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Reversal of Stereoselectivity in the Evans Aldol Reaction of α,α-Difluoro and α,α,α-Trifluoro Carbonyl Compounds

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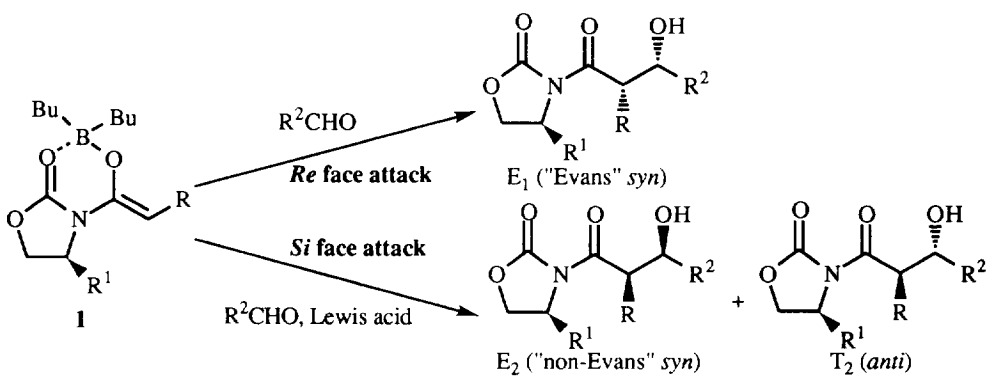
Abstract: The Evans aldol reaction of hexafluoroacetone and trifluoroacetaldehyde causes complete reversal of diastereofacial selectivity. The boron enolate derived from *N*-acyloxazolidinone **2** reacts with trifluoroacetaldehyde to give anti and "non-Evans" syn aldols with stereoselectivity in the range of 7:3-17:3. With α,α-difluoroaldehyde **4b**, a small amount of the normal syn aldol was formed. However, the anti aldol was the major product.

INTRODUCTION

The synthesis of chiral fluoroorganic compounds is an important aspect of organofluorine chemistry in connection with biological and medicinal chemistry in consideration of the influence of fluorine's unique properties on biological activity.[1] Recently, these compounds have become focal points of interest due to potential application to optoelectronic substances such as liquid crystals.[2] Fluorine-containing molecules with unexpected and generally unusual reactivity are often difficult to synthesize, and methodologies for synthesizing nonfluorinated chiral compounds are frequently impractical, giving rise to the term "flustrate" by Seebach.[3]

In the Evans aldol reaction, aldehyde reacts preferentially on the *Re* face of the double bond of boron enolate **1** to provide the normal Evans syn aldol (E_1) selectively.[4] The reversal in diastereofacial selectivity of **1** has been shown possible through addition of dibutylboron triflate (Bu_2BOTf) in excess[5] or Lewis acids[6] to give non-Evans syn (E_2) and anti (T_2) aldols (Scheme 1).



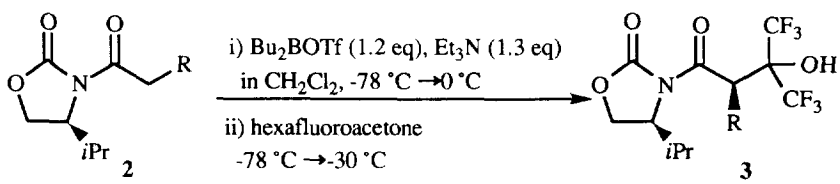
Scheme 1

In this study, the unexpected reversal of stereochemistry in the Evans aldol reaction of *N*-acyloxazolidinone **2** with α,α-difluoro and α,α,α-trifluoro carbonyl compounds and applications of this finding to phenylglyoxal and ethyl glyoxylate are discussed.[7]

RESULTS AND DISCUSSION

Reactions with hexafluoroacetone. Reactions of the boron enolate prepared from chiral *N*-acyloxazolidinone **2a-b** with hexafluoroacetone were examined by the standard procedure reported by Evans *et al.*[8] Imide **2** was first treated with Bu_2BOTf and triethylamine (Et_3N) to obtain boron enolate **1**, and gaseous hexafluoroacetone was added at -78 °C. After warming to -30 °C,[9] the reaction mixture was quenched with phosphate buffer and MeOH followed by oxidative workup. Aldols **3** were isolated by flash chromatography. As shown in Table 1, hexafluoroacetone gave **3** selectively in synthetically significant yields. These results are intriguing, as hexafluoroacetone has been shown to react predominantly on the *Si* face of the enolate double bond to bring about the complete reversal of normal Evans stereoselectivity even *in the absence of excess Bu_2BOTf or Lewis acids.* Relative stereochemical assignments of **3** were made by X-ray crystallography.

Table 1. Aldol Reactions of Imide **2** with hexafluoroacetone

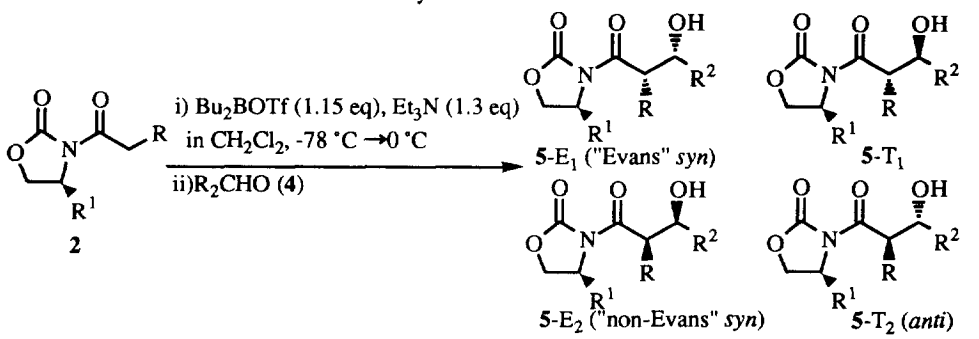


Entry	Imide **2** R		Product **3** % yield[a]	% de[b]	
1	Me	(**2a**)	90	>99 (*R*)[c]	(**3a**)
2	Bn	(**2b**)	86 (94)	>99 (*R*)[c]	(**3b**)

a) All yields are those of isolated compounds. Value in parentheses are conversion yields; b) Des were determined by capillary GC; c) Configuration of a new asymmetric center. Relative stereochemical assignments were definitely established based on X-ray structure analysis.

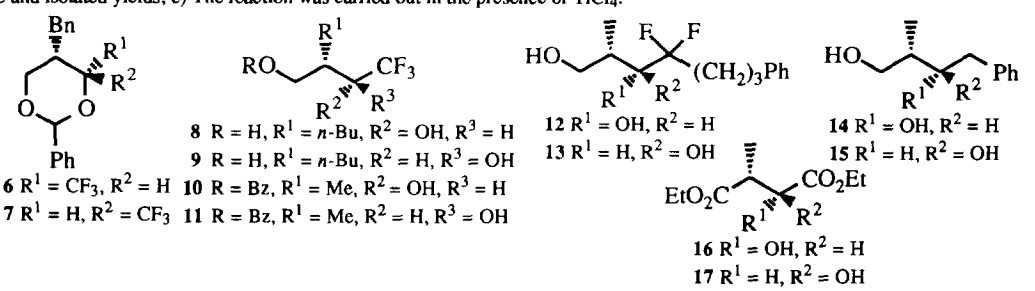
Reactions with aldehydes. Aldehyde **4** was allowed to react with boron enolate **1** according to the standard procedure.[8] Gaseous trifluoroacetaldehyde (**4a**) was added to the boron enolate at -78 °C and the reaction system was warmed to 0 °C over 2h prior to quenching.[10] As shown in Table 2, **4a** reacted preferentially on the *Si* face of the enolate double bond and caused the complete reversal of normal Evans stereoselectivity to provide anti aldols (T_2) selectively along with "non-Evans" syn aldols (E_2) (entries 1-4). Anti-syn ratios ranged from 7:3 to 17:3. The addition of $TiCl_4$[6a] to the boron enolate prior to the aldehyde resulted in loss of anti-syn selectivity (46:54, entry 5). Since α,α-difluoroaldehyde **4b**, phenylglyoxal (**4c**) and ethyl glyoxylate (**4d**) easily undergo self-condensation, these aldehydes were added at -5 °C followed by stirring at the same temperature for 30 min prior to quenching. With α,α-difluoroaldehyde **4b**, a small amount of the normal Evans syn aldol (E_1) was formed. However, anti aldol T_2 was the major product (entry 6). Reaction with phenylglyoxal (**4c**) gave "non-Evans" syn aldol E_2 and anti aldol T_2 in the ratio of 7:9, and the "Evans" syn aldol (E_1) was produced only to a slight degree (entry 7). With ethyl glyoxylate (**4d**), the E_2-T_2-E_1-T_1 ratio was 35:44:20:1 (entry 8). Although these three aldehydes (**4b-d**) reacted partially on the *Re* face of the enolate double bond, the *Si* face attack was a predominant factor in bringing about the reversal of normal Evans diastereofacial selectivity.

Table 2. Aldol Reactions of Imide **2** with Aldehydes



Entry	Imide **2**			Aldehyde **4**	Aldol **5**		
	R	R^1		R^2	% yield[a]	E_2 : T_2 : E_1 : T_1[b]	
1	Me	*i*Pr	(**2a**)	CF_3 (**4a**)	62 (65)	15 : 85 : 0 : 0	(**5a**)
2	Bn	*i*Pr	(**2b**)	CF_3 (**4a**)	64 (75)	30 : 70 : 0 : 0	(**5b**)
3	*n*-Bu	*i*Pr	(**2c**)	CF_3 (**4a**)	60 (64)	19 : 81 : 0 : 0	(**5c**)
4	Me	Bn	(**2d**)	CF_3 (**4a**)	80	22 : 78 : 0 : 0	(**5d**)
5[c]	Me	*i*Pr	(**2a**)	CF_3 (**4a**)	83 (88)	54 : 46 : 0 : 0	(**5a**)
6	Me	*i*Pr	(**2a**)	$Ph(CH_2)_3CF_2$ (**4b**)	33 (56)	12 : 82 : 6 : 0	(**5e**)
7	Me	*i*Pr	(**2a**)	PhCO (**4c**)	55 (65)	42 : 54 : 4 : 0	(**5f**)
8	Me	*i*Pr	(**2a**)	EtOCO (**4d**)	50 (55)	35 : 44 : 20 : 1	(**5g**)

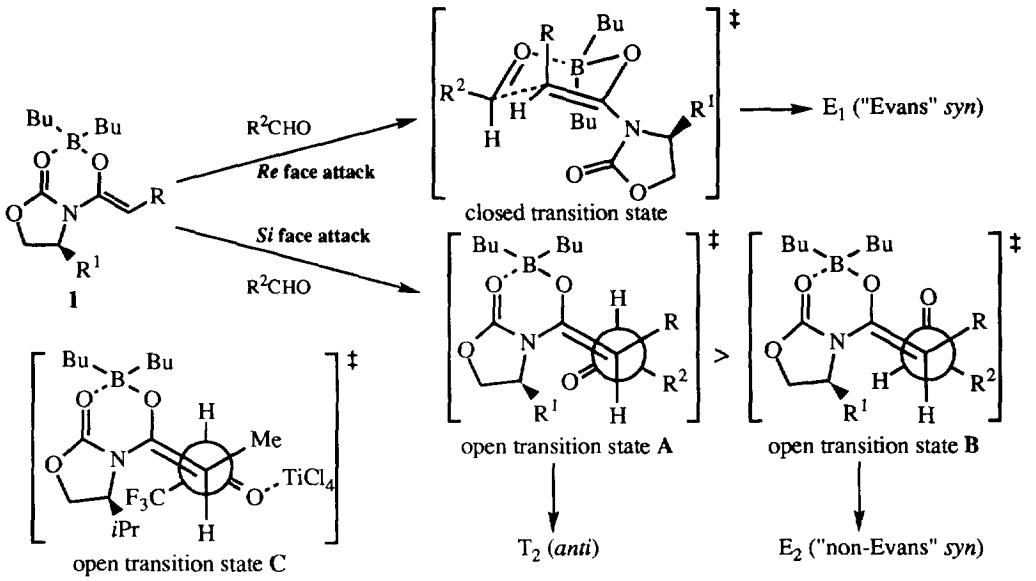
a) All yields are those of isolated compounds. Value in parentheses are conversion yields; b) Ratios were determined by capillary GC and isolated yields; c) The reaction was carried out in the presence of $TiCl_4$.



All the aldol products in Table 2 are new compounds. The relative and absolute stereochemical assignments were confirmed based on X-ray structure analysis (**5a**) and conversion to stereochemically confirmed compounds (except for **5a**). Aldol **5b**-E_2 was converted to acetal **6** by reduction ($LiBH_4$) and acetalization ($PhCH(OMe)_2$, TsOH), and **5b**-T_2 was converted to **7** in the same manner.[11] The reduction of **5c**-E_2 and **5c**-T_2 with $LiBH_4$ gave diols **8** and **9**, respectively.[12] That of **5d**-E_2 with $LiBH_4$ and benzoylation gave **10** which was prepared from **5a**-E_2. In the same manner, **5d**-T_2 was converted to **11** which was prepared from **5a**-T_2. The reduction of aldols **5e**-E_2 and **5e**-T_2 gave diols **12** and **13**, respectively.[13] Aldol **5e**-E_1 was converted to the enantiomer of **12** in the same manner. Aldols **5f**-E_2 and **5f**-T_2 were converted to diols **14** and **15**, respectively by reduction ($LiBH_4$), acetylation (Ac_2O, Py), hydrogenolysis (H_2, Pd-C) and deacetylation (K_2CO_3 in MeOH).[14] In the same manner, **5f**-E_1 was converted to the enantiomer of **14**. Ethanolysis (NaH in EtOH, 0 °C) of **5g**-E_2 and **5g**-T_2 gave diesters **16** and **17**, respectively.[15] In the same manner, **5g**-E_1 and **5g**-T_1 were converted to the enantiomers of **16** and **17**, respectively.

Mechanism. The present results call for the mechanism shown in Scheme 2. We think that with aldehydes such as CH_3CHO, PhCHO, etc., aldol reaction occurs *via the closed transition state* to yield the

normal Evans syn aldol (E_1) as proposed by Evans et al.[4] Hexafluoroacetone and aldehydes **4a-d** may react with boron enolate **1** only or preferentially *through open transition states* to cause the reversal of stereoselectivity. The anti (T_2) and non-Evans syn (E_2) aldols result from the open transition states **A** and **B**, respectively, and transition state **A** is preferred because of electrostatic and steric interactions. In the presence of $TiCl_4$, open transition state **C** may compete with **A** (Table 2, entry 5).



Scheme 2

Table 3. Ab Initio Calculations of Carbonyl Compounds with the RHF/3-21G Basis Set[16]

Carbonyl Compounds	MO Energy Levels HOMO	LUMO	Mulliken Atomic Charges (C=O) O	C	Stereoselectivities (boron enolate **1**)
CH_3CHO	-0.4145	**0.1542**	**-0.519**	0.520	*Re* (normal Evans)
PhCHO	-0.3535	**0.0843**	**-0.549**	0.425	*Re* (normal Evans)
CF_3COCF_3	-0.5164	**0.0434**	**-0.415**	0.274	*Si* (non- Evans)
CF_3CHO (**4a**)	-0.4937	**0.0699**	**-0.431**	0.246	*Si* (non- Evans)
$Ph(CH_2)_3CF_2CHO$ (**4b**)	-0.3280	**0.1134**	**-0.487**	0.303	*Re* : *Si* = 6 : 94
PhCOCHO (**4c**)	-0.3549	**0.0446**	**-0.559**	0.469	*Re* : *Si* = 4 : 96
EtOCOCHO (**4d**)	-0.4239	**0.0807**	**-0.476**	0.302	*Re* : *Si* = 21 : 79

This reversal in facial selectivity of the enolate may possibly be related to low Lewis basicity and high electrophilicity of the carbonyl of hexafluoroacetone and aldehydes **4a-d**. As shown in Table 3, hexafluoroacetone and aldehyde **4a** have lower LUMO levels (higher electrophilicity) and lower negative charges of the carbonyl oxygen (lower Lewis basicity) than the aldehydes (CH_3CHO and PhCHO) showing the *Re* face attack. Aldehydes **4b-d** show either lower LUMO or lower negative charges of the carbonyl oxygen than CH_3CHO or PhCHO. With hexafluoroacetone and **4a**, the low Lewis basicity prevents the carbonyl oxygen from coordinating with the boron, and the high electrophilicity promots the reaction via open transition states *even though the carbonyl does not coordinate with the Lewis acid such as* $TiCl_4$.[6]

CONCLUSION

The Evans aldol reaction of hexafluoroacetone, trifluoroacetaldehyde (**4a**) and α,α-difluoroaldehyde **4b** causes the reversal of stereoselectivity and proceeds predominantly through open transition states. This reversal in facial selectivity of enolate **1** may possibly be related to low Lewis basicity and the high electrophilicity of these fluorinated carbonyl compounds. This finding was extended to phenylglyoxal (**4c**) and ethyl glyoxylate (**4d**), which were shown to react preferentially on the *Si* face of the enolate double bond of **1**. Some other carbonyl compounds having an electron-withdrawing group at the α-position may also lead to the reversal of stereoselectivity.

EXPERIMENTAL

General. Reactions were run under an argon atmosphere with magnetic stirring in oven-dried glassware. CH_2Cl_2 was distilled from CaH_2 immediately before use. THF and ether were freshly distilled from sodium benzophenone ketyl. Trifluoroacetaldehyde (**4a**) was generated by the addition of trifluoroacetaldehyde methyl hemiacetal to conc. H_2SO_4 at 120 °C. Phenylglyoxal (**4c**) was obtained from the corresponding hydrate by distillation immediately prior to use, and ethyl glyoxylate (**4d**) was prepared according to T. R. Kelly *et al.*[17] Bu_2BOTf was prepared according to the literature.[18] Other solvents and reagents were used as supplied or purified. Anhydrous magnesium sulfate was used as the drying agent. Silica gel 60 (Merck, 230 -400 mesh) was used for column chromatography. Analytical gas chromatography (GLC) was carried out using a GL Science (30-m x 0.25-mm) NEUTRABOND-1 capillary column with a thickness of 1.5 μm. GLC data were obtained for the mixture of isomers produced by aldol condensation. Melting points were uncorrected. Optical rotations were measured at a wavelength of 589 nm using a 1.0-dm cell with a total volume of 1 ml. Infrared spectra were obtained either neat or in KBr pellets. Absorption was expressed as reciprocal centimeters (cm^{-1}). ^1H NMR were recorded at 200 MHz and expressed in parts per million (ppm) downfield from TMS as the internal standard (δ). ^{19}F NMR spectra were measured at 188 MHz and given in parts per million (ppm) 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 under 70 eV electron-impact (EI) conditions. Elemental analyses were conducted at Toray Research Center Inc., Tokyo. X-ray structure analyses were made at Rigaku Corporation, Tokyo.

Preparation of N-acyloxazolidinone (2). (*S*)-4-Isopropyl-3-propionyl-2-oxazolidinone (**2a**) was purchased from Aldrich. (*S*)-4-Isopropyl-3-(3-phenylpropionyl)-2-oxazolidinone (**2b**), (*S*)-3-hexanoyl-4-isopropyl-2-oxazolidinone (**2c**), (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**2d**) were prepared by literature methods.[8,19]

Preparation of α,α-difluoroaldehyde 4b: **Ethyl 2,2-difluoro-3-(imidazol-1-yl)thiocarbonyloxy-5-phenylpentanoate.** To a solution of ethyl 2,2-difluoro-3-hydroxy-5-pentanoate[20] (26.7 g, 103 mmol) in 1,2-dichloroethane (400 ml) was added dropwise *N,N'*-thiocarbonyldiimidazole (25.0 g, 126 mmol) in 1,2-dichloroethane (100 ml) at 72 °C. After 3 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Chromatography of the residue with *n*-hexane-EtOAc (3:1) as eluent gave the corresponding thiocarbonylimidazolide (16.9 g, 44.5%) as a colorless liquid; IR (neat) 1769, 1604; ^1H NMR 1.26 (t, J = 7.3, 3H), 2.26-2.39 (m, 2H), 2.80 (d, J = 7.7, 2H), 4.29 (q, J = 7.3, 2H), 6.11-6.29 (m, 1H), 7.05 (dd, J = 2.0, 1.0, 1H), 7.17-7.32 (m, 5H), 7.57 (t, J = 1.5, 1H), 8.26 (t, J = 0.9, 1H); ^{19}F NMR 113.21 (dd, J = 266.1, 7.8, 1F), 117.40 (dd, J = 266.1, 13.7, 1F); MS (FAB) *m/z* 369 [M+1]; HRMS (FAB) Calcd for $C_{17}H_{19}N_2O_3SF_2$ [M+H] 369.109, found 369.109.

Ethyl 2,2-difluoro-5-pentanoate. To a solution of *n*-Bu_3SnH (25.0 ml, 92.9 mmol) in refluxing toluene (350 ml) was added dropwise the thiocarbonylimidazolide (16.9 g, 45.8 mmol) in toluene (150 ml). After 3 h at reflux, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Chromatography of the residue with *n*-hexane-EtOAc (3:1) gave ethyl 2,2-difluoro-5-pentanoate (9.1 g, 81.9%) as a colorless oil; IR (neat) 2941, 1768, 1603; ^1H NMR 1.33 (t, J = 7.1, 3H), 1.74-2.21 (m, 4H), 2.68 (t, J = 7.4, 2H), 4.30 (q, J

= 7.1, 2H), 7.14-7.35 (m, 5H); ^{19}F NMR 106.12 (t, J = 17.6); MS *m/z* 242 [M$^+$], 213, 196, 169, 105, 91, 77; HRMS Calcd for $C_{13}H_{16}O_2F_2$ [M$^+$] 242.112, found 242.112.

2,2-Difluoro-5-phenylpentanal (4b). To a solution of ethyl 2,2-difluoro-5-pentanoate (1.25 g, 5.16 mmol) was added dropwise DIBAL-H (1.0 ml, 5.61 mmol) at -78 °C. After 30 min, the reaction mixture was quenched by the addition of MeOH, poured into 0.5 N aqueous HCl and extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (10:1) gave 2,2-difluoro-5-phenylpentanal ethyl hemiacetal (1.05 g, 83.3%); IR (neat) 3375, 1603; ^{1}H NMR 1.23 (t, J = 7.1, 3H), 1.80-2.18 (m, 4H), 2.64-2.72 (m, 2H), 3.51-3.99 (m, 3H), 4.62 (ddd, J = 10.4, 8.3, 4.8, 1H), 7.17-7.35 (m, 5H); ^{19}F NMR 112.86-114.37(m, 1F), 117.71-119.25 (m, 1F); MS *m/z* 242 [M$^+$], 213, 196, 169, 105, 91, 77; HRMS Calcd for $C_{13}H_{16}O_2F_2$ [M$^+$] 242.112, found 242.112. The hemiacetal was converted to **4b** by heating in refluxing toluene and concentrated *in vacuo* immediately before use. Data for **4b**; ^{1}H NMR 1.77-2.12 (m, 4H), 2.68 (t, J = 7.3, 2H), 7.14-7.36 (m, 5H), 9.47 (s, 1H); ^{19}F NMR 110.89 (t, J = 18.0);

General Procedure for Reactions with Hexafluoroacetone: **(2'*R*,4*S*)-4-Isopropyl-3-(4',4',4'-trifluoro-3'-hydroxy-2'-methyl-3'-trifluoromethylbutyryl)-2-oxazolidinone (3a).** To a solution of *N*-acyloxazolidinone **2a** (5.06 g, 27.3 mmol) in CH_2Cl_2 (40 ml) was added *n*-Bu_2BOTf (7.9 ml, 31.4 mmol) at -78 °C over 2 min. After 10 min at the same temperature, Et_3N (5.2 ml, 37.3 mmol) was added over 10 min and the reaction mixture was allowed to warm to 0 °C. After 1 h at 0 °C, the solution was cooled to -78 °C and gaseous hexafluoroacetone (4 ml at -78 °C, 31.8 mmol) was added with a cannula. After 0.5 h at -78 °C, the reaction mixture was brought to and left at -30 °C for 2 h and quenched with pH 7.0 phosphate buffer (0.1 M, 100 ml) and MeOH (100 ml) followed by the addition of 30% H_2O_2-MeOH (50 ml-50 ml). After 1h at 0 °C, the mixture was concentrated *in vacuo*. The residue was diluted with 10% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (3:1) as eluent gave **3a** (8.65 g, 90.1%) as colorless needles; mp 96.0-98.1 °C (*n*-hexane-ether); $[\alpha]_D^{24}$ 48.3°(c 1.00, $CHCl_3$); IR (KBr) 3295, 1769, 1682; ^{1}H NMR 0.88 (d, J = 6.9, 3H), 0.94 (d, J = 7.0, 3H), 1.43 (dq, J = 7.1, 2.7, 3H), 2.37 (dsep, J = 7.1, 2.8, 1H), 4.28-4.49 (m, 3H), 4.75 (q, J = 7.0, 1H), 6.53 (s, 1H); ^{19}F NMR 73.32 (dq, J = 11.5, 1.5, 3F), 76.17 (q, J = 11.5, 3F); MS *m/z* 351 [M$^+$], 282, 223, 175, 86, 69; Anal. Calcd for $C_{12}H_{15}NO_4F_6$: C, 41.0; H, 4.3; N, 4.1. Found: C, 41.1; H, 4.5; N, 4.1.

(2'*R*,4*S*)-3-(2'-Benzyl-4',4',4'-trifluoro-3'-hydroxy-3'-trifluoromethylbutyryl)-4-isopropyl-2-oxazolidinone (3b). The general procedure was followed, using 526 mg (2.0 mmol) of **2b**. Chromatography of the residue with *n*-hexane-CH_2Cl_2 (2:1) gave **3b** (737 mg, 85.7%) and starting material **2b** (45 mg, 8.6%): **3b** colorless needles; mp 114.9-115.3 °C (*n*-hexane-ether); $[\alpha]_D^{26}$ 145.5°(c 0.99, $CHCl_3$); IR (KBr) 3406, 1777, 1686; ^{1}H NMR 0.74 (d, J = 6.8, 3H), 0.82 (d, J = 7.0, 3H), 2.10-2.28 (m, 1H), 2.99-3.26 (m, 2H), 3.20 (dd, J = 8.8, 7.9, 1H), 3.68 (ddd, J = 7.9, 3.5, 1.8, 1H), 3.87 (dd, J = 8.8, 1.8, 1H), 5.18 (dd, J = 11.4, 5.5, 1H), 6.53 (s, 1H), 7.13-7.35 (m, 5H); ^{19}F NMR 72.76 (q, J = 11.2, 3F), 76.03 (q, J = 11.2, 3F); MS *m/z* 427 [M$^+$], 260, 131, 91, 69; Anal. Calcd for $C_{18}H_{19}NO_4F_6$: C, 50.6; H, 4.5; N, 3.3. Found: C, 50.6; H, 4.6; N, 3.3.

General Procedure for Reactions with trifluoroacetaldehyde (4a): **(2'*R*,3'*S*,4*S*)- and (2'*R*,3'*R*,4*S*)-4-Isopropyl-3-(4',4',4'-trifluoro-3'-hydroxy-2'-methylbutyryl)-2-oxazolidinone (5a-T_2 and 5a-E_2).** To a solution of the boron enolate, prepared from **2a** (371 mg, 2.0 mmol) by the procedure given for **3a**, was added gaseous trifluoroacetaldehyde (6 mmol) with a cannula at -78 °C. After 30 min at -78 °C, the reaction mixture was brought to and left at 0 °C for 2 h and quenched with pH 7.0 phosphate buffer (0.1 M, 4 ml) and MeOH (6 ml) followed by the addition of 30% H_2O_2-MeOH (3 ml-9 ml). After 1h at 0 °C, the mixture was concentrated *in vacuo*. The residue was diluted with 10% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (5:1) gave **5a**-T_2 (295 mg, 52.0%), **5a**-E_2 (58 mg, 10.2%) and starting material **2a** (19 mg, 5.0%): **5a**-T_2 colorless needles; mp 99.0-99.5 °C (*n*-hexane-ether); $[\alpha]_D^{24}$ 49.4°(c 0.96, $CHCl_3$); IR (KBr) 3422, 1803, 1680; ^{1}H NMR 0.88 (d, J = 6.9, 3H), 0.93 (d, J = 7.0, 3H), 1.41 (d, J = 7.0, 3H), 2.30-2.46 (m, 1H), 3.92-4.10 (m, 1H), 4.22-4.49 (m, 4H), 4.57 (d, J = 9.9, 1H); ^{19}F

NMR 77.57 (d, J = 7.9); MS m/z 283 [M^+], 265, 240, 214, 196, 155, 127, 86, 69; Anal. Calcd for $C_{11}H_{16}NO_4F_3$: C, 46.7; H, 5.7; N, 5.0. Found: C, 46.7; H, 5.7; N, 5.0; **5a**-E_2 colorless needles; mp 99.2-100.4 °C (n-hexane-ether); $[\alpha]_D^{26}$ 62.6°(c 0.87, $CHCl_3$); IR (KBr) 3430, 1794, 1697; ^1H NMR 0.88 (d, J = 7.0, 3H), 0.93 (d, J = 7.1, 3H), 1.32 (dd, J = 7.0, 0.9, 3H), 2.30-2.46 (m, 1H), 2.95 (d, J = 5.8, 1H), 4.20-4.50 (m, 5H); ^{19}F NMR 76.90 (d, J = 7.3); MS m/z 283 [M^+], 265, 240, 214, 196, 155, 127, 86, 69; Anal. Calcd for $C_{11}H_{16}NO_4F_3$: C, 46.7; H, 5.7; N, 5.0. Found: C, 46.6; H, 5.6; N, 5.0.

(2'*R*,3'*S*,4*S*)- and (2'*R*,3'*R*,4*S*)-3-(2'-Benzyl-4',4',4'-trifluoro-3'-hydroxybutyryl)-4-isopropyl-2-oxazolidinone (5b-T_2 and 5b-E_2). The general procedure was followed, using 526 mg (2.0 mmol) of **2b**. Chromatography with n-hexane-EtOAc (9:1) gave **5b**-T_2 (323 mg, 44.6%), **5b**-E_2 (138 mg, 19.1%) and starting material **2b** (75 mg, 14.3%): **5b**-T_2 colorless needles; mp 65.3-66.5 °C (n-hexane-ether); $[\alpha]_D^{25}$ 110.8°(c 0.98, $CHCl_3$); IR (KBr) 3354, 1767, 1698; ^1H NMR 0.83 (d, J = 6.9, 3H), 0.89 (d, J = 7.1, 3H), 2.12-2.38 (m, 1H), 3.05 (dd, J = 13.1, 8.9, 1H), 3.15 (dd, J = 13.1, 7.9, 1H), 3.83-4.24 (m, 4H), 4.71 (dt, J = 8.4, 2.4, 1H), 4.85 (d, J = 10.6, 1H), 7.24-7.35 (m, 5H); ^{19}F NMR 77.64 (d, J = 6.5); MS m/z 359 [M^+], 341, 260, 231, 131, 91, 69; Anal. Calcd for $C_{17}H_{20}NO_4F_3$: C, 56.9; H, 5.6; N, 3.9. Found: C, 56.7; H, 5.4; N, 4.0; **5b**-E_2 colorless needles; mp 112.4-113.2 °C (n-hexane-ether); $[\alpha]_D^{25}$ 164.2°(c 0.78, $CHCl_3$); IR (KBr) 3378, 1780, 1664; ^1H NMR 0.77 (d, J = 7.0, 3H), 0.83 (d, J = 7.0, 3H), 2.12-2.24 (m, 1H), 2.86-3.00 (m, 2H), 3.29 (dd, J = 13.1, 5.4, 1H), 3.45 (dd, J = 9.1, 8.5, 1H), 3.86-3.95 (m, 2H), 4.41-4.58 (m, 1H), 4.85 (dq, J = 7.2, 5.4, 1H), 7.16-7.32 (m, 5H); ^{19}F NMR 77.37 (d, J = 7.2 Hz); MS m/z 359 [M^+], 341, 260, 231, 131, 91, 69; Anal. Calcd for $C_{17}H_{20}NO_4F_3$: C, 56.9; H, 5.6; N, 3.9. Found: C, 56.7; H, 5.4; N, 4.0.

(2'*R*,3'*S*,4*S*)- and (2'*R*,3'*R*,4*S*)-3-(2'-Butyl-4',4',4'-trifluoro-3'-hydroxybutyryl)-4-isopropyl-2-oxazolidinone (5c-T_2 and 5c-E_2). The general procedure was followed, using 459 mg (2.0 mmol) of **2c**. Chromatography with n-hexane-EtOAc (20:1) gave **5c**-T_2 (312 mg, 47.6%), **5c**-E_2 (75 mg, 11.5%) and starting material **2c** (28 mg, 6.0%): **5c**-T_2 colorless needles; mp 49.8-50.7 °C (n-hexane-ether); $[\alpha]_D^{25}$ 61.9°(c 0.53, $CHCl_3$); IR (KBr) 3437, 1783, 1673; ^1H NMR 0.87 (d, J = 6.9, 3H), 0.91 (t, J = 6.6, 3H), 0.93 (d, J = 7.1, 3H), 1.20-1.50 (m, 4H), 1.76-1.87 (m, 2H), 2.30-2.46 (m, 1H), 3.99-4.50 (m, 5H), 4.75 (d, J = 10.3, 1H); ^{19}F NMR 77.70 (d, J = 8.0); MS m/z 325 [M^+], 307, 197, 130, 86, 69; Anal. Calcd for $C_{14}H_{22}NO_4F_3$: C, 51.7; H, 6.8; N, 4.3. Found: C, 51.6; H, 6.7; N, 4.4; **5c**-E_2 colorless needles; mp 109.6-110.0 °C (n-hexane-ether); $[\alpha]_D^{24}$ 85.4°(c 0.59, $CHCl_3$); IR (KBr) 3403, 1758, 1701; ^1H NMR 0.87 (d, J = 6.8, 3H), 0.90 (t, J = 5.9, 3H), 0.93 (d, J = 7.2, 3H), 1.20-1.40 (m, 4H), 1.76-1.88 (m, 2H), 2.29-2.44 (m, 1H), 2.71 (d, J = 6.0, 1H), 4.21-4.52 (m, 5H); ^{19}F NMR 77.14 (d, J = 6.0); MS m/z 325 [M^+], 307, 197, 130, 86, 69; Anal. Calcd for $C_{14}H_{22}NO_4F_3$: C, 51.7; H, 6.8; N, 4.3. Found: C, 51.6; H, 6.8; N, 4.4.

(2'*R*,3'*S*,4*S*)- and (2'*R* , 3 '*R*,4*S*)-4-Benzyl-3-(4',4',4'-trifluoro-3'-hydroxy-2'-methylburyryl)-2-oxazolidinone (5d-T_2 and 5d-E_2). The general procedure was followed, using 468 mg (2.0 mmol) of **2d**. Chromatography with n-hexane-EtOAc (4:1) gave **5d**-T_2 (367 mg, 55.3%), a mixture of **5d**-T_2 and **5d**-E_2 (53 mg, 8.0%) and **5d**-E_2 (111 mg, 16.7%): **5d**-T_2 colorless needles; mp 74.5-75.3 °C (n-hexane-ether); $[\alpha]_D^{24}$ 25.1°(c 0.99, $CHCl_3$); IR (KBr) 3413, 1788, 1678; ^1H NMR 1.44 (d, J = 7.1, 3H), 2.72 (dd, J = 13.4, 9.8, 1H), 3.34 (dd, J = 13.5, 3.2, 1H), 3.98-4.28 (m, 3H), 4.38 (dq, J = 7.0, 4.0, 1H), 4.49 (d, J = 9.9, 1H), 4.63-4.75 (m, 1H), 7.20-7.40 (m, 5H); ^{19}F NMR 77.34 (d, J = 7.0); MS m/z 331 [M^+], 313, 262, 155, 86, 69; Anal. Calcd for $C_{15}H_{16}NO_4F_3$: C, 54.3; H, 4.9; N, 4.2. Found: C, 54.3; H, 4.8; N, 4.3; **5d**-E_2 colorless needles; mp 78.2-79.4 °C (n-hexane-ether); $[\alpha]_D^{25}$ 35.8°(c 0.19, $CHCl_3$); IR (KBr) 3441, 1766, 1690; ^1H NMR 1.35 (d, J = 7.1, 3H), 2.74 (dd, J = 13.3, 9.9, 1H), 3.02 (d, J = 5.7, 1H), 3.33 (dd, J = 13.3, 3.3, 1H), 4.18-4.30 (m, 3H), 4.41-4.55 (m, 1H), 4.62-4.74 (m, 1H), 7.20-7.40 (m, 5H); ^{19}F NMR 76.78 (d, J = 6.7); MS m/z 331 [M^+], 313, 155, 86, 69; Anal. Calcd for $C_{15}H_{16}NO_4F_3$: C, 54.3; H, 4.9; N, 4.2. Found: C, 54.1; H, 4.9; N, 4.2.

*Reaction of **2a** with **4a** in the presence of $TiCl_4$:* To a solution of the boron enolate, prepared from **2a** (372 mg, 2.0 mmol) by the procedure given for **3a**, was added in one portion $TiCl_4$ (220 µl, 2.0 mmol) in CH_2Cl_2 (2 ml) at -78 °C. After 0.5 h at -78 °C, gaseous trifluoroacetaldehyde (**4a**, 6 mmol) was added. The reaction mixture was brought to and left at 0 °C for 1.5 h and quenched with pH 7.0 phosphate buffer (0.1 M, 4 ml) and MeOH (6 ml) followed by the addition of 30% H_2O_2-MeOH (3 ml-9 ml). After 1h at 0 °C, the mixture was concentrated *in vacuo*. The residue was diluted with 10% aqueous $NaHCO_3$ and extracted with

CH_2Cl_2. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography of the residue gave **5a**-T_2 (199 mg, 35.0%), **5a**-E_2, (273 mg, 48.0%) and starting material **1a** (23 mg, 6.2%).

Reaction with difluoroacetaldehyde 4b: **(2'*R*,3'*S*,4*S*)-, (2'*R*,3'*R*,4*S*)- and (2'*S*,3'*S*,4*S*)-3-(4',4'-Difluoro-3'-hydroxy-2'-methyl-7'-phenylheptanoyl)-4-isopropyl-2-oxazolidinone (5e-T_2, 5e-E_2 and 5e-E_1).** To a solution of the boron enolate, prepared from **2a** (168 mg, 0.9 mmol) by the procedure given for **3a**, was added **4b** (235 mg, 1.19 mmol) in CH_2Cl_2 (2 ml) at -5 °C over 45 min. After 30 min at -5 °C, the reaction mixture was quenched with pH 7.0 phosphate buffer (0.1 M, 4 ml) and MeOH (6 ml) followed by the addition of 30% H_2O_2-MeOH (3 ml-9 ml). After 1h at 0 °C, the mixture was concentrated *in vacuo*. The residue was diluted with 10% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (9:1) gave **5e**-T_2 (93 mg, 26.8%), **5e**-E_2 (13 mg, 3.8%), **5e**-E_1 (6.8 mg, 2.0%) and starting material **2a** (69 mg, 41.3%): **5e**-T_2 a colorless oil; $[\alpha]_D^{25}$ 33.4°(c 0.99, $CHCl_3$); IR (neat) 3444, 1782, 1698, 1603; ^1H NMR 0.86 (d, *J* = 6.8, 3H), 0.90 (d, *J* = 7.1, 3H), 1.38 (d, *J* = 7.1, 3H), 1.76-2.20 (m, 4H), 2.28-2.45 (m, 1H), 2.67 (t, *J* = 7.5, 2H), 3.70 (dddd, *J* = 22.5, 10.3, 4.1, 3.0, 1H), 4.19-4.32 (m, 2H), 4.37-4.49 (m, 2H), 4.60 (d, *J* = 10.3, 1H), 7.13-7.33 (m, 5H); ^{19}F NMR 107.34-108.87 (m, 1F), 110.56-112.15 (m, 1F); MS *m/z* 383 [M^+], 214, 198, 184, 130, 91; HRMS Calcd for $C_{20}H_{27}NO_4F_2$ [M^+] 383.191, found 383.191; **5e**-E_2 a colorless oil; $[\alpha]_D^{25}$ 36.7°(c 1.04, $CHCl_3$); IR (neat) 3468, 1778, 1698, 1603; ^1H NMR 0.86 (d, *J* = 6.9, 3H), 0.90 (d, *J* = 7.0, 3H), 1.38 (d, *J* = 7.0, 3H), 1.78-2.23 (m, 4H), 2.26-2.45 (m, 2H), 2.67 (t, *J* = 7.5, 2H), 4.08-4.32 (m, 4H), 4.42-4.48 (m, 1H), 7.13-7.33 (m, 5H); ^{19}F NMR 107.08-108.63 (m, 1F), 111.61-113.18 (m, 1F); MS *m/z* 383 [M^+], 214, 198, 130, 105, 91; HRMS Calcd for $C_{20}H_{27}NO_4F_2$ [M^+] 383.191 found 383.192; **5e**-E_1 a colorless oil; $[\alpha]_D^{25}$ 25.4°(c 0.68, $CHCl_3$); IR (neat) 3444, 1785, 1696, 1604; ^1H NMR 0.84 (d, *J* = 7.0 , 3H), 0.87 (d, *J* = 6.8, 3H), 1.38 (d, *J* = 7.1, 3H), 1.80-2.20 (m, 4H), 2.37-2.51 (m, 1H), 2.67 (t, *J* = 7.5, 2H), 4.02-4.48 (m, 5H), 5.48-5.62 (m, 1H), 7.16-7.33 (m, 5H); ^{19}F NMR 109.40-111.00 (m, 1F), 112.83-114.40 (m, 1F); MS *m/z* 383 [M^+], 214, 198, 130, 105, 91; HRMS Calcd for $C_{20}H_{27}NO_4F_2$ [M^+] 383.191 found 383.192.

Reaction with phenylglyoxal (4c): **(2'*R*,3'*S*,4*S*)-, (2'*R*,3'*R*,4*S*)- and (2'*S*,3'*S*,4*S*)-3-(3'-Hydroxy-2'-methyl-4'-oxo-4'-phenylbutyryl)-4-isopropyl-2-oxazolidinone (5f-T_2, 5f-E_2 and 5f-E_1).** The procedure given for **5e** was carried out using **2a** (373 mg, 2.0 mmol) and phenylglyoxal **4c** (340 mg, 2.50 mmol). Chromatography with *n*-hexane-EtOAc (9:1) afforded **5f**-T_2 (189 mg, 29.4%), **5f**-E_2 (148 mg, 23.0%), **5f**-E_1 (14 mg, 2.1%) and starting material **2a** (64 mg, 17.1%): **5f**-T_2 a colorless oil; $[\alpha]_D^{25}$ 65.0°(c 1.00, $CHCl_3$); IR (neat) 3467, 1778, 1681, 1597; ^1H NMR 0.92 (d, *J* = 7.1, 3H), 0.94 (d, *J* = 6.9, 3H), 1.34 (d, *J* = 7.1, 3H), 2.30-2.48 (m, 1H), 4.20-4.43 (m, 4H), 4.28 (d, *J* = 4.5, 1H), 5.01 (dd, *J* = 10.4, 4.8, 1H), 7.46-7.64 (m, 3H), 7.98-8.05 (m, 2H); MS *m/z* 319 [M^+], 301, 214, 130, 105, 86, 77; HRMS Calcd for $C_{17}H_{21}NO_5$ [M^+] 319.142, found 319.142; **5f**-E_2 a colorless oil; $[\alpha]_D^{24}$ -29.8°(c 0.81, $CHCl_3$); IR (neat) 3469, 1769, 1712, 1681, 1598; ^1H NMR 0.84 (d, *J* = 6.8 , 3H), 0.95 (d, *J* = 7.1, 3H), 0.98 (d, *J* = 6.9, 3H), 2.34-2.50 (m, 1H), 3.96 (d, *J* = 6.3, 1H), 4.17 (dq, *J* = 6.8, 3.3, 1H), 4.27-4.42 (m, 2H), 4.57-4.65 (m, 1H), 5.68 (dd, *J* = 6.3, 3.3, 1H), 7.50-7.69 (m, 3H), 8.22-8.28 (m, 2H); MS *m/z* 319 [M^+], 301, 214, 130, 105, 86, 77; HRMS Calcd for $C_{17}H_{21}NO_5$ [M^+] 319.142, found 319.142; **5f**-E_1 a colorless oil; $[\alpha]_D^{24}$ -14.5°(c 0.51, $CHCl_3$); IR (neat) 3471, 1786, 1720, 1693, 1600; ^1H NMR 0.88 (d, *J* = 6.9, 3H), 0.91 (d, *J* = 7.1, 3H), 0.95 (d, *J* = 7.0, 3H), 2.39-2.55 (m, 1H), 3.90-4.00 (m, 1H), 4.22 (dq, *J* = 6.9, 3.9, 1H), 4.23-4.38 (m, 2H), 4.44-4.51 (m, 1H), 5.50-5.58 (m, 1H), 7.49-7.69 (m, 3H), 8.14-8.20 (m, 2H); MS *m/z* 319 [M^+], 301, 214, 130, 105, 86, 77; HRMS Calcd for $C_{17}H_{21}NO_5$ [M^+] 319.142, found 319.142.

Reaction with ethyl glyoxylate (4d): **(2'*R*,3'*S*,4*S*)-, (2'*R*,3'*R*,4*S*)-, (2'*S*,3'*S*,4*S*)- and (2'*S*,3'*R*,4*S*)-3-(3'-Ethoxycarbonyl-3'-hydroxy-2'-methylpropionyl)-4-isopropyl-2-oxazolidinone (5g-T_2, 5g-E_2, 5g-E_1 and 5g-T_1).** The procedure given for **5e** was conducted using **2a** (370 mg, 2.0 mmol) and ethyl glyoxylate (**4d**, 250 mg, 2.5 mmol). Chromatography with *n*-hexane-EtOAc (4:1) gave **5g**-T_2 (102 mg, 17.8%), **5g**-E_2 (85 mg, 14.9%), **5g**-E_1 (31 mg, 5.4%), a mixture of **5g**-T_2 and **5g**-E_2 (25 mg, 4.3%), a mixture of **5g**-T_2, **5g**-T_1 and **5g**-E_1 (42 mg, 7.2%) and starting material **2a** (36 mg, 9.8%). Aldol **5g**-T_1 (1.5 mg) was obtained by the chromatography of the mixture **5g**-T_2, **5g**-T_1 and **5g**-E_1 (42 mg) with *n*-hexane-EtOAc (10:1): **5g**-T_2 colorless

needles; mp 56.1-57.9 °C (*n*-hexane-ether); $[\alpha]_D^{25}$ 59.5°(c 0.58, $CHCl_3$); IR (KBr) 3458, 1748, 1680; ^1H NMR 0.89 (d, *J* = 6.9, 3H), 0.91 (d, *J* = 7.0, 3H), 1.28 (d, *J* = 6.8, 3H), 1.29 (t, *J* = 7.1, 3H), 2.30-2.48 (m, 1H), 3.43 (d, *J* = 9.1, 1H), 4.17-4.49 (m, 7H); MS *m/z* 288 [M+1], 269, 214, 196, 130; Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.4; H, 7.4; N, 4.9. Found: C, 54.2; H, 7.2; N, 4.9; **5g**-E_2 a colorless oil; $[\alpha]_D^{25}$ 46.9°(c 1.02, $CHCl_3$); IR (neat) 3499, 1778, 1732, 1704; ^1H NMR 0.90 (d, *J* = 6.9, 3H), 0.92 (d, *J* = 7.1, 3H), 1.16 (d, *J* = 7.0, 3H), 1.33 (t, *J* = 7.1, 3H), 2.30-2.48 (m, 1H), 3.08 (d, *J* = 4.8, 1H), 4.18-4.39 (m, 5H), 4.46-4.54 (m, 1H), 4.64 (dd, *J* = 4.8, 3.8, 1H); MS *m/z* 288 [M+1], 269, 214, 196, 130; HRMS Calcd for $C_{13}H_{22}NO_6$ [M+H] 288.145, found 288.146; **5g**-E_1 a colorless oil; $[\alpha]_D^{22}$ 79.6°(c 0.38, $CHCl_3$); IR (neat) 3487, 1780, 1738, 1698; ^1H NMR 0.88 (d, *J* = 7.0, 3H), 0.92 (d, *J* = 7.2, 3H), 1.31 (d, *J* = 7.2, 3H), 1.32 (t, *J* = 7.2, 3H), 2.27-2.45 (m, 1H), 3.21 (d, *J* = 4.4, 1H), 4.17-4.37 (m, 5H), 4.42-4.51 (m, 2H); MS *m/z* 288 [M+1], 269, 214, 196, 130; HRMS Calcd for $C_{13}H_{22}NO_6$ [M+H] 288.145, found 288.144; **5g**-T_1 a colorless oil; $[\alpha]_D^{25}$ 67.4°(c 0.15, $CHCl_3$); IR (neat) 3460, 1780, 1750, 1689; ^1H NMR 0.87 (d, *J* = 6.9, 3H), 0.92 (d, *J* = 7.1, 3H), 1.28 (t, *J* = 7.1, 3H), 1.39 (d, *J* = 6.9, 3H), 2.25-2.41 (m, 1H), 3.42 (d, *J* = 9.4, 1H), 4.18-4.34 (m, 6H), 4.43-4.51 (m, 1H); MS *m/z* 288 [M+1], 269, 214, 196, 130; HRMS Calcd for $C_{13}H_{22}NO_6$ [M+H] 288.145, found 288.144;

Stereochemical assignments of ***5b***. **The dioxane 6 and the enantiomer of 7 from ethyl (2*R*,3*R*)- and (2*S*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate.** To a suspension of $LiAlH_4$ (5.0 mg, 132 μmol) in ether (0.5 ml) was added a solution of ethyl (2*R*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate[11] (6.7 mg, 24 μmol) in ether (0.2 ml) at 0 °C. After 5 min at 0 °C, the reaction mixture was quenched with MeOH, followed by the addition of H_2O-15% aqueous NaOH-H_2O (5 μl-5 μl-15 μl), and filtered. The residue was washed with ether, and the combined ethereal extracts were dried and filtered. After evaporation of the solvent, the diol was dissolved in toluene (1 ml) followed by the addition of benzaldehyde dimethyl acetal (0.1 ml, 660 μmol) and TsOH (1 mg). After stirring at room temperature for 1 h, the reaction was quenched with Et_3N (50 μl) and concentrated *in vacuo*. Chromatography of the residue with *n*-hexane-ether (10:1) gave **6** (5.0 mg, quantitatively) as a colorless oil; $[\alpha]_D^{23}$ 120.3°(c 0.71, $CHCl_3$); IR (neat) 1600, 1129; ^1H NMR 1.97-2.08 (m, 1H), 2.95-3.05 (m, 1H), 3.20 (dd, *J* = 13.7, 12.1, 1H), 3.81 (dt, *J* = 11.7, 2.1, 1H), 4.00 (d, *J* = 12.0, 1H), 4.53 (dq, *J* = 7.3, 2.7, 1H), 5.50 (s, 1H), 7.15-7.50 (m, 10H); ^{19}F NMR 74.44 (d, *J* = 7.3); MS *m/z* 322 [M^+], 245, 216, 199, 105, 91, 77, 69; HRMS Calcd for $C_{18}H_{17}O_2F_3$ [M^+] 322.118, found 322.115. In the same manner, ethyl (2*S*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate[11] (82 mg, 298 μmol) was converted to the enantiomer of **7** (44 mg, 63.7%) as a colorless oil; $[\alpha]_D^{24}$ -14.2°(c 0.87, $CHCl_3$); IR (neat) 1600, 1170, 1143; ^1H NMR 2.34 (dd, *J* = 13.7, 10.5, 1H), 2.42-2.62 (m, 1H), 3.06-3.16 (m, 1H), 3.59 (t, *J* = 11.5, 1H), 4.02 (dd, *J* = 11.5, 4.7, 1H), 4.12 (dq, *J* = 10.7, 6.4, 1H), 5.63 (s, 1H), 7.20-7.30 (m, 5H), 7.40-7.45 (m, 3H), 7.55-7.60 (m, 2H); ^{19}F NMR 74.53 (d, *J* = 6.4); MS *m/z* 322 [M^+], 245, 216, 199, 105, 91, 77, 69; HRMS Calcd for $C_{18}H_{17}O_2F_3$ [M^+] 322.118, found 322.117.

(2*R*,4*R*,5*S*)-5-Benzyl-4-trifluoromethyl-2-phenyl-1,3-dioxane (6). To a solution of **5b**-E_2 (27 mg, 74 μmol) in THF (2 ml) was added $LiBH_4$ (2.0 M in THF, 150 μl, 300 μmol) at 0 °C. After 1 h at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were dried and filtered. After evaporation of the solvent, the diol was converted to **6** (17 mg, 71.4%) according to the procedure described above. This material was identical with **6** prepared from ethyl (2*R*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate.

(2*S*,4*S*,5*S*)-5-Benzyl-4-trifluoromethyl-2-phenyl-1,3-dioxane (7). The procedure given for **6** was employed using **5b**-T_2 (74 mg, 172 μmol). Chromatography afforded **7** (14 mg, 42.4%) as a colorless oil; $[\alpha]_D^{25}$ 16.2°(c 1.18, $CHCl_3$). This material was identical with the enatiomer of **7** prepared from ethyl (2*S*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate except for optical rotation.

Stereochemical assignments of ***5c***. **The diol 8 and the enantiomer of 9 from ethyl (*R*)-3-hydroxy-4,4,4-trifluorobutanoate.** Crotylation of ethyl (*R*)-3-hydroxy-4,4,4-trifluorobutanoate[12] (413 mg, 2.22 mmol) was carried out according to the procedure reported by D. Seebach *et al.*[11] Chromatography with *n*-hexane-EtOAc (10:1) gave ethyl (2*S*,3*S*)-2-(2-butenyl)-4,4,4-trifluoro-3-hydroxybutanoate (20 mg, 3.8%) and its (2*R*,3*S*)-isomer (115 mg, 21.7%). A solution of ethyl (2*S*,3*S*)-2-(2-butenyl)-4,4,4-trifluoro-3-hydroxybutanoate (18 mg, 76 μmol) in EtOH (1 ml) was stirred in the presence of 5% Pd-C (5 mg) under H_2 (1 atm) at room

temperature for 24 h and filtered. Evaporation of the solvent gave the hydrogenated ester, which was reduced with $LiAlH_4$ according to the procedure described for the reaction of ethyl (2*R*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate to give **8** (4.6 mg, 30.3%) as a colorless oil; $[\alpha]_D^{24}$ 31.3°(c 0.70, $CHCl_3$); IR (neat) 3383; ^1H NMR 0.91 (t, *J* = 7.0, 3H), 1.24-1.65 (m, 6H), 1.73 (t, *J* = 4.5, 1H), 1.92-2.60 (m, 1H), 3.19 (d, *J* = 6.3, 1H), 3.84 (t, *J* = 5.1, 2H), 4.18-4.34 (m, 1H); ^{19}F NMR 75.52 (d, *J* = 8.0); MS *m/z* 164 [M-36], 132, 113, 95, 69; HRMS Calcd for $C_8H_{11}F_3$ [M-$(H_2O)_2$] 164.081, found 164.081. In the same manner, ethyl (2*R*,3*S*)-2-(2-butenyl)-4,4,4-trifluoro-3-hydroxybutanoate (113 mg, 470 μmol) was converted to the enantiomer of **9** (62 mg, 85.2%) as a colorless oil; $[\alpha]_D^{24}$ 5.9°(c 0.81, $CHCl_3$); IR (neat) 3344; ^1H NMR 0.92 (t, *J* = 7.0, 3H), 1.30-1.45 (m, 4H), 1.60-1.70 (m, 2H), 1.78-2.00 (m, 2H), 3.76-3.85 (m, 1H), 3.96-4.20 (m, 3H); ^{19}F NMR 77.21 (d, *J* = 7.6); MS *m/z* 164 [M-36], 132, 113, 95, 69; HRMS Calcd for $C_8H_{11}F_3$ [M-$(H_2O)_2$] 164.081, found 164.081.

(2*S*,3*R*)-2-Butyl-4,4,4-trifluoro-1,3-butanediol (8). Aldol **5c**-E_2 (92 mg, 282 μmol) was reduced with $LiBH_4$ according to the procedure for the reaction of **5b**-E_2 to give **8** (54 mg, 96.3%). This material was identical with **8** prepared from ethyl (*R*)-3-hydroxy-4,4,4-trifluorobutanoate.

(2*S*,3*S*)-2-Butyl-4,4,4-trifluoro-1,3-butanediol (9). Aldol **5c**-T_2 (195 mg, 600 μmol) was reduced with $LiBH_4$ according to the procedure for the reaction of **5b**-E_2 to give **9** (60 mg, 50.0%); $[\alpha]_D^{25}$ -3.9°(c 0.76, $CHCl_3$). This material was identical with the enatiomer of **9** prepared from ethyl (*R*)-3-hydroxy-4,4,4-trifluorobutanoate except for optical rotation.

Stereochemical assignments of 5d. **The benzoates 10 and 11 from 5a-E_2 and 5a-T_2.** Aldol **5a**-E_2 (188 mg, 0.67 mol) was reduced according to the procedure described for the reaction of **5b**-E_2 to afford the corresponding diol, which was dissolved in CH_2Cl_2 (5 ml) followed by the addition of pyridine (170 μl, 2.14 mmol) and benzoyl chloride (0.1 ml, 859 μmol) at 0 °C. After 3.5 h at room temperature, the reaction mixture was poured into ice water and extracted with ether. The combined extracts were washed with 0.5 N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (10:1) gave **10** (42 mg, 24.2%) as a colorless oil; $[\alpha]_D^{25}$ 23.9°(c 0.41, $CHCl_3$); IR (neat) 3473, 1704, 1602; ^1H NMR 1.12 (dq, *J* = 7.0, 1.0, 3H), 2.38-2.50 (m, 1H), 2.57 (d, *J* = 6.4, 1H), 4.08-4.24 (m, 1H), 4.24 (dd, *J* = 11.1, 5.2, 1H), 4.43 (dd, *J* = 11.1, 9.0, 1H), 7.41-7.63 (m, 3H), 8.01-8.06 (m, 2H); ^{19}F NMR 76.33 (d, *J* = 7.0); MS *m/z* 262 [M^+], 244, 193, 164, 123, 105, 77, 69; HRMS Calcd for $C_{12}H_{13}O_3F_3$ [M^+] 262.082, found 262.080. In the same manner, **4a**-T_2 (411 mg, 1.45 mmol) was converted to **11** (90 mg, 23.6%) as a colorless oil; $[\alpha]_D^{25}$ -18.5°(c 0.39, $CHCl_3$); IR (neat) 3457, 1704, 1602; ^1H NMR 1.23 (dq, *J* = 7.0, 1.3 , 3H), 2.28-2.45 (m, 1H), 2.90 (d, *J* = 6.0, 1H), 3.86-4.03 (m, 1H), 4.41 (dd, *J* = 11.3, 4.1, 1H), 4.58 (dd, *J* = 11.3, 4.7, 1H), 7.40-7.65 (m, 3H), 8.00-8.05 (m, 2H); ^{19}F NMR 76.28 (d, *J* = 7.0); MS *m/z* 262 [M^+], 244, 193, 164, 123, 105, 77, 69; HRMS Calcd for $C_{12}H_{13}O_3F_3$ [M^+] 262.082, found 262.082.

(2*R*,3*S*)-4-Benzoyloxy-1,1,1-trifluoro-3-methyl-2-butanol (10). The procedure for the reaction of **5a**-E_2 was conducted using 53 mg (159 μmol) of **5d**-E_2. Chromatography afforded **10** (10 mg, 24.1%). This material was identical with **10** prepared from **5a**-E_2.

(2*S*,3*S*)-4-Benzoyloxy-1,1,1-trifluoro-3-methyl-2-butanol (11). The procedure for the reaction of **5a**-E_2 was conducted using 144 mg (435 μmol) of **5d**-T_2. Chromatography afforded **11** (28 mg, 24.3%). This material was identical with **11** prepared from **5a**-T_2.

Stereochemical assignments of 5e. **The diols 12 and 13 from (*S*)-3-benzyloxy-2-methylpropanal. Ethyl (4*S*)-5-benzyloxy-2,2-difluoro-3-(methoxymethyl)oxy-4-methylpentanoate (19).** To a suspension of zinc powder (5.80 g, 88.7 mmol) in refluxing THF (120 ml) was added a solution of (*S*)-3-benzyloxy-2-methylpropanal[13] (**18**, 7.6 g, 42.7 mmol) and ethyl bromodifluoroacetate (13.5 g, 66.5 mmol) in THF (30 ml) dropwise over a 1.5 h period. After 1 h at reflux, the reaction mixture was cooled to room temperature, poured into 2 N aqueous $KHSO_4$, filtered and extracted with ether. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (10:1) afforded a mixture of ethyl (3*S*,4*S*)- and (3*R*,4*S*)-5-benzyloxy-2,2-difluoro-3-hydroxy-4-methylpentanoate (8.84 g, 66.0 %) as a colorless oil; IR (neat) 3345, 1773; ^1H NMR 1.05-1.19 (m, 3H), 1.36

(t, J = 7.2, 3H), 2.20-2.35 (m, 1H), 2.91 (d, J = 6.0, 0.7H), 3.50-3.62 (m, 2H), 3.80-4.00 (m, 0.7H), 4.34 (q, J = 7.0, 2H), 4.24-4.55 (m, 2.6H), 7.30-7.40 (m, 5H); MS m/z 302 [M+], 284, 178, 91, 77. A solution of the mixture of the esters (3.45 g, 11.4 mmol) in THF (30 ml) was added to a suspension of 60% NaH (690 mg, 17.3 mmol) in THF (30 ml) at 0 °C. After 10 min, chloromethyl methyl ether (1.2 ml, 15.8 mmol) was added and the reaction mixture was stirred at room temperature for 1 h, poured into saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with n-hexane-EtOAc (10:1) afforded ester **19** (3.46 g, 87.4%) as a colorless oil; IR (neat) 1773; ^{1}H NMR 0.98 (dt, J = 7.0, 1.0 , 2H), 1.16 (dt, J = 7.1, 1.1, 1H), 1.30-1.37 (m, 3H), 2.18-2.32 (m, 1H), 3.35 (s, 3H), 3.35-3.64 (m, 2H), 4.00-4.40 (m, 1H), 4.31 (q, J = 7.1, 2H), 4.50 (s, 0.6H), 4.51 (s, 1.4H), 4.65 (d, J = 9.5, 1H), 4.66 (d, J = 9.5, 1H), 7.31-7.35 (m, 5H); ^{19}F NMR 110.18 (dd, J = 281.0, 9.6, 0.3F), 111.97 (dd, J = 278.5, 11.5, 0.7F), 115.76 (dd, J = 278.5, 17.0, 0.7F), 116.26 (dd, J = 281.0, 16.6, 0.3F); MS m/z 301 [M-45], 255, 223, 195, 91, 77; HRMS Calcd for $C_{15}H_{19}O_4F_2$ [M-(CH_2OMe)] 301.125, found 301.125. **(6*S*)-7-Benzyloxy-4,4-difluoro-5-(methoxymethyl)oxy-6-methyl-1-phenylheptan-3-ol (20).** To a mixture of Mg (17 mg, 699 μmol) and I_2 (15 mg, 59 μmol) in ether (2 ml) was added dropwise (2-bromoethyl)benzene (87 μl, 637 μmol) at room temperature. After stirring for 1 h, the mixture was added to a solution of **19** (200 mg, 577 μmol) in ether (2 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, poured into saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with n-hexane-EtOAc (30:1) afforded the starting material (130 mg, 64.8%) and (6*S*)-7-benzyloxy-4,4-difluoro-5-(methoxymethyl)oxy-6-methyl-1-phenylheptan-3-one (34 mg, 14.6%) as a colorless oil; IR (neat) 1742, 1604; ^{1}H NMR 0.95 (d, J = 7.0, 1H), 1.12 (d, J = 7.1, 2H), 2.10-2.28 (m, 1H), 2.86-3.08 (m, 4H), 3.29 (s, 3H), 3.28-3.59 (m, 2H), 3.97-4.13 (m, 0.7H), 4.20-4.38 (m, 0.3H), 4.46-4.59 (m, 4H), 7.13-7.34 (m, 10H); ^{19}F NMR 109.57 (dd, J = 287.0, 9.2, 0.7F), 111.05 (dd, J = 287.0, 10.0, 0.3F), 118.00 (dd, J = 287.0, 17.6, 0.7F), 119.02 (dd, J = 287.0, 20.0, 0.3F); MS m/z 361 [M-45], 345, 283, 105, 91, 77; HRMS Calcd for $C_{21}H_{23}O_3F_2$ [M-(CH_2OMe)] 361.162, found 361.161. (6*S*)-7-Benzyloxy-4,4-difluoro-5-(methoxymethyl)oxy-6-methyl-1-phenylheptan-3-one (480 mg, 1.18 mmol) was reduced with $LiAlH_4$ according to the procedure for the reaction of ethyl (2*R*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate to give **20** (479 mg, 99.3%) as a colorless oil; IR (neat) 3423, 1603; ^{1}H NMR 0.90-1.20 (m, 3H), 1.80-2.10 (m, 3H), 2.51-3.10 (m, 3H), 3.29-3.60 (m, 5H), 3.78-4.08 (m, 2H), 4.48-4.52 (m, 2H), 4.64-4.68 (m, 2H), 7.18-7.34 (m, 10H); ^{19}F NMR 111.65-113.19 (m, 0.7F), 118.00-122.82 (m, 1.3F); MS m/z 363 [M-45], 345, 285, 257, 107, 91, 77; HRMS Calcd for $C_{21}H_{25}O_3F_2$ [M-(CH_2OMe)] 363.177, found 363.177. **(2*R*)-4,4-Difluoro-3-(methoxymethyl)oxy-2-methyl-5-phenylheptan-1-ol benzyl ether (21).** The procedure given for ethyl 2,2-difluoro-5-pentanoate was carried out using **20** (479 mg, 1.17 mmol). Chromatography with n-hexane-EtOAc (3:1) gave **21** (418 mg, 90.6% in two steps) as a colorless oil; IR (neat) 2939, 2857, 1603, 1454, 1101, 1035; ^{1}H NMR 0.94 (dt, J = 7.0, 0.8, 1H), 1.11 (dt, J = 7.2, 1.0, 2H), 1.81-2.20 (m, 5H), 2.65 (t, J = 7.5, 2H), 3.34 (s, 2H), 3.35 (s, 1H), 3.30-3.90 (m, 3H), 4.48 (s, 1.3H), 4.49 (s, 0.7H), 4.66 (s, 2H), 7.15-7.34 (m 10H); ^{19}F NMR 104.48-106.51 (m); MS m/z 347 [M-45], 329, 269, 107, 91, 77; HRMS Calcd for $C_{21}H_{25}O_2F_2$ [M-(CH_2OMe)] 347.182, found 347.182. **Conversion of 21 to the diols 12 and 13.** A solution of **21** (413 mg, 1.05 mmol) and conc. HCl (0.5 ml) in 1,4-dioxane (10 ml) was stirred at 60 °C for 0.5 h. The reaction mixture was cooled to room temperature and extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, the residue was dissolved in EtOH (3 ml) followed by the addition of Raney Ni (1 cm^3). After the mixture was stirred under H_2 (1 atm) at room temperature for 36 h, Raney Ni was filtered off and washed with EtOH. Concentrating of the filtrate and chromatography of the residue with n-hexane-EtOAc (3:2) gave **12** (62 mg, 22.8%) and **13** (148 mg, 54.3%): **12** a colorless oil; $[\alpha]_D^{25}$ 14.3°(c 0.69, $CHCl_3$); IR (neat) 3300, 1604; ^{1}H NMR 1.01 (d, J = 7.0, 3H), 1.63 (t, J = 5.1, 1H), 1.83-2.09 (m, 5H), 2.35 (d, J = 6.6, 1H), 2.67 (t, J = 7.6, 2H), 3.68 (t, J = 5.4, 2H), 3.92-3.99 (m, 1H), 7.17-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{19}F NMR 108.92-109.55 (m, 1F), 110.56-111.19 (m, 1F); MS m/z 258 [M+], 244, 181, 161, 147, 91, 77; HRMS Calcd for $C_{14}H_{20}O_2F_2$ [M+] 258.143 found 258.140; **13** a colorless oil; $[\alpha]_D^{25}$ -1.2°(c 0.75, $CHCl_3$); IR (neat) 3300, 1603; ^{1}H NMR

1.07 (d, J = 7.1, 3H), 1.84-2.15 (m, 6H), 2.68 (t, J = 7.6, 2H), 3.49 (d, J = 6.3, 1H), 3.61-3.70 (m, 2H), 3.95 (d, J = 10.5, 1H), 7.17-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{19}F NMR 107.63-108.26 (m, 1F), 11.67-111.80 (m, 1F); MS *m/z* 258 [M$^+$], 244, 181, 161, 147, 91, 77; HRMS Calcd for $C_{14}H_{20}O_2F_2$ [M$^+$] 258.143, found 258.144.

(2*S*,3*R*)-4,4-Difluoro-2-methyl-7-phenylheptane-1,3-diol (12). Aldol **5e**-E_2 (48 mg, 125 μmol) was reduced with $LiBH_4$ according to the procedure for the reaction of **5b**-E_2 to give **12** (29 mg, 89.2%). This material was identical with **12** prepared from **18**.

(2*S*,3*S*)-4,4-Difluoro-2-methyl-7-phenylheptane-1,3-diol (13). Aldol **5e**-T_2 (108 mg, 281 μmol) was reduced with $LiBH_4$ according to the procedure for the reaction of **5b**-E_2 to give **13** (41 mg, 56.8%). This material was identical with **13** prepared from **18**.

(2*R*,3*S*)-4,4-Difluoro-2-methyl-7-phenylheptane-1,3-diol (the enantiomer of 12). Aldol **5e**-E_1 (37 mg, 95 μmol) was reduced with $LiBH_4$ as described for the reaction of **5b**-E_2 to give the enantiomer of **12** (20 mg, 81.9%); $[\alpha]_D^{25}$ -14.5°(c 0.51, $CHCl_3$). This material was identical with the enantiomer of **12** prepared from **18** except for optical rotation.

Stereochemical assignments of 5f. **(2*S*,3*S*)-2-Methyl-4-phenylbutane-1,3-diol (14).** Aldol **5f**-E_2 (122 mg, 384 μmol) was reduced with $LiBH_4$ following the procedure for the reaction of **5b**-E_2 to give (2*S*,3*R*)-2-methyl-4-phenylbutane-1,3,4-triol (48 mg, 64.0%); IR (neat) 3395; ^{1}H NMR 1.06 (d, J = 7.1, 3H), 1.98-2.14 (m, 1H), 2.11 (d, J = 3.5, 1H), 2.20 (s, 1H), 2.42 (s, 1H), 3.61-3.80 (m, 2H), 3.90-3.98 (m, 1H), 4.65 (d, J = 7.8, 1H), 7.30-7.45 (m, 5H); MS *m/z* 196 [M$^+$], 178, 160, 147, 108, 77. To a solution of the triol (48 mg, 246 μmol) in pyridine (1 ml) was added Ac_2O (230 μl, 2.4 mmol) and DMAP (1.5 mg) at room temperature. The reaction mixture was stirred for 1 h, poured into ice water and extracted with ether. The combined extracts were washed with 2 N HCl, saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (5:1) gave the corresponding triacetate (75 mg, 95.0%) as a colorless oil; IR (neat) 1737; ^{1}H NMR 1.00 (d, J = 7.0, 3H), 1.86 (s, 3H), 2.03 (s, 3H), 2.10 (s, 3H), 2.13-2.28 (m, 1H), 3.91 (d, J = 6.8, 2H), 5.39 (dd, J = 7.4, 3.5, 1H), 5.90 (d, J = 7.4, 1H), 7.30-7.40 (m, 5H); MS *m/z* 263 [M-59], 220, 202, 173, 107, 91, 77. A mixture of the triacetate (75 mg, 233 μmol) and 5% Pd-C (150 mg) in AcOH (3 ml) was stirred under H_2 at room temperature for 36 h. The Pd-C catalyst was filtered off and washed with EtOAc. The combined filtrates were washed with saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (10:1) gave (2*S*,3*S*)-2-methyl-4-phenylbutane-1,3-diol diacetate (15 mg, 25.0%) as a colorless oil; IR (neat) 1741, 1604; ^{1}H NMR 1.03 (d, J = 7.0, 3H), 1.97 (s, 3H), 2.03 (s, 3H), 1.97-2.09 (m, 1H), 2.76-2.98 (m, 2H), 3.92 (dd, J = 9.0, 6.5, 1H), 4.00 (dd, J = 9.0, 7.0, 1H), 5.20 (ddd, J = 7.8, 6.5, 3.3, 1H), 7.20-7.34 (m, 5H); MS *m/z* 204 [M-60], 173, 144, 91, 77. To a solution of the diacetate (11 mg, 42.8 μmol) in MeOH (1 ml) was added anhydrous K_2CO_3 (34 mg, 246 μmol) at room temperature. The reaction mixture was stirred for 1 h, diluted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (1:1) afforded **14** (6.2 mg, 80.5%) as a colorless oil; $[\alpha]_D^{25}$ -17.1°(c 0.31, $CHCl_3$); IR (neat) 3346, 1605; ^{1}H NMR 1.04 (d, J = 7.1, 3H), 1.79-1.96 (m, 1H), 2.11 (d, J = 3.3, 1H), 2.25 (t, J = 5.3, 1H), 2.78 (d, J = 6.9, 2H), 3.74 (t, J = 5.3, 2H), 4.04-4.14 (m, 1H), 7.21-7.38 (m, 5H); MS *m/z* 162 [M-18], 121, 103, 91, 77; HRMS Calcd for $C_{11}H_{14}O$ [M-H_2O] 162.104, found 162.105. This diol **14** was identical with an authentic sample prepared by using literature procedures.[14]

(2*S*,3*R*)-2-Methyl-4-phenylbutane-1,3-diol (15). Aldol **5f**-T_2 (48 mg, 144 μmol) was converted to diol **15** according to the procedure given for **14**. Chromatography with *n*-hexane-EtOAc (11:1) afforded **15** (2.7 mg, 18.5% in four steps) as a colorless oil; $[\alpha]_D^{25}$ 59.3°(c 0.27, $CHCl_3$); IR (neat) 3329, 1602; ^{1}H NMR 1.01 (d, J = 7.0, 3H), 1.76-1.86 (m, 1H), 2.20 (s, 1H), 2.64 (dd, J = 13.7, 9.5, 1H), 2.82 (s, 1H), 3.00 (dd, J = 13.7, 3.3, 1H), 3.64-3.81 (m, 3H), 7.20-7.38 (m, 5H); MS *m/z* 180 [M$^+$], 121, 103, 91, 77; HRMS Calcd for $C_{11}H_{16}O_2$ [M$^+$] 180.115, found 180.114. This diol **15** was identical with an authentic sample prepared by literature procedures.[14]

The enantiomer of 14 from 5f-E_1. Aldol 5f-E_1 (85 mg, 257 μmol) was converted to the enantiomer of **14** by the procedure given for **14**. Chromatography with *n*-hexane-EtOAc (11:1) afforded the enantiomer of **14** (7.4 mg, 84.1% in four steps); $[\alpha]_D^{25}$ 25.9°(c 0.40, $CHCl_3$). This diol was identical with **14** except for optical rotation.

Stereochemical assignments of 5g. **Diethyl (2*R*,3*R*)-3-methylmalate (16).** To a suspension of 60% NaH (38 mg, 950 μmol) in EtOH (2 ml) was added 5g-E_2 (89 mg, 310 μmol) in EtOH (1.5 ml) at 0 °C. After 15 min at 0 °C, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried and filtered. After evaporation of the solvent, chromatography with *n*-hexane-EtOAc (4:1) gave **16** (41 mg, 64.0%) as a colorless oil; $[\alpha]_D^{23}$ 2.8°(c 1.47, ether); IR (neat) 3350, 1735; ^{1}H NMR 1.17 (d, *J* = 7.2, 3H), 1.28 (t, *J* = 7.1, 3H), 1.31 (t, *J* = 7.1, 3H), 2.92 (dq, *J* = 7.2, 3.6, 1H), 3.05 (d, *J* = 5.4, 1H), 4.19 (q, *J* = 7.1, 2H), 4.28 (q, *J* = 7.1, 2H), 4.60 (dd, *J* = 5.4, 3.6, 1H); MS *m/z* 204 [M^+], 131, 113, 85; HRMS Calcd for $C_9H_{16}O_5$ [M^+] 204.100, found 204.096. This diester **16** was identical with an authentic sample prepared by using literature procedures.[15]

Diethyl (2*S*,3*R*)-3-methylmalate (17). Aldol 5g-T_2 (100 mg, 349 μmol) was converted to diester **17** according to the procedure for **16**. Chromatography afforded **17** (62 mg, 87.2%) as a colorless oil; $[\alpha]_D^{23}$ -10.2°(c 1.14, ether); IR (neat) 3400, 1737; ^{1}H NMR 1.25 (t, *J* = 7.2, 3H), 1.29 (d, *J* = 7.3, 3H), 1.30 (t, *J* = 7.2, 3H), 3.02 (dq, *J* = 7.3, 3.5, 1H), 3.15 (d, *J* = 6.4, 1H), 4.15 (q, *J* = 7.2, 2H), 4.20-4.33 (m, 3H); MS *m/z* 204 [M^+], 131, 113, 85; HRMS Calcd for $C_9H_{16}O_5$ [M^+] 204.100, found 204.097. This diester **17** was identical with an authentic sample prepared by literature procedures except for optical rotation.[15]

The enantiomer of 16 from 5g-E_1. Aldol 5g-E_1 (14 mg, 49 μmol) was converted to the enantiomer of **16** as described for **16**. Chromatography afforded the enantiomer of **16** (3.3 mg, 33.0%) as a colorless oil. This diester was identical with an authentic sample prepared by literature procedures except for optical rotation.[15]

The enantiomer of 17 from 5g-T_1. Aldol 5g-T_1 (1.5 mg, 5.2 μmol) was converted to the enantiomer of **17** following the method for **16**. Chromatography afforded the enantiomer of **17** (0.6 mg, 56%) as a colorless oil. This diester was identical with an authentic sample prepared by literature procedures .[15]

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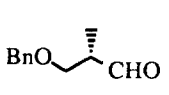
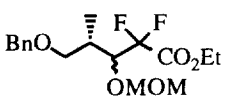
REFERENCES AND NOTES

1. For reviews see: a) *Biomedical Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y. Eds.; Kodansha Ltd. and Elsevier Biomedical Press: Tokyo and Amsterdam, **1982**. b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. c) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661. d) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons, Inc.: New York, **1991**. e) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T. Ed.; American Chemical Society: Washington, **1991**. f) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. Eds.; Elsevier: Amsterdam, **1993**. g) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. h) Iseki, K.; Kobayashi, Y. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 40.
2. a) Arakawa, S.; Nito, K.; Seto, J. *Mol. Cryst. Liq. Cryst.* **1991**, *204*, 15. b) Bömelburg, J.; Heppke, G.; Ranft, A. *Z. Naturforsch.* **1989**, 1127. c) Buchecker, R.; Kelly, S. M.; Fünfschilling, J. *Liquid Cryst.* **1990**, *8*, 217.
3. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320.

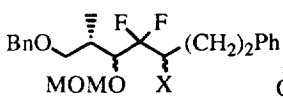
4. a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. b) Evans, D.A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, *Pure Appl. Chem.* **1981**, *53*, 1109. c) Evans, D.A. *Aldrichimica Acta* **1982**, *15*, 318.
5. a) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173. b) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99. c) Hayashi, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 7287.
6. a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. b) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99. c) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1992**, *33*, 4369.
7. A preliminary communication: Iseki, K.; Oishi, S.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 8147.
8. Evans, D. A. *Org. Synth.* **1990**, *68*, 83.
9. The reaction does not proceed at -78 °C.
10. The reaction scarcely proceeds at < -20 °C.
11. Acetal **6** and the enantiomer of **7** were prepared by the reduction of ethyl (2*R*,3*R*)- and (2*S*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate (Seebach, D.; Beck, A. K.; Renaud, P. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 98) with $LiAlH_4$ and acetalization of the resultant diols, respectively.
12. Diol **8** and the enantiomer of **9** were prepared as follows. Crotylation of ethyl (*R*)-3-hydroxy-4,4,4-trifluorobutanoate (Seebach, D.; Renaud, P.; Schweizer, W. B.; Züger, M. F.; Brienne, M.-J. *Helv. Chim. Acta* **1984**, *67*, 1843) gave ethyl (2*R*,3*R*)-2-crotyl-4,4,4-trifluoro-3-hydroxybutanoate and its (2*S*,3*R*)-isomer. The former was coverted to **8** by hydrogenation (H_2, Pd-C) and reduction ($LiAlH_4$). In the same manner, the enantiomer of **9** was obtained from the latter.
13. Diols **12** and **13** were prepared starting from (*S*)-3-benzyloxy-2-methylpropanal (Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron* **1988**, *44*, 2149) as follows. Treatment of **18** with zinc and ethyl bromodifluoroacetate and methoxymethylation gave ester **19**. Grignard reaction of **19** (Mg, $Br(CH_2)_2Ph$) and reduction with $LiAlH_4$ gave alcohol **20**. Treatment of **20** with *N*,*N*'-thiocarbonyldiimidazole and reduction (*n*-Bu_3SnH in toluene, reflux) afforded **21**. Finally, **21** was converted to **12** and **13** by the removal of the MOM group and hydrogenolysis (H_2, Raney Ni). The relative stereochemistry of **13** was shown to be anti by ^1H NMR spectroscopy of acetal **22**.



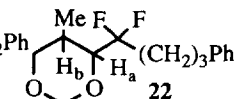
18



19



20 X = OH, **21** X = H



22 J_{Ha-Hb} 10.0 Hz (*anti*)

14. Tsukada, T.; Kakisawa, H.; Painuly, P.; Shimizu, Y. *Tetrahedron Lett.* **1989**, *30*, 4245.
15. a) Mori, K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87. b) Akita, H.; Matsukura, H.; Oishi, T. *Chem. Pharm. Bull.* **1986**, *34*, 2656.
16. Calculations were performed with GAUSSIAN 90: Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, **1990**.
17. Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544.
18. a) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.
19. a) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, Jr. J. F. *Tetrahedron* **1988**, *44*, 5525. b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77.
20. Linderman, R. J.; Graves, D. M. *J. Org. Chem.* **1989**, *54*, 661.

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