Diastereoselective Reduction of α,α-Difluoro β-Hydroxy Ketones to *syn*- and *anti*-2,2-Difluoro-1,3-diols

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While reduction of α,α-difluoro β-hydroxy ketones with diisobutylaluminium hydride gave a mixture of *syn*- and *anti*-diols in various ratios, the reduction in the presence of zinc bromide or zinc chloride-*N*,*N*,*N*′,*N*′-tetramethylethylenediamine was highly selective and gave *syn*-2,2-difluoro-1,3-diols predominantly. *anti*-2,2-Difluoro-1,3-diols were obtained by the reduction of α,α-difluoro β-hydroxy ketones with aluminium isopropoxide.

Fluorine-containing compounds have a unique chemical and/or biochemical properties and synthesis of fluorine-containing analogs of natural compounds is very interesting subject for not only organofluorine chemistry but also medicinal chemistry.[1] For this purpose, the fluorinated building blocks in an enantiomerically and/or a diastereomerically pure form are earnestly desired.[2,3] On the other hand, stereoselective construction of the 1,3-diol system is one of the most important problems because this system is a fundamental unit contained in many naturally occurring compounds,[4] and, therefore, fluorinated polyols are considered to be attractive target molecules. Recently, we reported the conventional method to obtain α,α-difluoro β-hydroxy ketones.[5] Stereoselective reduction of this ketones is expected to give the 2,2-difluorinated *syn*- and/or *anti*-1,3-diols. This type of compounds have two fluorine atoms adjacent to the hydroxyl group, and the chemical property of the hydroxyl group is expected to be different from that in the non-fluorinated counterparts.

Stereoselective reduction of β-hydroxy ketones has been studied well and, in general, *syn*-1,3-diols[6] are obtained through chelation-controlled reduction,[7-10] whereas *anti*-1,3-diols[6] are obtained through the intramolecular reduction.[7,11,12] This stereochemical selectivity applies also to the reduction of β-trifluoromethylated β-hydroxy ketones.[13]

The diastereoselective reduction of α,α-difluoro β-hydroxy ketones **1**, however, turned out not to be the simple case.

For example, reduction of the ketones **1** with diisobutylaluminium hydride (DIBAL-H: reagent for the *syn*-reduction[8]) did not necessarily give the corresponding *syn*-diols with high selectivity and, on the contrary, the corresponding *anti*-diols were obtained in some cases as the major products. We speculated an additional effect due to α-fluorine and intended to establish methods for synthesizing 2,2-difluorinated *syn*- and *anti*-1,3-diols with high stereoselectivity.

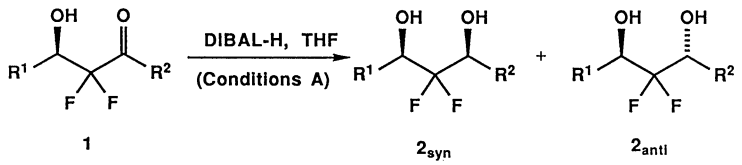
Results and Discussion

Synthesis of *syn*-1,3-Diols. The reduction of the ketones **1** using DIBAL-H (3 equiv) at −78 °C was first studied (Table 1). The chemical yields of diols **2** were almost quantitative but the reaction did not proceed highly diastereoselectively. *anti*-Diols $\mathbf{2}_{anti}$

Table 1. Reduction of Aldols **1** with DIBAL-H (Conditions A)[a]

Entry	**1** or **3b**			**2**		
	R^1	R^2		Yield/%[b]		Syn/Anti[c]
1	$CH_3(CH_2)_2$	Ph	(**1a**)	**2a**	98	13/ 87
2	(*E*)-CH_3CH=CH	Ph	(**1b**)	**2b**	93	31/ 69
3	(*E*)-CH_3CH=CH	Ph	(**3b**)	**2b**[d]	99	77/ 23
4	Ph	Ph	(**1c**)	**2c**	99	0/100
5[e]	**1c**			**2c**	100	43/ 57
6	$CH_3(CH_2)_2$	$CH_3(CH_2)_5$	(**1d**)	**2d**	97	46/ 54
7	$(CH_3)_2CH$	$CH_3(CH_2)_5$	(**1e**)	**2e**	100	47/ 53
8	$(CH_3)_3C$	$CH_3(CH_2)_5$	(**1f**)	**2f**	100	51/ 49
9	(*E*)-CH_3CH=CH	$CH_3(CH_2)_5$	(**1g**)	**2g**	97	73/ 27
10	Ph	$CH_3(CH_2)_5$	(**1h**)	**2h**	95	25/ 75
11[e]	**1h**			**2h**	100	82/ 18

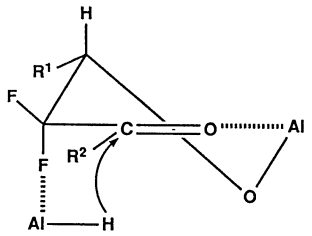
a) All the reductions were carried out with 3 equiv of DIBAL-H in a THF-hexane mixture at −78 °C, unless otherwise stated. b) The yields refer to pure isolated products. c) The syn/anti ratio was determined by ^{19}F NMR. d) Isolated after alkaline hydrolysis. e) Carried out at room temperature.



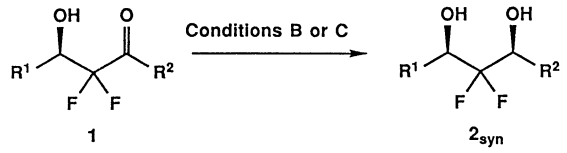
were obtained preferentially in some cases in contrast to the DIBAL-H reduction of fluorine-free counterparts.[8] The stereochemical outcome is hardly explained by the normal chelated transition state models, and thus the selectivity reversal should be attributed to a new type of substituent effect due to α-fluorines. However, whatever the effect may be, it is not so striking, since the formation of *syn*-diols prevailed at room temperature (Table 1, Entries 5 and 11).

When (*E*)-3-acetoxy-2,2-difluoro-1-phenyl-4-hexen-1-one[14] (**3b**) was reduced with DIBAL-H (2 equiv) in THF at −78 °C, the corresponding diol **2b** was obtained in a quantitative yield with a syn/anti ratio of 77:23 after saponification (Table 1, Entry 3). Similar syn/anti ratio (79:21) was observed when the reduction of **3b** was carried out in the presence of zinc chloride-*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) complex (Table 2, Entry 5). These results suggest that an open-chain model is not suitable to explain the results of the reduction of **1** with DIBAL-H.

We tentatively propose a following mechanism. A 6-membered cyclic chelated transition state containing O(carbonyl)-Al-O(hydroxyl) is formed as usual. Since the van der Waals radius of fluorine is similar to that of hydrogen,[15] the steric effects in the 6-membered cyclic chelate transition state should be comparable. A pseudo-axial α-fluorine interacts with the aluminium of DIBAL-H, from which hydride is delivered. The metal-fluorine interaction suggested here is not unprecedented.[3,16]



It was expected that the F-Al interaction might be weakened by a Lewis acid and/or a Lewis base additive(s) and thus examined the effect of the additive like zinc chloride, zinc chloride-TMEDA complex, zinc bromide, zinc bromide-TMEDA complex, diethylzinc, nickel(II) chloride-TMEDA complex, titanium(IV) isopropoxide, tin(II) chloride, tin(IV) chloride, triethylaluminium, and 9-borabicyclo-[3.3.1]non-9-yl triflate. Of these, zinc chloride-TMEDA complex (Conditions B) and zinc bromide



Conditions B: DIBAL-H (3 eq.), $ZnCl_2$-TMEDA, THF
C: DIBAL-H (3 eq.), $ZnBr_2$, THF

(Conditions C) were the most efficient for the selective synthesis of *syn*-diols irrespective of R^1 and R^2 of the fluorinated β-hydroxy ketones **1** (Tables 2 and 3). The syn-selectivity did not depend on the reaction temperature when zinc salt was added to the reduction system. To be noted is that zinc chloride-TMEDA complex was highly effective for the *syn*-diol synthesis, but zinc bromide-TMEDA complex or zinc chloride alone was not effective enough. In solution, zinc chloride-TMEDA complex is expected to dissociate into each component which works as a general acid and base[17] favoring the *syn*-diol synthesis, that is, the F-Al interaction might be weakened or prevented through the coordination of zinc chloride to α-fluorine and the coordination of TMEDA to aluminium in DIBAL-H may decrease the Lewis acidity of DIBAL-H. On the other hand, zinc bromide-TMEDA would not dissociate to affect the stereoselective reduction. For the reduction of α,α-difluoro-β-hydroxyalkyl alkyl ketones **1d—h** to *syn*-diols **2d—h**, a catalytic amount of zinc chloride-TMEDA complex was efficient enough (Table 2, Entries 9—17) whereas one equivalent of the complex was required for aryl ketones **1a—c** (Table 2, Entries 1—4, 6, and 7). In contrast, one equimolar amount of zinc bromide was needed for the reduction of both types of substrates (Table 3).

Synthesis of *anti*-1,3-Diols. The Wagner-Meerwein-Ponndorf-Verley reduction[18] of **1** was first studied. The reduction using 1.1 equivalents of aluminium isopropoxide proceeded smoothly in benzene at room temperature to give *anti*-1,3-diols, as expected,[7] in almost quantitative yields with high selectivity (Table 4). The selectivity became worse at higher reaction temperature or with an excess amount of the reagent. This suggests that the reduction proceeds

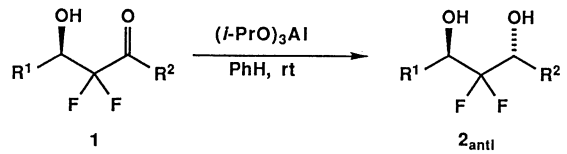


Table 2. Reduction of Aldols **1** with DIBAL-H and $ZnCl_2$-TMEDA (Conditions B)[a]

Entry	**1** or **3b**				**2**		
	R^1		R^2			Yield/%[b]	Syn/Anti[c]
1[d]	$CH_3(CH_2)_2$		Ph	(**1a**)	**2a**	98	91/ 9
2[e]		**1a**			**2a**	98	68/ 32
3[d]	(*E*)-CH_3CH=CH		Ph	(**1b**)	**2b**	99	96/ 4
4[e]		**1b**			**2b**	90	89/ 11
5[d]	(*E*)-CH_3CH=CH		Ph	(**3b**)	**2b**[f]	100	79/ 21
6[d]	Ph		Ph	(**1c**)	**2c**	98	80/ 20
7[e]		**1c**			**2c**	98	61/ 39
8[d,g]		**1c**			**2c**	99	81/ 19
9[d]	$CH_3(CH_2)_2$		$CH_3(CH_2)_5$	(**1d**)	**2d**	93	92/ 8
10[e]		**1d**			**2d**	92	92/ 8
11[d]	$(CH_3)_2CH$		$CH_3(CH_2)_5$	(**1e**)	**2e**	99	88/ 12
12[e]		**1e**			**2e**	100	87/ 13
13[d]	$(CH_3)_3C$		$CH_3(CH_2)_5$	(**1f**)	**2f**	100	77/ 23
14[d]	(*E*)-CH_3CH=CH		$CH_3(CH_2)_5$	(**1g**)	**2g**	91	94/ 6
15[e]		**1g**			**2g**	100	94/ 6
16[d]	Ph		$CH_3(CH_2)_5$	(**1h**)	**2h**	100	92/ 8
17[e]		**1h**			**2h**	100	94/ 6
18[d,g]		**1h**			**2h**	98	86/ 14

a) All the reactions were performed at −78 °C, unless otherwise stated. b) The yields refer to pure isolated products. c) The syn/anti ratio was determined by ^{19}F NMR. d) The amount of $ZnCl_2$-TMEDA complex used was 1.0 equiv. e) A catalytic amount (0.1 equiv) of $ZnCl_2$-TMEDA was used. f) Isolated after alkaline hydrolysis. g) Performed at room temperature.

Table 3. Reduction of Aldols **1** with DIBAL-H and $ZnBr_2$ (Conditions C)[a]

Entry	**1**			**2**		
	R^1	R^2			Yield/%[b]	Syn/Anti[c]
1	$CH_3(CH_2)_2$	Ph	(**1a**)	**2a**	98	78/22
2	(*E*)-CH_3CH=CH	Ph	(**1b**)	**2b**	98	88/12
3	Ph	Ph	(**1c**)	**2c**	100	84/16
4[d]	**1c**			**2c**	98	85/15
5	$CH_3(CH_2)_2$	$CH_3(CH_2)_5$	(**1d**)	**2d**	97	86/14
6	(*E*)-CH_3CH=CH	$CH_3(CH_2)_5$	(**1g**)	**2g**	98	95/ 5
7	Ph	$CH_3(CH_2)_5$	(**1h**)	**2h**	100	95/ 5
8[d]	**1h**			**2h**	97	90/10

a) All the reactions were effected using one equiv. of zinc bromide at −78 °C, unless otherwise stated. b) The yields refer to pure isolated products. c) The ratio syn/anti was determined by ^{19}F NMR. d) Conducted at room temperature.

Table 4. Reduction of Aldols **1** with Aluminium Isopropoxide

Entry	**1**			**2**		
	R^1	R^2			Yield/%[a]	Syn/Anti[b]
1	$CH_3(CH_2)_2$	Ph	(**1a**)	**2a**	98	11/ 89
2	(*E*)-CH_3CH=CH	Ph	(**1b**)	**2b**	95	8/ 92
3	Ph	Ph	(**1c**)	**2c**	91	0/100
4	$CH_3(CH_2)_2$	$CH_3(CH_2)_5$	(**1d**)	**2d**	99	9/ 91
5	$(CH_3)_2CH$	$CH_3(CH_2)_5$	(**1e**)	**2e**	92	0/100
6	(*E*)-CH_3CH=CH	$CH_3(CH_2)_5$	(**1g**)	**2g**	93	5/ 95
7	Ph	$CH_3(CH_2)_5$	(**1h**)	**2h**	95	0/100

a) The yields refer to pure isolated products. b) The syn/anti ratio was determined by ^{19}F NMR.

intramolecularly. The reduction of **1** with tetrabutylammonium triacetoxyhydroborate[11] in acetic acid gave a complex mixture of products.

Experimental

General. ^1H NMR spectra were recorded with a Varian EM-390, XL-200, or JEOL JNM-PMX60SI spectrometer using tetramethylsilane as an internal standard and ^{19}F NMR spectra with a JEOL FX90Q spectrometer using trichlorofluoromethane as an internal standard. IR data were taken as a neat liquid film, unless otherwise noted, on a Shimadzu IR-400 or JASCO IR-810 spectrometer. Mass spectra (MS) were obtained by using a Shimadzu QP1000

GC-mass spectrometer at 25 eV. Column chromatography was carried out with silica gel (Wakogel C-200) at an atmospheric pressure.

All chemicals were of reagent grade and used without further purification. Solvents were distilled and, if necessary, were purified in the usual manner prior to use.

The ratios of *syn*-diol $\mathbf{2}_{syn}$ to *anti*-diol $\mathbf{2}_{anti}$ were determined by ^{19}F NMR analysis of the reaction products before isolation by silica-gel column chromatography. The structures of the diols **2** were confirmed by the splitting patterns and the coupling constants in ^{1}H NMR (200 MHz) and ^{19}F NMR (84.25 MHz) spectra of the acetonides **4** of the diols, which were obtained via acetalization of **2** with 2,2-dimethoxypropane.

General Procedure for the Reduction of 1 with DIBAL-H (Conditions A). To a solution of **1** (1.00 mmol) in THF (5 mL) was added a solution of DIBAL-H (1 mol dm^{-3}) in hexane (3.0 mL, 3.0 mmol) dropwise at −78 °C or 0 °C under an argon atmosphere, and the mixture was stirred for 3 h at −78 °C or room temperature, respectively. The reaction mixture was poured into a mixture of hydrochloric acid (6 mol dm^{-3}, 5 mL) and a saturated ammonium chloride aqueous solution (5 mL), and the resultant was extracted with diethyl ether (20 mL×3). The combined extracts were dried over anhydrous sodium sulfate and concentrated. After the *syn*- and *anti*-diol ratio was determined by ^{19}F NMR, the residue was purified by silica-gel column chromatography to give a mixture of *syn*- and *anti*-diol **2**. The results are summarized in Table 1.

General Procedure for the Reduction of 1 with DIBAL-H in the Presence of Zinc Chloride-TMEDA Complex (Conditions B). To a mixture of **1** (1.00 mmol) , zinc chloride-TMEDA complex (0.250 g, 1.00 mmol) and THF (5 mL) was added a solution of DIBAL-H (1 mol dm^{-3}) in hexane (3.0 mL, 3.0 mmol) at −78 °C or 0 °C under an argon atmosphere, and the resultant was stirred for 6 h at −78 °C or room temperature, respectively. Work-up was effected as described in the Conditions A. The results are summarized in Table 2.

General Procedure of the Reduction of 1 with DIBAL-H in the Presence of Zinc Bromide (Conditions C). The reduction was conducted in the same procedure as noted above except that zinc bromide (0.248 g, 1.10 mmol) was used instead of zinc chloride-TMEDA complex. The results are summarized in Table 3.

Preparation of (*E*)-3-Acetoxy-2,2-difluoro-1-phenyl-4-hexen-1-one (3b). To a solution of 4-(dimethylamino)-pyridine (13 mg, 0.10 mmol), 2,2-difluoro-3-hydroxy-1-phenyl-4-hexen-1-one (**1b**) (0.226 g, 1.00 mmol) in dichloromethane (5 mL) were added acetic anhydride (0.112 g, 1.10 mmol) and triethylamine (0.121 g, 1.20 mmol) at 0 °C. The resulting mixture was stirred for 12 h at room temperature, and then poured into a mixture of ice and a saturated sodium hydrogencarbonate aqueous solution. The resultant was extracted with dichloromethane (20 mL×3) and the combined extracts were dried over anhydrous sodium sulfate and concentrated. The title compound was obtained by silica-gel column chromatography (0.263 g, 98%). IR (neat) 1758, 1703, 1599, 1581, 1450, 1372, 1283, 1223, 1187, 1119, and 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=8.1—7.7 (m, 2H), 7.6—7.2 (m, 3H), 6.2—5.1 (m, 2H), 1.97 (s, 3H), and 1.71 (d, J=6.0 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ=−108.24 (dd, J=282.0, 11.0 Hz, 1F) and −112.68 (dd, J=282.0, 12.2 Hz, 1F); MS, m/z (rel intensity) 225 (M^+−Ac, 20), and 105 (100). Found: C, 62.92; H, 5.31%. Calcd for $C_{14}H_{14}F_2O_3$: C, 62.68; H, 5.26%.

Reduction of 3b with DIBAL-H (Conditions A). A solution of DIBAL-H (1 mol dm^{-3}) in hexane (2.0 mL, 2.0 mmol) was added to the mixture of **3b** (0.284 g, 1.0 mmol) and THF (5 mL) at −78 °C. The resulting mixture was stirred for 3 h at the same temperature, and then poured into a mixture of hydrochloric acid (6 mol dm^{-3}, 5 mL) and a saturated ammonium chloride aqueous solution (5 mL). The resultant was extracted with diethyl ether (20 mL×3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was saponified with 2 mol dm^{-3} KOH and methanol for 12 h at room temperature. After evaporation of methanol, the residue was extracted with diethyl ether (20 mL×3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. After the *syn*-/*anti*-diol ratio was determined by ^{19}F NMR, the residue was purified by silica-gel column chromatography to give a mixture of *syn*- and *anti*-diol **2b**.

Reduction of 3b with DIBAL-H in the Presence of Zinc Chloride-TMEDA Complex (Conditions B). As described above, **3b** (0.284 g, 1.0 mmol) was treated with a solution of DIBAL-H (1 mol dm^{-3}) in hexane (2.0 mL, 2.0 mmol) in the presence of zinc chloride-TMEDA complex (0.250 g, 1.0 mmol) in THF (5 mL). After being stirred for 6 h at −78 °C, the reaction mixture was poured into a mixture of hydrochloric acid (6 mol dm^{-3}, 5 mL) and a saturated ammonium chloride aqueous solution (5 mL). The mixture was extracted with diethyl ether (20 mL×3). The combined extracts were dried over anhydrous sodium sulfate and concentrated. The residue was hydrolyzed with 2 mol dm^{-3} KOH and methanol for 12 h at room temperature. After evaporation of methanol, the residue was extracted with diethyl ether (20 mL×3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. After the *syn*-/*anti*-diol ratio was determined by ^{19}F NMR, the residue was purified by silica-gel column chromatography to give a mixture of *syn*- and *anti*-diol **2b**.

Reduction of 5,5-Difluoro-4-hydroxy-6-dodecanone (1d) with Aluminiun Isopropoxide. A Typical Procedure for *anti*-Diol Synthesis. Aluminium isopropoxide (0.214 g, 1.05 mmol) was dissolved in benzene (5 mL) and to this solution was added **1d** (0.236 g, 1.0 mmol) at room temperature. After being stirred for 18 h at room temperature, the reaction mixture was poured into a mixture of hydrochloric acid (6 mol dm^{-3}, 5 mL), a saturated ammonium chloride aqueous solution (5 mL) and ice. The resultant was extracted with diethyl ether (20 mL×3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The ratio of *syn*- to *anti*-5,5-difluoro-1,3-dodecanediol was determined by ^{19}F NMR before purification. The diol was purified by silica-gel column chromatography.

Spectral data of the diols follow.

2,2-Difluoro-1-phenyl-1,3-hexanediol (2a): IR (CH_2Cl_2) 3582, 3390, 2962, 2932, 1200, 1177, 1109, 1085, 1058, 1038, and 1028 cm^{-1} for syn : anti=91 : 9, 3580, 3378, 3056, 2962, 2932, 1203, 1177, 1109, 1086, 1059, and 1028 cm^{-1} for syn : anti=11 : 89; ^{1}H NMR ($CDCl_3$) δ=7.28 (s, 5H), 5.00 (ddd, J=13.4, 13.4, 3.2 Hz, 1H), 4.1—3.2 (m, 1H), 3.2—2.8 (br s,

1H), 2.2 (br d, J=7.2 Hz, 1H), 2.0—1.2 (m, 4H), and 0.90 (t, J=5.8 Hz, 3H) for **2a**$_{syn}$, 7.26 (s, 5H), 4.99 (ddd, J=12.2, 9.8, 4.2 Hz, 1H), 4.3—3.7 (br s, 1H), 3.7—3.4 (br s, 1H), 2.79 (br d, J=5.4 Hz, 1H), 1.9—1.2 (m, 4H), and 1.1—0.7 (m, 3H) for **2a**$_{anti}$; ^{19}F NMR ($CDCl_3$) δ=−120.00 (d, J=255.1 Hz, 1F) and −129.23 (ddd, J=255.1, 13.4, 13.4 Hz, 1F) for **2a**$_{syn}$, −122.02 (ddd, J=12.2, 9.8, 9.8 Hz, 2F) for **2a**$_{anti}$; MS, m/z (rel intensity) 230 (M^+, 0.5), 212 (0.8), 107 (100). Found: C, 62.83; H, 7.18%. Calcd for $C_{12}H_{16}F_2O_2$: C, 62.60; H, 7.00%.

(*E*)-2,2-Difluoro-1-phenyl-4-hexene-1,3-diol (2b): IR (CH_2Cl_2) 3350, 3062, 3032, 2916, 1672, 1495, 1455, 1380, 1198, 1126, 1083, 1052, 1029, 1010, and 968 cm^{-1} for syn:anti=96:4, 3326, 3034, 2948, 2916, 1673, 1496, 1456, 1439, 1393, 1351, 1241, 1202, 1175, 1125, 1088, 1056, 1029, 1003, and 966 cm^{-1} for syn:anti=8:92; ^{1}H NMR ($CDCl_3$) δ=7.29 (s, 5H), 6.1—5.2 (m, 2H), 4.95 (dd, J=14.6, 9.8 Hz, 1H), 4.16 (ddd, J=14.6, 9.8, 6.0 Hz, 1H), 3.2—2.6 (br s, 1H), 2.6—1.9 (br s, 1H), and 1.69 (d, J=5.8 Hz, 3H) for **2b**$_{syn}$, 7.6—7.1 (br s, 5H), 6.2—5.1 (m, 2H), 4.97 (dd, J=10.8, 10.8 Hz, 1H), 4.30 (ddd, J=10.8, 6.2, 6.2 Hz, 1H), 3.5—2.3 (br s, 2H), and 1.71 (d, J=5.0 Hz, 3H) for **2b**$_{anti}$; ^{19}F NMR ($CDCl_3$) δ=−119.48 (ddd, J=254.0, 9.8, 9.8 Hz, 1F) and −128.08 (ddd, J=254.0, 14.7, 14.7 Hz, 1F) for **2b**$_{syn}$, −120.82 (t, J=11.2 Hz, 2F) for **2b**$_{anti}$; MS, m/z (rel intensity) 210 (M^+-H_2O, 1.0), 140 (45), 107 (33), 104 (100), and 71 (19). Found: C, 63.42; H, 6.33%. Calcd for $C_{12}H_{14}F_2O_2$: C, 63.15; H, 6.18%.

2,2-Difluoro-1,3-diphenyl-1,3-propanediol (2c): IR (CH_2Cl_2) 3336, 3054, 1497, 1457, 1088, 1060, and 1023 cm^{-1} for syn:anti=80:20, 3294, 3092, 3062, 3034, 3014, 2954, 1496, 1457, 1395, 1086, and 1024 cm^{-1} for syn:anti=0:100; ^{1}H NMR (acetone-d_6) δ=7.6—7.0 (m, 10H) and 5.2—4.6 (m, 4H) for **2c**$_{syn}$, 7.5—7.0 (m, 10H) and 5.5—4.9 (m, 4H) for **2c**$_{anti}$; ^{19}F NMR (acetone-d_6) δ=−120.42 (ddd, J=251.5, 11.0, 11.0 Hz, 1F) and −125.77 (ddd, J=251.5, 13.4, 13.4 Hz, 1F) for **2c**$_{syn}$, −120.81 (dd, J=11.0, 11.0 Hz, 2F) for **2c**$_{anti}$; MS, m/z (rel intensity) 264 (M^+, 0.2), 256 (1), 140 (100), and 107 (32). Found: C, 68.35; H, 5.52%. Calcd for $C_{15}H_{14}F_2O_2$: C, 68.17; H, 5.34%.

5,5-Difluoro-4,6-dodecanediol (2d): IR (CH_2Cl_2) 3248, 2922, 2856, 1468, 1402, 1377, 1359, 1326, 1297, 1280, 1235, 1094, 1041, 1022, and 994 cm^{-1} for syn:anti=92:8; 3278, 2956, 2928, 1468, 1235, 1211, 1122, 1110, 1051, 1040, 1022, and 965 cm^{-1} for syn:anti=9:91; ^{1}H NMR ($CDCl_3$) 4.3—3.4 (br s, 1H), 3.2—2.7 (br s, 1H), 2.0—1.1 (m, 14H), and 0.94 (t, J=7.4 Hz, 3H) for **2d**$_{syn}$, 4.3—3.4 (br s, 1H), 2.8—2.2 (br s, 1H), 1.9—1.1 (m, 14H), 0.94 (t, J=5.6 Hz, 3H), and 0.84 (t, J=4.8 Hz, 3H) for **2d**$_{anti}$; ^{19}F NMR ($CDCl_3$) δ=−119.43 (ddd, J=256.4, 7.3, 7.3 Hz, 1F) and −130.92 (ddd, J=256.4, 17.1, 17.1 Hz, 1F) for **2d**$_{syn}$, −124.79 (dd, J=11.0, 11.0 Hz, 2F) for **2d**$_{anti}$; MS, m/z (rel intensity) 238 (M^+, 0.5), 115 (42), 97 (82), and 73 (100). Found: C, 60.55; H, 10.21%. Calcd for $C_{12}H_{24}F_2O_2$: C, 60.48; H, 10.15%.

4,4-Difluoro-2-methyl-3,5-undecanediol (2e): IR (CH_2Cl_2) 3360, 2856, 2926, 1468, 1211, 1182, 1120, 1088, and 1023 cm^{-1} for syn:anti=88:12; 3296, 2956, 2922, 1476, 1470, 1214, 1126, 1110, 1089, 1062, and 1052 cm^{-1} for syn:anti=0:100; ^{1}H NMR ($CDCl_3$) δ=4.2—3.3 (m, 2H), 3.1—2.6 (m, 2H), 2.4—1.8 (m, 1H), 1.8—1.2 (m, 10H), and 1.2—0.7 (m, 9H) for **2e**$_{syn}$, 4.2—3.3 (m, 2H), 2.6—2.2 (m, 2H), 2.2—1.8 (m, 1H), 1.8—1.1 (m, 10H), 0.97 (d, J=7.0 Hz, 6H), and 0.91 (t, J=5.4 Hz, 3H) for **2e**$_{anti}$; ^{19}F NMR ($CDCl_3$) δ=−117.19 (dt, J=258.80, 6.1 Hz, 1F) and −128.04 (dt, J=258.8, 18.3 Hz, 1F) for **2e**$_{syn}$, −122.39 (dd, J=24.4, 9.8 Hz, 2F) for **2e**$_{anti}$; MS, m/z (rel intensity) 195 (M^+-i-Pr, 24) and 73 (100). Found: C, 60.53; H, 10.25%. Calcd for $C_{12}H_{24}F_2O_2$: C, 60.48; H, 10.15%.

4,4-Difluoro-2,2-dimethyl-3,5-undecanediol (2f): IR (CH_2Cl_2) 3360, 2956, 2926, 1468, 1069, and 1019 cm^{-1} for syn:anti=77:23; ^{1}H NMR ($CDCl_3$) δ=4.2—3.2 (m, 2H), 2.9—2.4 (m, 2H), 2.0—1.2 (m, 10H), and 1.2—0.8 (m, 12H) for **2f**$_{syn}$; ^{19}F NMR ($CDCl_3$) δ=−112.88 (d, J=256.4 Hz, 1F) and −128.18 (ddd, J=256.4, 23.2, 13.4 Hz, 1F) for **2f**$_{syn}$, −117.32 (dd, J=260.0, 15.9 Hz, 1F) and −122.48 (dd, J=260.0, 24.4 Hz, 1F) for **2f**$_{anti}$; MS, m/z (rel intensity) 197 (M^+-2H_2O, F, 10) and 87 (100). Found: C, 62.01; H, 10.43%. Calcd for $C_{13}H_{26}F_2O_2$: C, 61.88; H, 10.39%.

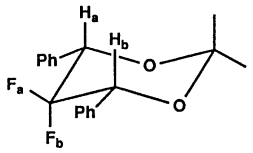
(*E*)-5,5-Difluoro-2-dodecene-4,6-diol (2g): IR (CH_2Cl_2) 3356, 2952, 2924, 1458, 1449, 1119, 1080, 1042, and 967 cm^{-1} for syn:anti=94:6, 3302, 2950, 2926, 1471, 1203, 1121, 1097, 1079, 1052, and 1026 cm^{-1} for syn:anti=5:95; ^{1}H NMR ($CDCl_3$) δ=6.2—5.2 (m, 2H), 4.7—3.4 (m, 2H), 2.6—1.9 (br s, 2H), 1.9—1.1 (m, 10H), 1.73 (d, J=5.2 Hz, 3H), and 0.86 (t, J=4.8 Hz, 3H) for **2g**$_{syn}$, 6.2—5.2 (m, 2H), 4.7—3.4 (m, 2H), 3.1—2.4 (br s, 2H), 1.9—1.1 (m, 10H), 1.75 (d, J=5.6 Hz, 3H), and 0.87 (t, J=5.0 Hz, 3H) for **2g**$_{anti}$; ^{19}F NMR ($CDCl_3$) δ=−119.80 (d, J=255.1 Hz, 1F) and −129.70 (ddd, J=255.1, 15.9, 14.7 Hz, 1F) for **2g**$_{syn}$, −123.39 (ddd, J=13.4, 9.8, 8.6 Hz, 2F) for **2g**$_{anti}$; MS, m/z (rel intensity) 236 (M^+, 0.05), 115 (12), and 71 (100). Found: C, 61.23; H, 9.51%. Calcd for $C_{12}H_{22}F_2O_2$: C, 61.00; H, 9.38%.

2,2-Difluoro-1-phenyl-1,3-nonanediol (2h): IR (CH_2Cl_2) 3298, 2954, 2926, 1467, 1455, 1193, 1116, 1081, 1046, 1027, and 1004 cm^{-1} for syn:anti=92:8, 3350, 2946, 2924, 1469, 1458, 1174, 1119, 1085, and 1047 cm^{-1} for syn:anti=5:95; ^{1}H NMR ($CDCl_3$) δ=7.26 (s, 5H), 4.98 (dd, J=18.3, 18.3 Hz, IH), 4.1—3.2 (m, 1H), 3.1—2.8 (br s, 1H), 2.08 (br d, J=7.4 Hz, 1H), 1.9—1.0 (m, 10H), and 0.83 (t, J=4.8 Hz, 3H) for **2h**$_{syn}$, 7.5—7.1 (m, 5H), 5.4—4.7 (m, 2H), 4.5—3.7 (m, 2H), 1.8—1.0 (m, 10H), and 0.87 (t, J=4.8 Hz, 3H) for **2h**$_{anti}$; ^{19}F NMR ($CDCl_3$) δ=−120.16 (d, J=260.0 Hz, 1F) and −129.30 (ddd, J=260.0, 18.3, 18.3 Hz, 1F) for **2h**$_{syn}$, −121.84 (dd, J=13.4, 23.2 Hz, 2F) for **2h**$_{anti}$; MS, m/z (rel intensity) 272 (M^+, 0.1), 254 (0.5), and 107 (100). Found: C, 66.33; H, 8.24%. Calcd for $C_{15}H_{22}F_2O_2$: C, 66.16; H, 8.14%.

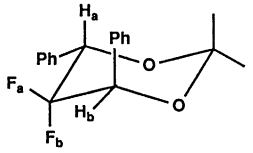
Dimethyl Acetal (4h) of 2h: In a 50-mL one-necked flask equipped with a magnetic stirrer bar and a refluxing condenser with an inlet tube for argon, were placed **2h** (0.272 g, 1.0 mmol), p-toluenesulfonic acid monohydrate (0.020 g, 0.11 mmol), 2,2-dimethoxypropane (1.04 g, 10.0 mmol), and THF (5 mL). The mixture was heated at reflux temperature for 24 h, cooled to room temperature. The reaction mixture was poured into a saturated sodium hydrogencarbonate aqueous solution (10 mL), and extracted with diethyl ether (20 mL×3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica-gel column chromatography to give **4h** (0.302 g, 97% yield): IR (neat) 2986, 2952, 2926, 1378, 1244, 1227, 1197, 1171, 1122, 1098, 1061, and 1032 cm^{-1} for the 1,3-anti isomer; ^{1}N NMR ($CDCl_3$, 200 MHz) δ=7.6—7.3 (m, 5H), 4.95 (dd, J=23.2, 2.0 Hz, 1H), 4.00 (ddd, J=23.2, 8.0, 3.5 Hz, 1H), 1.9—1.6 (m, 2H), 1.62 (s, 3H), 1.57 (s, 3H), 1.4—1.2 (m, 8H), and 0.91 (t, J=6.0 Hz, 3H) for the 1,3-syn isomer, 7.6—7.3 (m, 5H), 4.98 (dd, J=18.3, 9.8 Hz, 1H), 3.97 (dddd, J=18.3, 9.8, 9.8, 4.6 Hz, 1H), 1.9—1.6 (m, 2H), 1.51 (s, 3H), 1.47 (s, 3H), 1.4—1.2 (m, 8H), and 0.92 (t, J=6.0 Hz, 3H) for the 1,3-anti isomer;

^{19}F NMR ($CDCl_3$) δ=−121.34 (d, J=247.8 Hz, 1F) and −136.10 (dt, J=247.8, 23.2 Hz, 1F) for the 1,3-syn isomer, −113.56 (ddd, J=236.8, 18.3, 9.8 Hz, 1F) and −118.05 (ddd, J=236.8, 18.3, 9.8 Hz, 1F) for the 1,3-anti isomer; MS, m/z (rel intensity) 297 (M^+−Me, 2.5), 107 (100), and 60 (92).

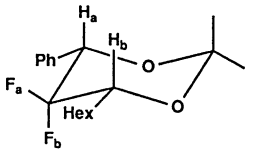
Dimethyl acetal (**4c**) of **2c** was prepared in a similar manner. **4c**: IR (neat) 1261, 1226, 1097, 1069, 1055, and 1029 cm^{-1} for the 1,3-anti isomer; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=7.6—7.3 (m, 10H), 5.15 (dd, J=22.0, 2.0 Hz, 2H), 1.75 (s, 3H), and 1.71 (s, 3H) for the 1,3-syn isomer, 7.6—7.4 (m, 10H), 5.17 (t, J=14.7 Hz, 2H), and 1.61 (s, 6H) for the 1,3-anti isomer; ^{19}F NMR ($CDCl_3$) δ=−119.17 (d, J=251.5 Hz, 1F) and −133.00 (dt, J=251.5, 22.0 Hz, 1F) for the 1,3-syn isomer, −111.44 (t, J=14.7 Hz, 2F) for the 1,3-anti isomer; MS, m/z (rel intensity) 304 (M^+, 0.1) and 140 (100).



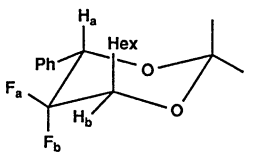
$4c_{syn}$
$J_{Ha\text{-}Fa}=J_{Hb\text{-}Fa}$= 2.0 Hz
$J_{Ha\text{-}Fb}=J_{Hb\text{-}Fb}$=22.0 Hz



$4c_{anti}$
$J_{Ha\text{-}Fa}=J_{Hb\text{-}Fa}$=14.7 Hz
$J_{Ha\text{-}Fb}=J_{Hb\text{-}Fb}$=14.7 Hz



$4h_{syn}$
$J_{Ha\text{-}Fa}$=2.0 Hz
$J_{Hb\text{-}Fa}$=0 Hz
$J_{Ha\text{-}Fb}=J_{Hb\text{-}Fb}$=23.2 Hz



$4h_{anti}$
$J_{H\text{-}F}$=18.3, 9.8 Hz.

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15) The van der Waals radius of fluorine is 0.147 nm. Cf. 0.120 nm for hydrogen.

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