reaction mixture was quenched with 2 N HCl and extracted with ether. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, the crude diol was treated with 2.2-dimethoxypropane (160 µL, 1.3 mmol) in the presence of p-TsOH·H₂O (5 mg) in benzene at room temperature for 48 h. The mixture was quenched with saturated NaHCO₃ and extracted with ether. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, the residue was passed through a short silica gel column (n-hexane-EtOAc) to give a crude acetonide, 5-bromo-5-fluoro-2,2-dimethyl-4-((E)-2'-phenylethenyl)-1,3dioxane. HPLC analysis of the acetonide: t_R (major), 4.4 min (97.3%); t_R (minor), 8.9 min (2.7%) (Chiralcel AD, n-hexane/EtOH 50/1, 1.0 mL/min); the acetate of anti-14: a colorless oil; $[\alpha]_D^{22}$ -28.8° (c 0.47, CHCl₃) (95% ee); ¹H NMR 1.29 (d, J = 6.3 Hz, 3H), 1.34 (d, J = 6.3 Hz, 3H), 2.06 (s, 3H), 5.18 (ag, J = 6.3, 6.3 Hz, 3H), 5.18 (ag, J = 6.3, 6.3 Hz, 3H), 3.18 (ag, J = 6.3, 6.3 Hz, 3H), 3H, 3 1H), 6.03 (dd, J = 22.8, 8.4 Hz, 2H), 6.25 (dd, J = 15.9, 8.4 Hz, 1H), 6.92 (d, J = 15.9 Hz, 1H), 7.28-7.51 (m, 5H); ¹⁹F NMR -134.63 (d, J = 22.8 Hz); IR (neat): 2984, 1763, 1216, 1104, 1037 cm⁻¹; MS: m/z 374 [M⁺], 372 [M+], 293, 251, 209, 133; HRMS calcd for C16H18BrFO4 [M+]: 372.0373. Found: 372.0363. HPLC analysis: t_R (minor), 11.0 min (2.6%); t_R (major), 12.0 min (97.4%) (Chiralcel AD, n-hexane/EtOH 50/1, 0.5 mL/min)

Isopropyl 2-bromo-2-fluoro-3-hydroxy-5-methylhexanoate (15). Compound 15 (syn/anti = 13/87) was obtained in 84% yield from 3-methylbutanal at -20°C using the same procedure as 2: syn-15: a colorless oil; $[\alpha]_D^{24}$ +12.2° (c 0.29, CHCl₃) (55% ee); ¹H NMR 0.92 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.18-1.40 (m, 1H), 1.34 (d, J = 6.2 Hz, 6H), 1.55-2.05 (m, 2H), 2.59 (d, J = 5.1 Hz, 1H), 4.12 (dddd, J = 15.9, 10.4, 5.3, 2.1 Hz, 1H), 5.18 (dt, J = 6.4, 6.2 Hz, 2H); ¹⁹F NMR -130.72 (d, J = 15.9 Hz); IR (neat): 3468, 2983, 1745, 1287, 1044 cm⁻¹; MS (FAB): m/z 287 [MH⁺], 285 [MH⁺]; HRMS (FAB) calcd for C₁₀H₁₉BrFO₃ [MH⁺]: 285.0502. Found: 285.0509. HPLC analysis: t_R (minor), 11.1 min (22.4%); t_R (major), 11.6 min (77.6%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 0.5 mL/min); anti-15: a colorless oil; $[\alpha]_D^{25}$ -16.5° (c 0.91, CHCl₃) (67% ee); ¹H NMR 0.97 (d, J = 6.2 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 1.35 (d, J = 6.3 Hz, 6H), 1.45-2.02 (m, 3H), 2.20 (d, J = 8.6 Hz, 1H), 4.10-4.32 (m, 1H), 5.19 (dt, J = 6.3, 6.3 Hz, 1H); ¹⁹F NMR -137.24 (d, J = 18.4 Hz); IR (neat): 3469, 2960, 1746, 1294, 892 cm⁻¹; MS (FAB): m/z 287 [MH⁺], 285 [MH⁺]; HRMS (FAB) calcd for C₁₀H₁₉BrFO₃ [MH⁺]: 285.0502. Found: 285.0494. HPLC analysis: t_R (major), 10.3 min (83.7%); t_R (minor), 11.1 min (16.3%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 0.5 mL/min).

Methyl 2-bromo-2-fluoro-3-hydroxy-5-methylhexanoate (17). Compound 17 (syn/anti = 14/86) was obtained in 83% yield from 3-methylbutanal at -20°C using the same procedure as 2: syn-17: a colorless oil; $[\alpha]_D^{24}$ -3.2° (c 0.37, CHCl₃) (21% ee); ¹H NMR 0.92 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.19-1.35 (m, 1H), 1.58-2.02 (m, 2H), 2.63 (d, J = 5.2 Hz, 1H), 3.91 (s, 3H), 4.11 (dddd, J = 15.4, 10.4, 5.3, 2.2 Hz, 1H); ¹⁹F NMR -129.42 (d, J = 15.4 Hz); IR (neat): 3467, 2959, 1766, 1290, 888 cm⁻¹; MS (FAB): m/z 259 [MH⁺], 257 [MH⁺]; HRMS (FAB) calcd for C₈H₁₅BrFO₃ [MH⁺]: 257.0189. Found: 257.0194. HPLC analysis: $t_{\rm R}$ (major), 16.3 min (60.5%); $t_{\rm R}$ (minor), 17.3 min (39.5%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 0.5 mL/min); anti-17: a colorless oil; $[\alpha]_D^{24}$ -27.5° (c 1.11, CHCl₃) (88% ee); ¹H NMR 0.98 (d, J = 6.1 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H), 1.45-2.01 (m, 3H), 2.20 (d, J = 8.8 Hz, 1H), 3.93 (s, 3H), 4.12-4.38 (m, 1H); ¹⁹F NMR -137.82 (d, J = 20.7 Hz); IR (neat): 3460, 2960, 1755, 1296, 886 cm⁻¹; MS (FAB): m/z 259 [MH⁺], 257 [MH⁺]; HRMS (FAB) calcd for C₈H₁₅BrFO₃ [MH⁺]: 257.0189. Found: 257.0194. HPLC analysis: $t_{\rm R}$ (major), 16.2 min (94.1%); $t_{\rm R}$ (minor), 20.5 min (5.9%) (Chiralcel OD-H, *n*-hexane/EtOH 50/1, 0.5 mL/min).

The camphanate of syn-2. A mixture of syn-2 (34 mg, 0.12 mmol), (1S)-(-)-camphanic chloride (126 mg, 0.58 mmol), pyridine (95 μ L, 1.16 mmol), and 4-(dimethylamino)pyridine (3 mg) in CH₂Cl₂ (2 mL) was stirred at room temperature for 19 h, poured into water and extracted with ether. The combined extracts were washed

with 2 N HCl and saturated NaHCO₃, dried and filtered. After evaporation of the solvent, the residue was purified by flash chromatography (*n*-hexane-EtOAc) to afford the camphanate of *syn*-2 (54 mg, 98%) as colorless needles: mp 117.6-118.4°C (*n*-hexane-ether); ¹H NMR 0.97 (s, 3H), 1.13 (s, 3H), 1.14 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.65-1.81 (m, 1H), 1.90-2.20 (m, 1H), 2.49-2.66 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 6.52 (d, J = 22.5 Hz, 1H), 7.30-7.52 (m, 5H); ¹⁹F NMR -131.37 (d, J = 22.5 Hz); IR (KBr): 2990, 1788, 1762, 1259, 1057 cm⁻¹; MS: *m/z* 391, 287, 194, 181, 125, 83; HRMS calcd for C₂₁H₂₄FO₆ [M⁺-Br]: 391.1557. Found: 391.1549; anal. calcd for C₂₁H₂₄BrFO₆: C, 53.5; H, 5.1; F, 4.0. Found: C, 53.3; H, 5.1; F, 4.0.

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