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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.

Keywords: Aldehydes; Aldol reactions; Asymmetric synthesis; Fluorine and compounds.

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

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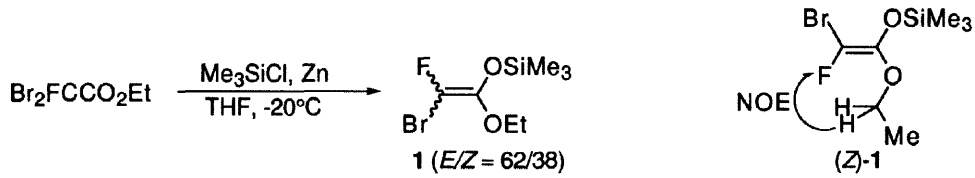
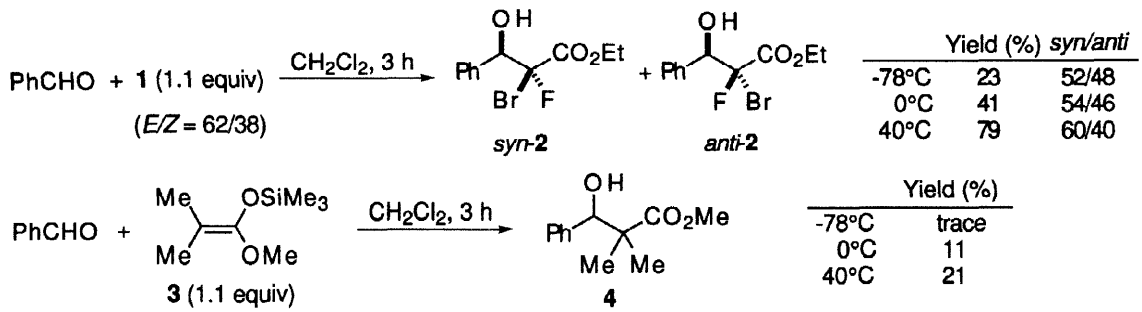
be 62/38 by ^{19}F NMR, and the minor isomer was confirmed to be the (Z)-acetal by the NOE between the fluorine atom and the methylene proton of the ethoxy group (Scheme 1).



Scheme 1

Interestingly, the bromofluoroketene acetal **1** as well as the reported difluoroketene silyl acetal[7] 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]



Scheme 2

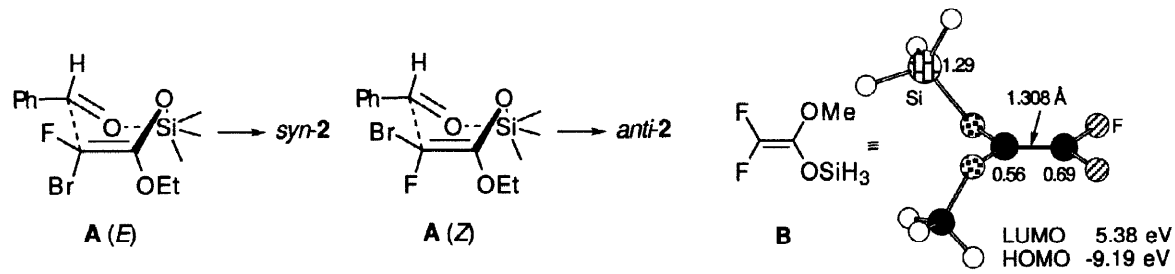
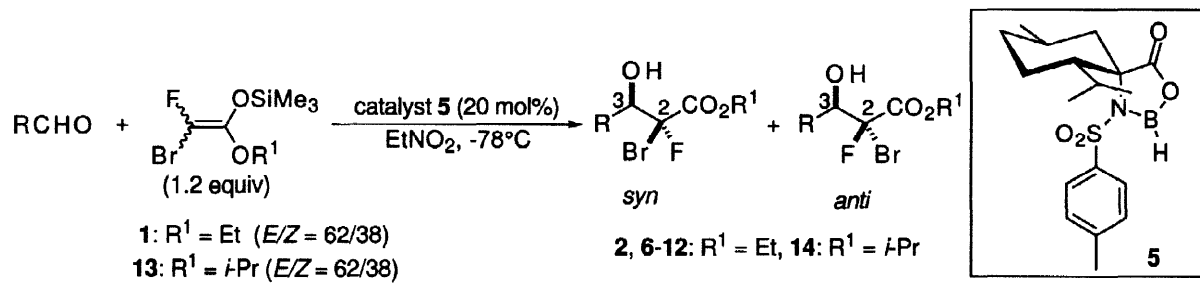


Fig. 1. Possible transition states for the uncatalyzed aldol reaction of bromofluoroketene acetal **1**

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**



1: R^1 = Et (*E*/*Z* = 62/38)
13: R^1 = *i*-Pr (*E*/*Z* = 62/38)

2, 6-12: R^1 = Et, **14**: R^1 = *i*-Pr

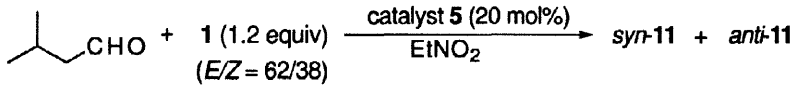
Entry	RCHO	Yield[a] (%)	*syn*/*anti*[b]	Ee (*syn*)[c] (%)	Ee (*anti*)[c] (%)	Product
1	PhCHO	90	69/31	98 (2*S*,3*R*)[d]	90 (2*R*,3*R*)	**2**
2	(*E*)-PhCH=CHCHO	96	57/43	83 (+)	83 (+)	**6**
3	$PhCH_2CH_2CHO$	89	46/54	98 (+)	98 (+)	**7**
4	$PhCH_2OCH_2CHO$	81	57/43[e]	97 (-)[e]	97 (+)[e]	**8**
5	*c*-$C_6H_{11}CHO$	74	52/48	94 (+)	89 (+)	**9**
6	$CH_3CH_2CH_2CHO$	90	46/54	97 (+)[f]	98 (+)	**10**
7	$(CH_3)_2CHCH_2CHO$	96	48/52	98 (+)	98 (+)	**11**
8	$(C_2H_5)_2CHCHO$	70	54/46	99 (+)	98 (+)	**12**
9[g]	(*E*)-PhCH=CHCHO	89	39/61[e]	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 3,5-dinitrobenzoate; 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 (2*S*,3*R*)-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.

Table 2. Effects of reaction temperature on the enantiofacial selection of 3-methylbutanal



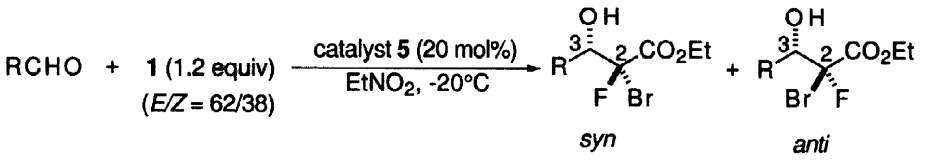
Entry	Temp.	Yield[a] (%)	*syn/anti* [b]	Ee (*syn*)[c] (%)	Ee (*anti*)[c] (%)
1	-78°C	96	48/52	98 (+)	98 (+)
2	-45°C	94	51/49	14 (-)	24 (-)
3	-20°C	87	11/89	31 (-)	91 (-)
4	-10°C	80	16/84	31 (-)	86 (-)
5	-78°C, then -20°C (2 h)	91	47/53	99 (+)	99 (+)
6[d]	-78°C	81	50/50	97 (+)	99 (+)
7[d]	-20°C	14	61/39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

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°C[a]

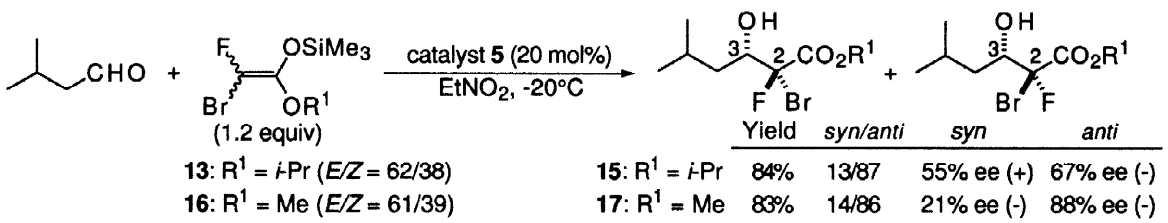


Entry	RCHO	Yield[b] (%)	*syn/anti* [c]	Ee (*syn*)[d] (%)	Ee (*anti*)[d] (%)	Product
1	PhCHO	89	49/51	13 (2*S*,3*R*)[e]	13 (2*S*,3*S*)	**2**
2	$PhCH_2CH_2CHO$	85	13/87	48 (-)	92 (-)	**7**
3	$PhCH_2OCH_2CHO$	80	26/74[f]	29 (+)[f]	72 (-)[f]	**8**
4	*c*-$C_6H_{11}CHO$	90	20/80	18 (-)	81 (-)	**9**
5	$CH_3CH_2CH_2CHO$	87	11/89	49 (-)[g]	93 (-)	**10**
6	$(C_2H_5)_2CHCHO$	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.



Scheme 3

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 ^{19}F 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 ^{13}C NMR of a 1:1

mixture of the ^{13}C-labelled fluorine-free acetal **3** [$^{13}Me{\cdot}MeC{=}C(OMe)OSiMe_3$] and the catalyst **5** in $C_2D_5NO_2$ at -20°C showed almost the same spectrum as that at -78°C.

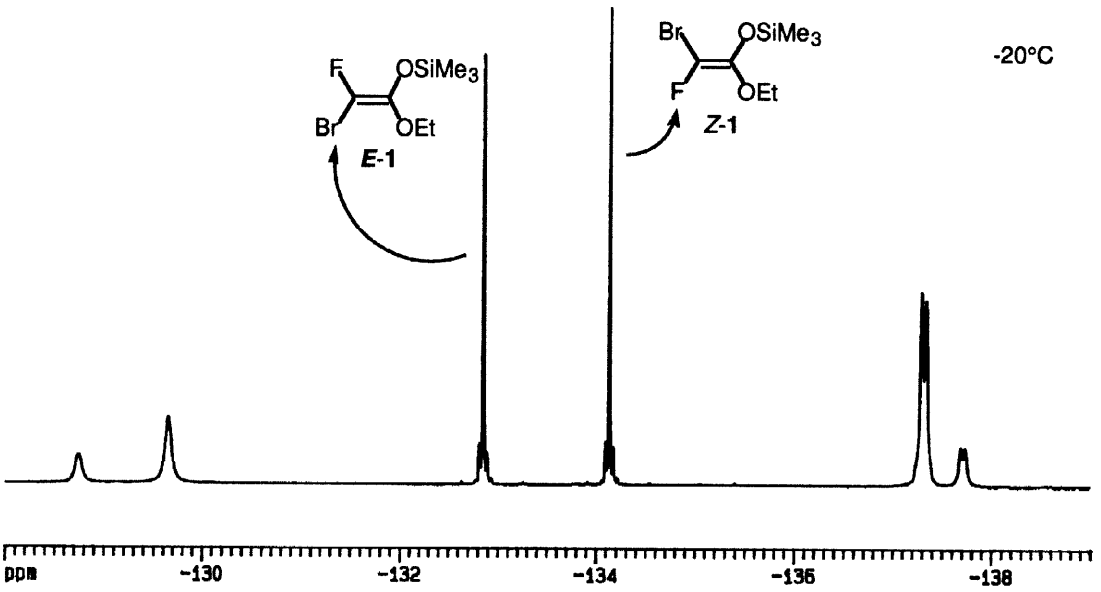
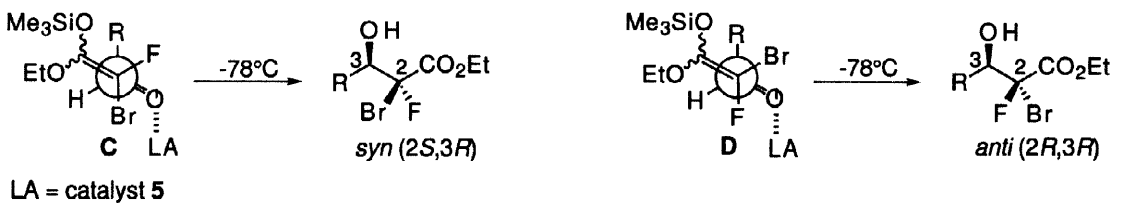


Fig. 2. ^{19}F NMR of a 1:1 mixture of acetal **1** and catalyst **5** in $C_2D_5NO_2$ at -20°C

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.



LA = catalyst **5**

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 (2*S*,3*S*)-*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]

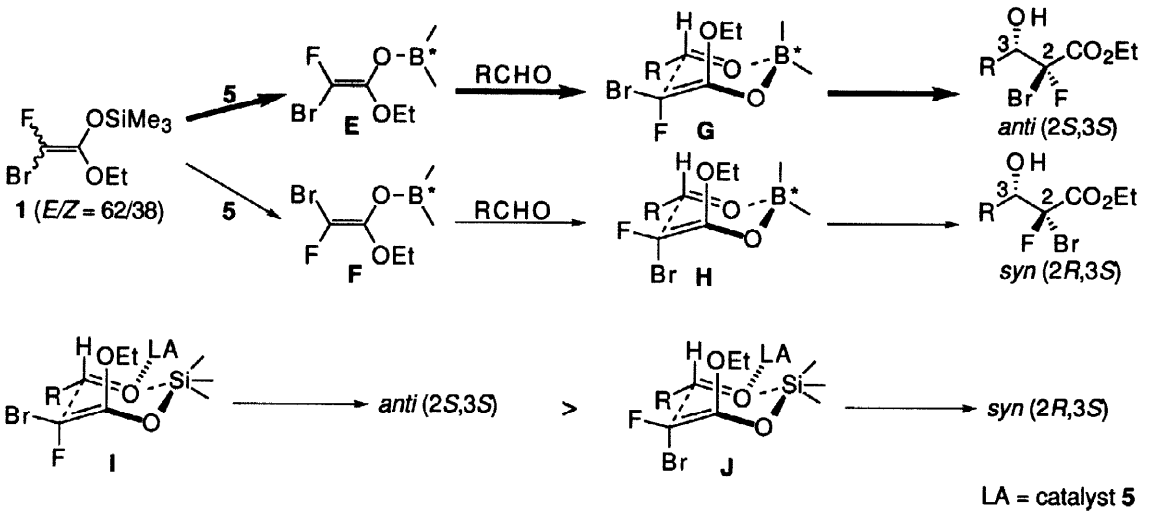


Fig. 4. Possible transition states for the aldol reaction at -20°C

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 $MgSO_4$ and Na_2SO_4 were used as the drying agents. TLC was carried out with pre-coated Kieselgel $60F_{254}$ 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 ^{19}F 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. ^{19}F NMR spectra were given upfield from CCl_3F as the internal standard. Coupling constants are in hertz. $CDCl_3$ served as solvent for ^1H and ^{19}F 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 μL, 4.35 mmol) and chlorotrimethylsilane (450 μL, 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; ^{1}H 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); ^{19}F 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 $C_7H_{14}BrFO_2Si$ [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; ^{1}H 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); ^{19}F 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 $C_8H_{16}BrFO_2Si$ [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; ^{1}H NMR 0.26 (s, 5.47H), 0.28 (s, 3.53H), 3.58 (s, 1.83H), 3.69 (s, 1.17H); ^{19}F 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 $C_6H_{12}BrFO_2Si$ [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 (1*S*,2*S*,5*R*)-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 BH_3·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 $NaHCO_3$ 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 $NaHCO_3$ 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° (*c* 1.23, $CHCl_3$) (98% ee); ^{1}H 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); ^{19}F 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 $C_{11}H_{12}BrFO_3$ [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; $[\alpha]_D^{23}$ -57.8° (*c* 0.93, $CHCl_3$) (90% ee); ^{1}H 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 $C_{11}H_{12}BrFO_3$ [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, $CHCl_3$) (83% ee); ^{1}H 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); ^{19}F NMR -130.10

(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 $C_{13}H_{14}BrFO_3$ [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° (c 0.85, $CHCl_3$) (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); ^{19}F 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 $C_{13}H_{14}BrFO_3$ [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, $CHCl_3$) (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); ^{19}F 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 $C_{13}H_{16}BrFO_3$ [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, $CHCl_3$) (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); ^{19}F NMR -136.85 (d, J = 19.9 Hz); IR (neat): 3468, 1749, 1298, 1053, 700 cm^{-1}; MS: m/z 320 [M^+], 318 [M^+], 239, 221, 129, 91; HRMS calcd for $C_{13}H_{16}BrFO_3$ [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 purified by flash chromatography: the acetate of *syn*-**8**: a colorless oil; $[\alpha]_D^{27}$ -0.2° (c 0.89, $CHCl_3$) (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); ^{19}F 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 $C_{15}H_{18}BrFO_5$ [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, n-hexane/EtOH 50/1, 1.0 mL/min); the acetate of *anti*-**8**: a colorless oil; $[\alpha]_D^{26}$ +15.3° (c 0.83, $CHCl_3$) (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, 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); ^{19}F 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 $C_{15}H_{18}BrFO_5$ [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, $CHCl_3$) (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); ^{19}F 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 $C_{11}H_{19}BrFO_3$ [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, $CHCl_3$) (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); ^{19}F 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 $C_{11}H_{19}BrFO_3$ [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, $CHCl_3$) (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); ^{19}F 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 $C_8H_{15}BrFO_3$ [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, $CHCl_3$) (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); ^{19}F 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 $C_8H_{15}BrFO_3$ [MH+]: 257.0189. Found: 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).

*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° (*c* 0.66, $CHCl_3$) (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); ^{19}F 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 $C_9H_{17}BrFO_3$ [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° (*c* 0.91, $CHCl_3$) (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); ^{19}F 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 $C_9H_{17}BrFO_3$ [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, $CHCl_3$) (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); ^{19}F 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 $C_{10}H_{19}BrFO_3$ [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, $CHCl_3$) (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); ^{19}F 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 $C_{10}H_{19}BrFO_3$ [MH+]: 285.0502. Found: 285.0503. 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, $CHCl_3$) (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); ^{19}F 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 $C_{16}H_{18}BrFO_4$ [M$^+$]: 372.0373. Found: 372.0360. The acetate of *syn*-**14** (50 mg, 0.13 mmol) was reduced with $NaBH_4$ (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·H_2O (5 mg) in benzene at room temperature for 48 h. The mixture was quenched with saturated $NaHCO_3$ 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)-1,3-dioxane. 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, $CHCl_3$) (95% ee); ^{1}H NMR 1.29 (d, J = 6.3 Hz, 3H), 1.34 (d, J = 6.3 Hz, 3H), 2.06 (s, 3H), 5.18 (qq, J = 6.3, 6.3 Hz, 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); ^{19}F 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 $C_{16}H_{18}BrFO_4$ [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, $CHCl_3$) (55% ee); ^{1}H 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); ^{19}F 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 $C_{10}H_{19}BrFO_3$ [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, $CHCl_3$) (67% ee); ^{1}H 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); ^{19}F 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 $C_{10}H_{19}BrFO_3$ [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, $CHCl_3$) (21% ee); ^{1}H 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); ^{19}F 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 $C_8H_{15}BrFO_3$ [MH$^+$]: 257.0189. Found: 257.0194. HPLC analysis: t_R (major), 16.3 min (60.5%); t_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, $CHCl_3$) (88% ee); ^{1}H 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); ^{19}F 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 $C_8H_{15}BrFO_3$ [MH$^+$]: 257.0189. Found: 257.0194. HPLC analysis: t_R (major), 16.2 min (94.1%); t_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), (1*S*)-(-)-camphanic chloride (126 mg, 0.58 mmol), pyridine (95 μL, 1.16 mmol), and 4-(dimethylamino)pyridine (3 mg) in CH_2Cl_2 (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 $NaHCO_3$, 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); ^{19}F 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 $C_{21}H_{24}FO_6$ [M^+-Br]: 391.1557. Found: 391.1549; anal. calcd for $C_{21}H_{24}BrFO_6$: C, 53.5; H, 5.1; F, 4.0. Found: C, 53.3; H, 5.1; F, 4.0.

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