Catalyzed Reformatsky Reactions with Ethyl Bromofluoroacetate for the Synthesis of α-Fluoro-β-hydroxy Acids

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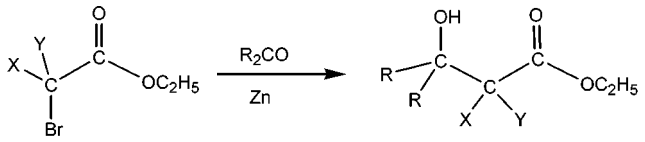
Received May 21, 2001

The presence of catalytic amounts of $CeCl_3$ improves yields and simplifies procedure in the Reformatsky reactions of ethyl bromofluoroacetate with aldehydes and ketones to generate diastereomeric mixtures of α-fluoro-β-hydroxy esters, some of which can be separated by crystallization or column flash chromatography. Diastereomerically pure α-fluoro-β-hydroxy acids are obtained by mild alkaline hydrolysis of the resolved α-fluoro-β-hydroxy esters. Detailed NMR data of new α-fluoro-β-hydroxy esters and α-fluoro-β-hydroxy acids are also presented.

Introduction

The Reformatsky reactions of ethyl bromoacetate **1c** or its fluorinated analogues **1a** and **b** with carbonyl compounds, to generate β-hydroxyesters **4** or their fluorinated analogues **2** and **3** (Scheme 1), is a well-known synthetic methodology, with widespread use in a number of multistep syntheses. The version of the Reformatsky that uses ethyl bromofluoroacetate **1a** to obtain α-fluoro-β-hydroxy esters **2** was first attempted 45 years ago[1] with zinc and benzene, toluene, or xylene as the solvent. At about the same time, classical Aldol-type condensation reactions of ethyl fluoroacetate with carbonyl compounds were reported to give the same products, using the sodium enolate of this ester, which was generated by sodium hydride[2] or sodium ethoxide.[3] Poor yields (∼20%) were generally obtained in these studies, but over the last two decades such condensation reactions, using the lithium enolate of the monofluoroester, have given better results.[4,5] This direct condensation process is reported to give good yields of aldol-type products and also to provide some significant diastereoselectivity, but it has the serious disadvantage of using the very toxic ethyl fluoroacetate.[6] Some improvements of the original Reformatsky methodology of halomonofluoro esters have appeared in the more recent literature. One of these involves the use of ethyl chlorofluoroacetate with Mg and I_2 in benzene,[7] and recently, it was reported that the Reformatsky reaction of aldehydes with ethyl chlorofluoroacetate in the presence of lanthanide catalysts, using DMA as the solvent,[8] provides high isolated yields with aldehydes but only 40% with ketones. Machleidt and Wessendorf reported the use of bromofluoro ester **1a** and Zn, in the presence of I_2, in a binary mixture of ether−THF,[9] whereas Brandänge and co-workers were able to carry out the condensation by refluxing the starting bromofluoroester **1a** and a ketone with a THF slurry of Zn to give acceptable yields.[10] Linderman and co-workers mimicked Hallinan and Fried's difluoro-Reformatsky methodology[11] to synthesize a number of α-fluoro-β-hydroxy esters.[12]

Scheme 1. Classical Reformatsky Reaction



1a: X = H; Y = F
b: X = Y = F
c: X = Y = H

2: X = H; Y = F
3: X = Y = F
4: X = Y = H

In almost all of the above cases, the reported Reformatsky reactions are reasonably efficient. However, improvements in yields, shorter reaction times, and procedure simplifications are possible, and some such improvements are reported in this paper.

On the other hand, until the present work, no good method had been reported for the hydrolysis of the α-fluoro-β-hydroxy esters to their respective carboxylic acids. Indeed, reports indicated that such esters are largely destroyed when subjected to alkaline hydrolysis, with very poor yields of acids (14%) being obtained.[2] Apparently, use of aqueous NaOH, even at low concentrations, gives rise to destructive fluoride elimination. If one protects the β-hydroxyl group, for example by ben-

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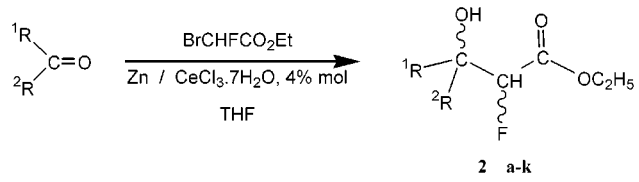
10.1021/jo015778x CCC: $22.00
Published on Web 12/14/2001

Scheme 2. $CeCl_3$-Catalyzed Reformatsky Reaction of Ethyl Bromofluoroacetate



2 a-k

zylation,[7,13] the problems with hydrolysis disappear, but protection and eventual deprotection will make any synthesis longer. Acid-catalyzed hydrolysis of α-fluoro-β-hydroxy esters is also a low-yield procedure, with typical yields of 10−14%. Under these conditions, elimination competes with the desired hydrolysis,[14] making this approach also not useful for the synthesis of α-fluoro-β-hydroxy acids. α-Fluoro-β-hydroxyacids *have* been previously prepared in 43−54% yield by a procedure of very limited general applicability, via the diazotization reactions of β-hydroxy-α-amino acids such as threonine or serine using polyhydrogen fluoride/pyridine.[15]

In this paper, we report that alkaline hydrolysis can be accomplished under very mild conditions and using short reaction times with excellent yields being obtained *if water is not used as the solvent*. In this way, we have been able to synthesize a variety of α-fluoro-β-hydroxy acids **5**, some of them as pure racemic diastereomers.

We wish to present our experiences on the Reformatsky reaction of ethyl bromofluoroacetate **1a**, catalyzed by $CeCl_3$, by using formally the same methodology which Shen and Qi reported with ethyl bromodifluoroacetate and the mild alkaline hydrolysis of α-fluoro-β-hydroxy esters **2** to obtain α-fluoro-β-hydroxy acids **5**. A detailed information on NMR data of **2** and **5** is also presented.

Results and Discussion

Recent years have seen the development of synthetic procedures involving lanthanide metals, especially cerium, in organometallic reactions. One of the most important examples is the conversion of organollithium compounds to organocerium derivatives by $CeCl_3$.[16] It is well-known that this salt exerts a strong activation of carbonyl compounds toward addition of organometallics.[17] Inspired in this fact and by Shen and Qi's use of cerium methodology for the *di*fluoro-Reformatsky reaction,[9,18] we carried out a systematic examination of the Reformatsky reaction of ethyl bromofluoroacetate **1a** with ketones and aldehydes, in the presence of 4 molar % $CeCl_3 \cdot 7H_2O$ (Scheme 2).

The procedure involves simply mixing the reactants and stirring them vigorously at room temperature for 0.5−2 h under a blanket of dry N_2. Completion of the reaction is observed by a change of the typical color of Zn to a brownish slurry. The reaction is very clean, with few side products, and when starting with symmetrical ketones a simple flash filtration of the crude product through a short silica gel pad is sufficient to purify the product. Yields of isolated products range from 60 to 95%, and the results are summarized in Table 1.

As seen in Table 1, even relatively unreactive ketones, such as benzophenone (entry 9) and pinacolone (entry 7), react very efficiently and give products in acceptable yield.

It has been reported that organocerium reagents retain strong nucleophilicity but show a very reduced tendency to effect deprotonation.[19] This is probably the reason $CeCl_3$ enhances the outcome of the Reformatsky process. In the absence of carbonyl compounds, the bromofluoroesters do not appear to react with the Zn, as evidenced by ^{19}F NMR analyses of the crude reaction mixtures. However, addition of pinacolone to the mixture leads to rapid reaction. It seems that the presence of carbonyl compounds stimulates the formation of the organometallic intermediate, creating an environment that favors formation of condensation product in preference to the reduction pathway. Although severe steric hindrance around the carbonyl group causes the reduction product to increase somewhat, the condensation pathway is still favored.

Stereochemistry. As expected, unsymmetrical ketones and aldehydes gave rise to the diastereoisomeric erythro and threo mixtures, separable in some cases by conventional flash column chromatography or by fractional crystallization (Table 1). In all cases, both diastereomers are readily distinguishable from each other by their NMR spectra. When starting from aldehydes, the correlation found by Elkik and Francesch[20] works out consistently in such way that the erythro isomer always exhibits a ^{19}F NMR signal at lower field compared to that exhibited by the respective threo isomer. The threo isomer is also recognized to have a typical coupling constant $J_{H\beta-F}$ of 16−20 Hz, significantly larger than that of the erythro isomer.

After the cerium chloride-catalyzed Reformatsky reaction with acetophenone, it was possible to crystallize the (*RR*/*SS*) diastereomer of ethyl 2-fluoro-3-hydroxy-3-phenylbutanoate **2h** (Table 1, entry 8) directly from the crude product mixture giving 92.5% purity. Further purification by recrystallization from hot hexanes could produce 95% diastereomerically pure (*RR*/*SS*) **2h**, the relative stereochemistry of which was confirmed by X-ray crystallographic analysis. In a similar fashion, both diastereomers of ethyl 2-fluoro-3-hydroxy-3,4-diphenylbutanoate (**2k** and **2l**) (Table 1, entry 10) could be separated by flash column chromatography, with the stereochemistry of **2k** also being confirmed by X-ray analysis.

No attempts were made to separate the diasteromeric mixtures derived from aldehydes. However, because of adequate signal resolution, spectroscopic NMR assignments were able to be made. Thus, on the basis of ^{19}F NMR integration, it was possible to estimate that, within experimental error, the ratio of isomers was in each case

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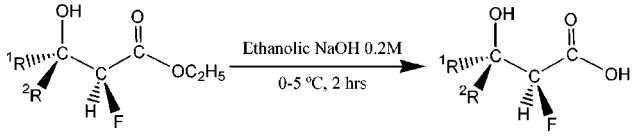
Table 1. Catalyzed Reformatsky Reactions of Ethyl Bromofluoroacetate

entry	product	R_1	R_2	yield[a] (%)	reported yield (%)	erythro/threo ratio
			From Aldehydes			
1	**2a**	H	*n*-C_4H_9	83		48:52[b]
2	**2b**	H	n- C_5H_{11}	90	77	48:52[b]
3	**2c**	H	Ph	92	65[c]	50:50[b]
			From Symmetrical Ketones			
4	**2d**	Me	Me	89	14[d]	
5	**2e**	Et	Et	90		
6	**2f**	$CH_2CH_2CH_2CH_2CH_2$		94	44[e]	

entry	product	R_1	R_2	yield[a] (%)	reported yield (%)	(*RR*/*SS*)/(*RS*/*SR*) ratio
			From Unsymmetrical Ketones			
7	**2g**	*t*-Bu	Me	61		59:41[b]
8	**2h** and **2i**	Ph	Me	90	29[e]	42:58[f]
9	**2j**	Ph	Ph	85	14[e]	
10	**2k** and **2l**	Ph	Bn	92		42:58[f]
11	**2m**	Bn	Bn	86		

[a] Yield of isolated products. [b] Relative composition estimated by ^{19}F NMR integration and the diastereomers were not separated. [c] Reference 10. [d] Reference 2. [e] Reference 1. [f] The diastereomeric mixture could be separated (95% pure) by crystallization and column chromatography.

Scheme 3. Mild Alkaline Hydrolysis of α-Fluoro-β-hydroxy Esters 1



2 h-m

5 h : R_1 = Ph ; R_2 = Me , 90%
i : R_1 = Me; R_2 = Ph , 89%
j : R_1 = Ph ; R_2 = Ph , 88%
k : R_1 = Ph ; R_2 = Bn , 95%
l : R_1 = Bn ; R_2 = Ph , 93%
m : R_1 = R_2 = Bn ; 96%

1:1. Such lack of significant diastereoselectivity would certainly constitute a disadvantage of this method, if stereocontrol is needed. A somewhat higher diastereoselectivity is reported for the condensations of ethyl fluoroacetate enolate (promoted with HMDS)[21] but, as mentioned before, such starting material is a very toxic compound.

Mild Alkaline Hydrolysis of α-Fluoro-β-hydroxy Esters, 2. Use of dilute aqueous sodium hydroxide led to no success, even when at low concentration. Using "anhydrous hydroxide" (generated using potassium *tert*-butoxide in dry ether)[22] was equally unsuccessful, apparently because the strong basicity of the medium leads to decomposition of the α-fluoro-β-hydroxy esters.

Use of a cold solution of sodium hydroxide in absolute ethanol in concentrations of ~0.2 M provided a very effective condition for the hydrolysis, resulting in the synthesis of α-fluoro-β-hydroxy acids, **5**, in yields >90% (Scheme 3). In a typical experiment, the starting α-fluoro-β-hydroxy ester is dissolved in absolute ethanol to a concentration of ~0.2 M and then cooled. A cold solution of 0.2 M sodium hydroxide in absolute ethanol was then added dropwise and the mixture stirred for 1−2 h. Purification of the products can be accomplished by crystallization from a binary mixture of benzene/hexanes.

Although the hydrolyses reported here are only of those esters prepared *from ketones* (because these were the only α-fluoro-β-hydroxy acids that proved useful for conversion to the β-lactones), there is no reason to believe that the esters derived from aldehydes will not undergo equally efficient hydrolysis.

Stereochemistry. Typically, alkaline hydrolysis of esters occurs by nucleophilic addition to the carbonyl group without disturbing an α-chiral center, unless especially acidic protons are present in the α-position. It is known that fluorine atoms decrease acidity of α-hydrogens, because of the resultant Iπ repulsion in such planar carbanions.[23] α-Fluoro esters should therefore be less acidic than their nonfluorinated counterparts, and they should thus be hydrolyzed by the normal $B_{AC}2$ pathway. As such, it would be expected that the alkaline hydrolysis of α-fluoro-β-hydroxy esters **2** should occur with retention of the configuration at the α-chiral centers. Consistent with this assumption, ^{19}F NMR analyses of the crude reaction mixtures revealed a relative composition of diastereomers nearly identical to that of the starting materials. For example, a crude product with a composition of diastereomers 95:5 was obtained when starting from a mixture 95:5 of (*RR*/*SS*)/(*RS*/*SR*) of **2h**; the logical conclusion is that the 95% isomeric acid is also the *RR*/*SS* diasteromer. There is also a logical resemblance of the NMR data of the α-fluoro-β-hydroxy acids **5** to those of their starting α-fluoro-β-hydroxy esters **2**, particularly the chemical shift of the fluorine atom, the signal of the proton in the α-position, the signals of protons or carbons of the methyl or methylene groups attached to the β-carbon and the ^{13}C NMR signals of the β-carbon and of the carbonyl group (Table 2).

Additionally, as it can be seen in Table 2, the NMR data of the diasteromeric α-fluoro-β-hydroxy acids are consistent with the earlier reported empirical correlations reported by Welch for α-fluoro-β-hydroxy esters, that is that the ^{13}C NMR signal of the aliphatic carbon attached to the β-position of the (*RR*/*SS*) diastereomer usually appears somewhat upfield with respect to the analogous signal of the (*RS*/*SR*) diastereomer. Therefore, our assignment of the relative configuration of the acids is

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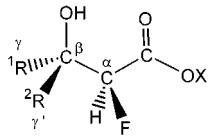
Table 2. Comparative NMR Data of α-Fluoro-β-hydroxy Esters 2 and α-Fluoro-β-hydroxy Acids 5: Representative Signals



					^{1}H NMR		^{19}F NMR	^{13}C NMR			
entry	substituents	compd			Hγ or Hγ′	Hα		Cγ or Cγ′	Cβ	Cα	−COO−
1	R^1 = Ph; R^2 = Me	(*R**,*R**)-**2h**	X = Et	δ (ppm)[a]	1.70	4.92	−195.12	25.59	74.94	93.03	168.22
				J (Hz)[b]	2.4	47.7	46.9	2.6	20.7	193.8	24.7
2	R^1 = Ph; R^2 = Me	(*R**,*R**)-**5h**	X = H	δ (ppm)[a]	1.74	4.98	−193.56	25.32	75.05	92.91	171.68
				J (Hz)[b]	2.4	47.4	47.4	2.7	20.8	194.8	25.1
3	R^1 = Me; R^2 = Ph	(*R**,*S**)-**2i**	X = Et	δ (ppm)[a]	1.67	5.00	−192.53	26.19	75.10	93.59	168.66
				J (Hz)[b]	2.4	47.7	46.9	4.0	19.7	197.8	23.7
4	R^1 = Me; R^2 = Ph	(*R**,*S**)-**5i**	X = H	δ (ppm)[a]	1.70	5.08	−191.32	26.34[c]	74.44[c]	93.89[c]	169.10[c]
				J (Hz)[b]	2.3	47.6	47.4	3.9	20.6	188.7	25.1
5	R^1 = R^2 = Ph	**2j**	X = Et	δ (ppm)[a]		5.48	−189.58		78.64	91.98	168.83
				J (Hz)[b]		47.1	46.9		20.1	198.9	23.6
6	R^1 = R^2 = Ph	**5j**	X = H	δ (ppm)[c]		6.10	−189.95		78.44	91.96	168.73
				J (Hz)[b]		46.2	44.9		21.7	188.9	25.1
7	R^1 = Ph; R^2 = Bn	(*R**,*R**)-**2k**	X = Et	δ (ppm)[a]	3.32, 3.38	5.12	−197.12	44.19	77.45	91.84	167.84
				J (Hz)[b]	1.5, 1.8	47.7	49.1	3.5	19.7	192.9	24.7
8	R^1 = Ph; R^2 = Bn	(*R**,*R**)-**5k**	X = H	δ (ppm)[a]	3.34, 3.39	5.15	−195.94	44.06	77.62	92.06	171.36
				J (Hz)[b]	1	47.7	47.4	4.2	19.8	193.5	25.3
9	R^1 = Bn; R^2 = Ph	(*R**,*S**)-**2l**	X = Et	δ (ppm)[a]	3.13, 3.34	4.88	−191.16	45.26	76.73	90.88	169.45
				J (Hz)[b]	2.7 ea	47.1	47.1	2.6	18.6	202.0	22.7
10	R^1 = Bn; R^2 = Ph	(*R**,*S**)-**5l**	X = H	δ (ppm)[a]	3.13, 3.34	4.92	−190.04	45.28	77.02	90.61	173.57
				J (Hz)[b]	2.7, 2.2	46.5	47.1		19.5	199.51	23.9
11	R^1 = R^2 = Bn	**2m**	X = Et	δ (ppm)[a]	2.74, 2.94, 2.97	4.52	−195.79	42.38, 42.75	75.06	88.51	169.87
				J (Hz)[b]	2.3, 3.3, 2.1	45.6	44.9		20.6	196.4	22.1
12	R^1 = R^2 = Bn	**5m**	X = H	δ (ppm)[a]	2.70, 2.94	4.57	−194.71	41.98	75.22	88.46	173.41
				J (Hz)[b]	2, 3	45.9	46.9		20.6	194.9	23.7

[a] In $CDCl_3$; reference: TMS for ^{1}H; $CFCl_3$ for ^{19}F NMR; $CDCl_3$ at 77.00 ppm for ^{13}C NMR. [b] J_{HF} values in ^{1}H and ^{19}F NMR; or J_{CF} values in ^{13}C NMR. [c] In DMSO-d_6.

dependent upon our assumption of retention of configuration during hydrolysis of the esters whose relative configurations were determined by X-ray analysis, also by extending the application of the Welch's configurational correlations.[4]

Pure diastereomers of α-fluoro-β-hydroxy acids **5h**,**i**,**k**,**l** could be obtained by conventional crystallization using binary mixtures of benzene/hexanes.

Conclusion

The Reformatsky reaction of ethyl bromofluoroacetate in the presence of $CeCl_3 \cdot 7H_2O$ is the most efficient procedure thus far reported for preparing α-fluoro-β-hydroxy esters from aldehydes or ketones. With a 4% molar concentration of $CeCl_3 \cdot 7H_2O$, isolated yields ranged from 60 to 95%. The reaction procedure is very simple, and fast flash column chromatography can be readily used to obtain pure products. As expected, aldehydes and unsymmetrical ketones give rise to mixtures of erythro and threo diastereomers[24] with low diastereoselectivity. However, in some cases the mixtures can be separated by conventional chromatography. Mild alkaline hydrolysis with a cold 0.2 M ethanolic solutions of sodium hydroxide gives rise to α-fluoro-β-hydroxy acids **5** in excellent yields. In this manner, the synthesis of α-fluoro-β-hydroxy acids **5** has become a straightforward process. Pure acid diastereomers were able to be obtained and used in our syntheses of α-fluoro-β-lactones and diastereomerically pure monofluoroalkenes, work that is underway.

(24) The terms erythro and threo make sense if aldehydes are the starting materials; for those products bearing two R groups in the β position, Welch used the terms anti and syn (ref 4).

Experimental Section

Reagents. Ethyl bromofluoroacetate of 98% purity was purchased from SynQuest and used without further purification. Aldehydes and ketones were purchased from Aldrich (purities ranging from 97% to 99.9%) and used without any additional treatment. THF from Fisher was dried with Na and K (with benzophenone as indicator). $CeCl_3 \cdot 7H_2O$ stored under argon was purchased from Aldrich; after each use, it was purged with argon.

Instruments and Materials. NMR spectra were recorded on a VXR300 instrument or a Gemini300 or a Mercury 300 at 299.95 MHz for ^{1}H, 75.42 MHz for ^{13}C, and 282.23 MHz for ^{19}F NMR spectra and in $CDCl_3$ as solvent, unless otherwise mentioned. TMS, $CDCl_3$, and $CFCl_3$ were used as internal standards for ^{1}H, ^{13}C, and ^{19}F NMR spectra, respectively. Melting points were measured in a Thomas-Hoover capillary apparatus and are not corrected. Distillation of starting materials and flame drying the reaction apparatus under a blanket of N_2 or argon are strongly encouraged to obtain better yields and shorter reaction times.

Synthesis of α-Fluoro-β-hydroxy Esters 2. General Procedure. A round-bottomed flask was dried, purged with argon, and charged with 0.60 g of freshly etched zinc, 48 mg of $CeCl_3 \cdot 7H_2O$, 5 mmol of the respective carbonyl starting material, and 8 mL of dry THF and capped with a septum. The slurry was stirred vigorously, and 7.5 mmol of ethyl bromofluoroacetate was added dropwise. The mixture was allowed to stir until the gray color of zinc was changed to a brownish slurry; typically, it takes 2−6 h, and depending on the use of some excess of zinc the change of color is not fully evident. Then 10 mL of ethyl acetate was added to quench the

reaction, followed by addition of 10 mL of a saturated aqueous solution of NH_4Cl and 10 mL of brine. The mixture was filtered by suction over a bed of silica, and the residue was washed with ethyl acetate. The filtrate was transferred to a separatory funnel, and the organic layer was separated, the aqueous phase was extracted with ethyl acetate (3 × 20 mL), and the organic phases were combined and dried with magnesium sulfate, filtered over a bed of silica, and evaporated. The products were then further purified by flash column chromatography, eluting with some appropriate solvent carefully chosen by TLC. For an improved resolution of erythro/threo mixtures, chromatography with a bigger column may be needed.

Ethyl 2-Fluoro-3-hydroxyheptanoate, 2a. Starting from Valeraldehyde. The diastereomeric product mixture (48:52) was purified by flash column chromatography, eluted with a binary mixture 85:15 hexanes/ethyl acetate. The stereoisomers were not separated by the column. Yield: 83%. Spectral properties: ^{1}H NMR of the diastereomeric mixture: δ 0.89 and 0.90 ppm, two doublets, J_{HH} = 7.2 Hz, 3H; 1.30 ppm, t, J_{HH} = 7.2 Hz, 3H; 1.36 and 1.60 ppm, m, 6H; 2.27 ppm, d, J_{HF} = 8.7 Hz (52% of 1H, threo isomer); 2.58 ppm, d, J_{HF} = 6.0 Hz (48% of 1H, erythro isomer); 3.96 ppm, m, overlapped with 4.02 ppm, m, 1H; 4.27 ppm, q, J_{HH} = 7.2 Hz, overlapped with 4.28 ppm, q, J_{HH} = 7.2 Hz, 2H; 4.81 ppm, dd, $J_{H\alpha-F}$ = 48.4 Hz, J_{HH} = 2.5 Hz, 52% de 1H; 4.85 ppm, dd, $J_{H\alpha-F}$ = 48.4 Hz; J_{HH} = 3.7 Hz, 48% de 1H. ^{19}F NMR: δ −200.11 ppm, dd, $J_{H\alpha-F}$ = 49.1 Hz, J_{HF} = 17.2 Hz (erythro isomer, 47.7% of the mixture); −208.73 ppm, dd, $J_{H\alpha-F}$ = 49.1 Hz, $J_{H\beta-F}$ = 24.4 Hz (threo isomer, 52.3% of the mixture).

Ethyl 2-Fluoro-3-hydroxyoctanoate, 2b. Starting from Hexanal. A diastereomeric product mixture (48:52) was obtained after aqueous workup and solvent evaporation. Yield of crude product mixture: 90%. Spectral properties: ^{19}F NMR: δ −199.8 ppm, dd, $J_{H\alpha-F}$ = 49.1 Hz, $J_{H\beta-F}$ = 18 Hz (48% of the mixture); −207.6 ppm, dd, $J_{H\alpha-F}$ = 49 Hz, $J_{H\beta-F}$ = 24 Hz (52% of the mixture), signals which match those reported previously.[13]

Ethyl 2-Fluoro-3-hydroxy-3-phenylpropanoate, 2c. Starting from Benzaldehyde. A diastereomeric product mixture (50:50) was obtained after aqueous workup and solvent evaporation. Yield of crude product mixture: 92%. Spectral properties: ^{19}F NMR: δ −199.0 ppm, dd, $J_{H\alpha-F}$ = 49 Hz, $J_{H\beta-F}$ = 18 Hz (49.8% of the mixture, erythro isomer); −204.4 ppm, dd, $J_{H\beta-F}$ = 49 Hz, $J_{H\beta-F}$ = 24 Hz (50.2% of the mixture, threo isomer), signals which match those reported previously.[13,21]

Ethyl 2-Fluoro-3-hydroxy-3-methylbutanoate, 2d. Starting from Acetone. The product was flash eluted with ethyl acetate, giving rise to 89% yield of an oil. Spectral properties: ^{1}H NMR: δ 1.28 ppm, s, overlapped with 1.31 ppm, t, J_{HH} = 7.2 Hz, 9H; 2.82 ppm, broad singlet, 1H; 4.28 ppm, q, J_{HH} = 7.2 Hz, 2H; 4.64 ppm, d, $J_{H\alpha-F}$ = 48.0 Hz, 1H. ^{19}F NMR: δ −196.06 ppm, d, $J_{H\alpha-F}$= 49.1 Hz. ^{13}C NMR: δ 14.24 ppm; 25.07 ppm, d, J_{CF} = 8.6 Hz, overlapped with 25.12 ppm, d J_{CF} = 8.1 Hz; 61.91 ppm; 71.55 ppm, d, J_{CF} = 21.2 Hz; 93.71 ppm, d, J_{CF} = 191.4 Hz; 168.58 ppm, d, J_{CF} = 23.7 Hz.

Ethyl 3-Ethyl-2-fluoro-3-hydroxypentanoate, 2e. Starting from 3-Pentanone. The product was flash eluted with ethyl acetate, giving rise to 90% yield of an oil. Spectral properties: ^{1}H NMR: δ 0.94 ppm, t, J_{HH} = 7.5 Hz, overlapped with 0.96 ppm, t, J_{HH} = 7.5 Hz, 6H; 1.34 ppm, t, J_{HH} = 7.2 Hz, 3H; 1.62 ppm, m, J_{HH} = 7.5 Hz, overlapped with 1.64 ppm, m, J_{HH} = 7.5 Hz, 4H total; 2.62 ppm, broad singlet, 1H; 4.31 ppm, q, J_{HH} = 7.2 Hz, 2H; 4.83 ppm, d, $J_{H\alpha-F}$ = 47.7 Hz, 1H. ^{19}F NMR: δ −199.66 ppm, d, $J_{H\alpha-F}$ = 49.1 Hz. ^{13}C NMR: δ 7.22 ppm; 7.50 ppm; 14.16 ppm; 26.92 ppm, d, J_{CF} = 3.0 Hz; 27.97 ppm, d, J_{CF} = 3.0 Hz; 61.81 ppm; 75.37 ppm, d, J_{CF} = 19.2 Hz; 91.52 ppm, d, J_{CF} = 191.9 Hz; 169.13 ppm, d, J_{CF} = 23.7 Hz.

Ethyl 2-Fluoro-2-(1′-hydroxycyclohexyl)acetate, 2f. Starting from Cyclohexanone. The product was purified by flash column chromatography, eluting with 85:15 hexanes/ethyl acetate to give a 94% yield of a yellow oil. Spectral properties: ^{1}H NMR: δ 1.29 ppm, t J_{HH} = 7.2 Hz, 3H; 1.54 ppm, m, 10H; 2.50 ppm, broad singlet, 1H; 4.25 ppm, q, J_{HH} = 7.2 Hz, 2H; 4.63 ppm, d, $J_{H\alpha-F}$ = 48.3 Hz, 1H. ^{19}F NMR: δ −199.80 ppm, d, $J_{H\alpha-F}$ = 46.9 Hz. ^{13}C NMR: δ 14.22 ppm; 21.23 ppm; 21.16 ppm; 25.48 ppm; 32.69 ppm, d, J_{CF} = 3.0 Hz; 32.82 ppm, d, J_{CF} = 3.5 Hz; 61.75 ppm; 72.43 ppm, d, J_{CF} = 19.7 Hz; 93.54 ppm, d, J_{CF} = 190.8 Hz; 168.51 ppm, d, J_{CF} = 24.2 Hz.

Ethyl 2-Fluoro-3-hydroxy-3,4,4-trimethylpentanoate, 2g. Starting from 3,3-Dimethyl-2-butanone (Pinacolone). The product was purified by flash column chromatography eluting with ethyl acetate, giving rise to 61% yield of yellow oil identified as a diastereomeric (*RR*/*SS*)/(*RS*/*SR*) mixture, in a 41:59 ratio. Spectral properties: ^{1}H NMR: δ 1.01 ppm, two doublets overlapped, J_{HF} = 1.2 Hz, 9H; 1.19 ppm, d, J_{HF} = 2.1 Hz overlapped with 1.22 ppm, d, J_{HF} = 2.4 Hz, 3H; 1.32 ppm, t J_{HH} = 7.2 Hz, overlapped with 1.33 ppm J_{HH} = 7.2 Hz, 2H; 4.12 ppm to 4.42 ppm, a cluster of signal which includes the CH_2 portion of the ethyl group of both isomers and the respective OH groups; 3H total; 4.94 ppm, d, $J_{H\alpha-F}$ = 48 Hz, 42% of 2H (probably *RR*/*SS* isomer); 4.99 ppm, d, $J_{H\alpha-F}$ = 48 Hz, 58% of 2H (probably *RS*/*SR* isomer). ^{19}F NMR: δ −190.58 ppm, d, $J_{H\alpha-F}$ = 49.1 Hz, (59%, probably *RS*/*SR* isomer); −192.22 ppm, d, $J_{H\alpha-F}$ = 49.1 Hz, (41%, probably *RR*/*SS* isomer). ^{13}C NMR: major isomer: δ 14.27 ppm, 18.12 ppm and 19.80 ppm (three methyl groups from the *tert*-butyl portion); 25.60 ppm (methyl group from the ethyl ester portion); 26.09 ppm (methyl group adjacent to the carbinol portion); 38.24 ppm (quaternary carbon from the *tert*-butyl portion); 62.13 ppm (methylene group from the ethyl ester portion); 76.86 ppm, d, J_{CF} = 19.6 Hz, (quaternary carbon from the carbinol portion); 91.12 ppm, d, J_{CF} = 197.4 Hz (CH−F); 170.49 ppm, d, J_{CF} = 23.7 Hz. Minor isomer: 14.20 ppm, 18.14 ppm and 19,83 ppm (three methyl groups from the *tert*-butyl portion); 25.64 ppm (methyl group from the ethyl ester portion); 26.12 ppm (methyl group adjacent to the carbinol portion); 37.94 ppm (quaternary carbon from the *tert*-butyl portion); 61.85 ppm (methylene group from the ethyl ester portion); 76.01 ppm, d, J_{CF} = 19.6 Hz, (quaternary carbon from the carbinol portion); 92.39 ppm, d, J_{CF} = 188.3 Hz (CH−F); 168.87 ppm, d, J_{CF} = 25.2 Hz.

Ethyl 2-Fluoro-3-hydroxy-3-phenylbutanoate: Isomers (*RR*/*SS*)-2h and (*RS*/*SR*)-2i. Starting from Acetophenone. The (*RR*/*SS*) isomer was isolated as crystals (mp 76.5−78.0 °C) directly from the crude mixture, contaminated with 5% of the (*RS*/*SR*) isomer. The remaining oil was resolved by flash column chromatography, giving rise to one crystalline isomer, identical to the first one; the other isomer remained as an oil. Combined yield: 90%, in a ratio 58:42. Further purification of the (*RR*/*SS*) isomer may be accomplished by fractional crystallization with hexane. Spectral properties of **2h**, [(*RR*/*SS*)-isomer]: ^{1}H NMR: δ 1.07 ppm, t J_{HH} = 7.2 Hz; 3H; 1.70 ppm, d, J_{HF} = 2.4 Hz, 3H; 3.23 ppm, broad singlet, 1H; 4.10 ppm, q J_{HH} = 7.2 Hz, 2H; 4.92 ppm, d, $J_{H\alpha-F}$ = 47.7 Hz, 1H; 7.25 ppm to 7.50 ppm, m, 10H. ^{19}F NMR: δ −195.12 ppm, d, $J_{H\alpha-F}$ = 46.9 Hz. ^{13}C NMR: δ 13.95 ppm; 25.59 ppm, d, J_{CF} = 2.6 Hz; 61.85 ppm; 74.94 ppm, d, J_{CF} = 20.7 Hz; 93.03 ppm, d, J_{CF} = 193.8 Hz; 125.57 ppm; 127.92 ppm; 128.42 ppm; 142.26 ppm, d, J_{CF} = 3.0 Hz; 168.22 ppm, d, J_{CF} = 24.7 Hz. The remainder oil partially resolved by flash column chromatography, giving rise to another crop of the crystalline isomer (76% pure, contaminated with the second isomer) and an oil (the second isomer, 87% pure, contaminated with the first isomer). Spectral properties of **2i**, [(*RS*/*SR*) isomer]: ^{1}H NMR: δ 1.06 ppm, t J_{HH} = 7.2 Hz; 3H; 1.67 ppm, d, J_{HF} = 2.4 Hz, 3H; 3.57 ppm, d, J_{HF} = 0.6 Hz, 1H; 4.09 ppm, dq, J_{HH} = 7.2 Hz, J_{HF} = 3.6 Hz, 2H; 5.00 ppm, d, $J_{H\alpha-F}$ = 47.7 Hz, 1H; 7.24 ppm to 7.36 ppm, and 7.44 to 7.50 ppm, 10H. ^{19}F NMR: −192.53 ppm, d, $J_{H\alpha-F}$ = 46.9 Hz. ^{13}C NMR: 13.92 ppm; 26.19 ppm, d, J_{CF} = 4.0 Hz; 61.94 ppm; 75.10 ppm, d, J_{CF} = 19.7 Hz; 93.59 ppm, d, J_{CF} = 197.8 Hz; 125.22 ppm, d, J_{CF} = 2.5 Hz; 127.83 ppm; 128.38 ppm; 142.88 ppm; 168.66 ppm, d, J_{CF} = 23.7 Hz.

Ethyl 2-Fluoro-3-hydroxy-3,3-diphenylpropanoate, 2j. Starting from Benzophenone. The product was purified by flash column chromatography, eluting with a binary mixture of 90:10 hexanes/ethyl acetate, giving rise to 85% yield of a

white solid (mp 112−113 °C). Spectral properties: ^{1}H NMR: δ 1.01 ppm, t J_{HH} = 7.2 Hz, 3H; 4.07 ppm, m J_{HH} = 7.2 Hz, overlapped with a broad singlet, 4H; 5.48 ppm, d, $J_{H\alpha-F}$ = 47.1 Hz; aromatic cluster, 7.20 ppm to 7.84 ppm, 10H. ^{19}F NMR: δ −189.58 ppm, d, $J_{H\alpha-F}$ = 46.9 Hz. ^{13}C NMR: δ −13.84 ppm; 62.11 ppm; 78.64 ppm, d, J_{CF} = 20.1 Hz; 91.98 ppm, d, J_{CF} = 198.9 Hz; aromatic signals from 126 to 142 ppm; 168.83 ppm, d, J_{CF} = 23.6 Hz.

Ethyl 2-Fluoro-3-hydroxy-3,4-diphenylbutanoate: Isomers (*RR*/*SS*)-2k and (*RS*/*SR*)-2l. Starting from 1,2-Diphenyletanone (Deoxybenzoin). The stereoisomeric mixture was resolved by flash column chromatography eluting with a binary mixture 85:15 hexanes/ethyl acetate, giving rise to 47.8% yield of a white solid (mp 99.5−101.0 °C) and 44.2% yield of an oil, which crystallizes later upon standing, mp 49−51 °C. Combined yield: 92%. A 5-g scale gave rise to similar results; a crop of the more polar isomer was obtained by crystallization from ethanol; the mother liquors (containing a 75:25 mixture of the less polar/more polar isomers), with solvent evaporated off and resolved by flash column chromatography, finally afforded isolated diastereomeric racemic mixtures. Spectral properties of **2k**, [(*RR*/*SS*) isomer]: ^{1}H NMR: δ 0.97 ppm, t J_{HH} = 7.2 Hz; 3H; 3.23 ppm, s, 1H; 3.32 ppm, dd, J^{gem}_{HH} = 13.8 Hz; J_{HF} = 1.5 Hz, 1H; 3.38 ppm, dd, J^{gem}_{HH} = 13.8 Hz; J_{HF} = 1.8 Hz, 1H; 3.98 ppm, qd, J_{HH} = 7.2 Hz; J_{HF} = 1.8 Hz, 2H; 5.12 ppm, d, $J_{H\alpha-F}$ = 47.7 Hz, 1H; aromatic clusters at 6.9 ppm to 7.4 ppm, 10H. **^{19}F NMR**: δ −197.12 ppm, d, $J_{H\alpha-F}$ = 49.1 Hz. Contaminated with 8.1% of the *RS*/*SR* isomer. ^{13}C NMR: δ 13.78 ppm; 44.19 ppm, d, J_{CF} = 3.5 Hz; 61.74 ppm; 77.45 ppm, d, J_{CF} = 19.7 Hz; 91.84 ppm, d, J^{gem}_{CF} = 192.9 Hz; 126.15 ppm; 127.01 ppm; 127.83 ppm; 128.12 ppm; 128.15 ppm; 131.04 ppm; 135.01 ppm; 140.38 ppm, d, J_{CF} = 3.5 Hz; 167.84 ppm, d, J_{CF} = 24.7 Hz. Spectral properties of **2l**, [(*RS*/*SR*) isomer]: ^{1}H NMR: δ 0.98 ppm, t J_{HH} = 7.2 Hz; 3H; 3.13 ppm, dd, J^{gem}_{HH} = 14.1 Hz; J_{HF} = 2.7 Hz, 1H; 3.34 ppm, dd, J^{gem}_{HH} = 14.1 Hz; J_{HF} = 2.70 Hz, 1H; 3.66 ppm, broad singlet, 1H; 4.02 ppm, m, J_{HH} = 7.2 and 10.2 Hz, 2H; 4.88 ppm, d, $J_{H\alpha-F}$ = 47.1 Hz, 1H; aromatic clusters at 7.07 ppm to 7.60 ppm, 10H. ^{19}F NMR: δ −191.16 ppm, d, $J_{H\alpha-F}$ = 47.1 Hz, contaminated with traces of the *RR*/*SS* isomer. ^{13}C NMR: δ 13.85 ppm; 45.26 ppm, d, J_{CF} = 2.6 Hz; 62.01 ppm; 76.73 ppm, d, J_{CF} = 18.6 Hz; 90.88 ppm, d, J^{gem}_{CF} = 202.0 Hz; 125.55 ppm; 125.60 ppm; 126.94 ppm; 128.11 ppm; 128.25 ppm; 133.29 ppm; 135.55 ppm, 142.20 ppm, 169.45 ppm, d, J_{CF} = 22.7 Hz.

Ethyl 3-Benzyl-2-fluoro-3-hydroxy-4-phenylbutanoate, 2m. Starting from 1,3-Diphenylacetone. The product was purified by flash column chromatography, eluting with 60:40 CH_2Cl_2/hexanes, giving rise to 86% yield of a yellow solid (mp 70.5−71.5 °C). A 10-g scale reaction gave rise to 90% yield of crude product, which was recrystallized from hot ethanol, giving rise to a total 80% isolated yield of pure product. Spectral properties: ^{1}H NMR: δ 1.24 ppm, t, J_{HH} = 7.2 Hz, 3H; 2.74 ppm, dd, J^{gem}_{HH} = 13.9 Hz, J_{HF} = 2.3 Hz, 1H; 2.94 ppm, dd, J^{gem}_{HH} = 14.1 Hz, J_{HF} = 3.3 Hz, 1H; 2.97 ppm, d, J_{HF} = 2.1 Hz, 2H; 3.27 ppm, s, 1H; 4.05 ppm, q, J_{HH} = 7.2 Hz, 2H; 4.52 ppm, d, $J_{H\alpha-F}$ = 45.6 Hz; 7.12 ppm to 7.36 ppm, m, 10H. ^{19}F NMR: δ −195.79 ppm, d, $J_{H\alpha-F}$ = 44.9 Hz. ^{13}C NMR: δ 14.13 ppm; 42.38 ppm; 42.75 ppm; 62.21 ppm; 75.06 ppm, d, J_{CF} = 20.6 Hz; 88.51 ppm, d, J_{CF} = 196.4 Hz; 127.00 ppm, 127.04 ppm, 128.33 ppm, 128.36 ppm, 131.18 ppm, 131.24, 135.77, and 135.93 ppm (aromatic signals); 169.87 ppm, d, J_{CF} = 22.1 Hz.

Synthesis of α-Fluoro-β-hydroxyacids 5. General Procedure. The starting ethyl α-fluoro-β-hydroxy ester was mixed with ethanol (to an approximate concentration of 0.2 M) in a round-bottomed flask and cooled in an ice−water bath. Then, cold NaOH, dissolved in ethanol (approximate concentration 0.2 M), was added dropwise to the starting material solution with vigorous agitation and cooling. The reactant mixture was stirred until room temperature was reached (it took about 1−2 h in each case). Completion of the reaction was monitored by ^{19}F NMR analysis. The solvent was evaporated, and the organic salt was formed as a white solid, which was dissolved in water and washed with ether to remove nonreacted organic materials. The aqueous phase was cooled, and a cold 1 M HCl aqueous solution was added dropwise until pH 3 (checked with litmus paper). The resultant cloudy mixture was extracted with ether three times, each one with a volume of ether equal to the volume of aqueous extract. The organic extract was dried with $MgSO_4$, filtered, and evaporated, and the resulting α-fluoro-β-hydroxy acids were crystallized in an appropriate solvent.

Synthesis of (*RR*/*SS*)-2-Fluoro-3-hydroxy-3-phenylbutyric Acid, 5h. Starting from 1.120 g (5.0 mmol) of ethyl (*RR*/*SS*)-2-fluoro-3-hydroxy-3-phenylbutyrate, 95% diastereomerically pure dissolved in 25.0 mL of ethanol, and 0.225 g of 98% NaOH (5.0 mmol) dissolved in 25 mL of ethanol. The product was crystallized from a binary mixture 20:80 benzene/hexanes. 0.883 g of a white solid was formed (90% yield of isolated product); mp 100−106 °C dec. ^{19}F NMR analysis of the composition of the product demonstrated the presence of 4.6% of the *RS*/*SR* isomer (δ −189.39 ppm, d, $J_{H\alpha-F}$ = 49.1 Hz) and 95.4% of the *RR*/*SS* isomer (δ −191.81 ppm, d, $J_{H\alpha-F}$ = Hz). ^{1}H NMR (DMSO-d_6): δ 7.48 ppm, d, $^3J_{HH}$ = 7.2 Hz, 2H; 7.31 ppm, t, $^3J_{HH}$ = 7.2 Hz, overlapped with 7.23 ppm, t, $^3J_{HH}$ = 7.2 Hz, 3H; 5.01 ppm, d, $J_{H\alpha-F}$ = 48.0 Hz, 1H; 1.55 ppm, d, $^4J_{HF}$ = 1.8 Hz, 3H. Recrystallization from the same binary solvent system, under more diluted conditions and collecting an early crop, gave rise to 0.50 g of 100% diastereomerically pure *RR*/*SS* isomer. Spectral properties: ^{1}H NMR: δ 7.46 to 7.51 ppm, m, 2H; 7.42 to 7.29 ppm, m, 3H; 4.98 ppm, d, $J_{H\alpha-F}$ = 47.4 Hz, 1H; 1.74 ppm, d, $^4J_{HF}$ = 2.4 Hz, 3H. ^{19}F NMR: δ −193.56 ppm, d, $J_{H\alpha-F}$ = 47.4 Hz. ^{13}C NMR: δ 25.32 ppm, d, J_{CF} = 2.7 Hz; 75.05 ppm, d, J_{CF} = 20.8 Hz; 92.91 ppm, d, J_{CF} = 194.76 Hz; 125.54 ppm; 128.26 ppm; 128.62 ppm; 141.75 ppm; 171.68 ppm, d, J_{CF} = 25.1 Hz. Anal. Calcd: C, 60.602; H, 5.594; F, 9.586. Found: C, 60.438; H, 5.631.

Synthesis of (*RS*/*SR*)-2-Fluoro-3-hydroxy-3-phenylbutyric Acid, 5i. Starting from 3.69 g (15.6 mmol) of 95% pure ethyl 2-fluoro-3-hydroxy-3-phenylbutyrate (a mixture 68% *RS*/*SR* and 32% *RR*/*SS*) dissolved in 80 mL of ethanol and 0.76 g of 98% NaOH (18.0 mmol) dissolved in 80 mL of ethanol, 2.75 g of a white product was obtained (89% yield). This product was recrystallized from a binary mixture 40:60 benzene: hexanes giving rise to a product 99.7% diastereomerically pure *RS*/*SR* (^{19}F NMR, (DMSO-d_6) δ = −189.46 ppm, d, $J_{H\alpha-F}$ = 47.7 Hz) and 0.3% *RR*/*SS* isomer (δ = −191.89 ppm, d, $J_{H\alpha-F}$ = 49.6 Hz); mp 114−118 °C dec. Spectral properties: ^{1}H NMR: δ 7.47 ppm, d, J_{HH} = 7.2 Hz, 2H; 7.27 to 7.40 ppm, m, 3H; 5.08 ppm, d, $J_{H\alpha-F}$ = 47.6 Hz, 1H; 4 to 6 ppm, br. s, 2 H; 1.70 ppm, d, $^4J_{HF}$ = 2.3 Hz, 3H. ^{1}H NMR (DMSO-d_6): δ 7.48 ppm, d, J_{HH} = 7.3 Hz, 2H; 7.31 ppm, t, J_{HH} = 7.1 Hz, 2H; 7.22 ppm, tt, J_{HH} = 7.2, 2.1 Hz, 1H; 5.08 ppm, d, $J_{H\alpha-F}$ = 47.6 Hz, 1H; 4.1 ppm, br s; 1.55 ppm, d, $^4J_{HF}$ = 1.5 Hz, 3H. ^{19}F NMR: δ −191.316 ppm only peak, d, $J_{H\alpha-F}$ = 47.4 Hz. ^{13}C NMR (DMSO-d_6): δ 26.34 ppm, d, J_{CF} = 3.9 Hz; 74.44 ppm, d, J_{CF} = 20.6 Hz; 93.89 ppm, d, J_{CF} = 188.7 Hz; 125.75 ppm; 126.90 ppm; 127.89 ppm; 144.99 ppm, d, J_{CF} = 3.0 Hz; 169.10 ppm, d, J_{CF} = 25.1 Hz. Anal. Clacd: C, 60.602; H, 5.594; F, 9.586. Found: C, 60.991; H, 5.409.

Synthesis of 2-Fluoro-3-hydroxy-3,3-diphenylpropionic Acid 5j. Starting from 0.580 g (2.0 mmol) of ethyl 2-fluoro-3-hydroxy-3,3-diphenylpropionate in 25 mL of ethanol and 100 mg (2.4 mmol) of 98% NaOH in 10 mL of ethanol; 0.45 g of a white solid were isolated after crystallization in a binary mixture 20:80 benzene/hexanes; 88% yield isolated product; mp 108 °C dec. Spectral properties: ^{1}H NMR (DMSO-d_6): δ 7.4 to 7.6 ppm, two doublets, $^3J_{HH}$ = 7.8 Hz, 4H; 7.1 to 7.3 ppm, m, $^3J_{HH}$ = 7.2 Hz, 6H; 6.104 ppm, d, $J_{H\alpha-F}$ = 46.2 Hz, 1H. ^{19}F NMR (DMSO-d_6): δ −189.954 ppm, d, $J_{H\alpha-F}$ = 44.88 Hz. ^{13}C NMR (DMSO-d_6): δ 78.44 ppm, d, J_{CF} = 21.7 Hz; 91.96 ppm, d, J_{CF} = 188.9 Hz; 126.10 ppm; 126.39 ppm; 126.59 ppm; 126.77 ppm; 127.62 ppm; 127.84 ppm; 143.87 ppm, d, J_{CF} = 4.1 Hz; 144.91 ppm; 168.73 ppm, d, J_{CF} = 25.1 Hz.

Synthesis of (*RR*/*SS*)-2-Fluoro-3-hydroxy-3,4-diphenylbutyric Acid, 5k. Starting from 3.024 g (10.0 mmol) of ethyl 2-fluoro-3-hydroxy-3,4-diphenylbutyrate (95% *RR*/*SS* and 5% *RS*/*SR*) dissolved in 50 mL of ethanol and 0.48 g of 98% NaOH

(10.0 mmol) dissolved in 50 mL of ethanol. A white solid (2.578 g, 94% yield) was obtained, mp 108−110 °C dec. The product was crystallized from a binary mixture 20:80 benzene/hexanes, giving rise to 100% diastereomerically pure *RR*/*SS* product. Spectral properties: ^{1}H NMR: δ 7.27−7.36 ppm, m, 5H; 7.10−7.20 ppm, m, 3H; 6.90 ppm, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.9 Hz, 2H; 5.7 ppm, broad singlet, 2H; 5.15 ppm, d, $J_{H\alpha-F}$ = 47.7 Hz, 1H; 3.39 ppm, d, $^2J_{HH}$ = 14.7 Hz; overlapped with 3.34 ppm, dd, $^2J_{HH}$ = 14.7 Hz, $^3J_{HF}$ = 1 Hz approximately, 2H total. ^{19}F NMR: δ −195.94 ppm, d, $J_{H\alpha-F}$ = 47.4 Hz. ^{13}C NMR: δ 44.06 ppm, d, J_{CF} = 4.2 Hz; 77.62 ppm, d, J_{CF} = 19.8 Hz; 92.06 ppm, d, J_{CF} = 193.48 Hz; 126.13 ppm; 127.29 ppm; 128.10 ppm; 128.31 ppm; 128.33 ppm; 131.02 ppm; 134.44 ppm; 139.78 ppm d, J_{CF} = 2.8 Hz; 171.36 ppm, d, J_{CF} = 25.3 Hz. Anal. Calcd: C, 70.062; H, 5.512; F, 6.926. Found: C, 70.014; H, 5.661.

Synthesis of *RS*/*SR*-2-Fluoro-3-hydroxy-3,4-diphenylbutyric Acid, 5l. Starting from 2.57 g (8.5 mmol) of ethyl 2-fluoro-3-hydroxy-3,4-diphenylbutyrate (98% diastereomerically pure *RS*/*SR* and 2% *RR*/*SS*) dissolved in 40 mL of ethanol and 0.40 g of 98% NaOH (8.5 mmol) dissolved in 45 mL of ethanol. A white solid (2.16 g, 93% yield) was obtained, mp 91−92 °C. The product was recrystallized from a binary mixture 15:75 benzene/hexanes, giving rise to 100% diastereomerically pure RS/SR isomer. Spectral properties: **^{1}H NMR**: δ 7.44 to 7.48 ppm, dt, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.4 Hz, 2H; 7.23 to 7.36 ppm, m, 6H; 7.15 to 7.20 ppm, m, 2H; 4.92 ppm, d, $J_{H\alpha-F}$ = 46.5 Hz, 1H; 3.34 ppm, dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HF}$ = 2.7 Hz, 1H; 3.13 ppm, dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HF}$ = 2.2 Hz, 1H. ^{19}F NMR: δ −190.04 ppm, d, $J_{H\alpha-F}$ = 47.1 Hz. ^{13}C NMR: δ 45.28 ppm; 77.02 ppm, d, J_{CF} = 19.5 Hz (overlapped with the $CDCl_3$ triplet); 90.61 ppm, d, J_{CF} = 199.51 Hz; 125.43 ppm; 125.47 ppm; 127.25 ppm; 128.18 ppm; 128.35 ppm; 131.21 ppm; 134.90 ppm; 141.23 ppm; 173.57 ppm, d, J_{CF} = 23.9 Hz.

Synthesis of 3-Benzyl-2-fluoro-3-hydroxy-4-phenylbutyric Acid, 5m. Starting from 3.16 g (10.0 mmol) of ethyl 3-benzyl-2-fluoro-3-hydroxy-4-phenylbutyrate in 50 mL of ethanol and 0.4 g of 98% NaOH (10.0 mmol) in 50 mL of ethanol. The product was crystallized from a mixture of 10:90 benzene/hexanes, 96% yield of isolated product, mp 117−119 °C dec. Spectral properties: ^{1}H NMR: δ 7.19−7.32 ppm, m, 10H; 6.6 ppm, broad singlet, 2H; 4.569 ppm, d, $J_{H\alpha-F}$ = 45.9 Hz, 1H; 2.98 ppm, s, 2H; 2.94 ppm, dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HF}$ = 3.0 Hz, 1H; 2.70 ppm, dd, $^2J_{HH}$ = 13.80 Hz, $^3J_{HF}$ = 2 Hz, 1H. ^{19}F NMR: δ −194.707 ppm, d, $J_{H\alpha-F}$ = 46.85 Hz. ^{13}C NMR: δ 41.98 ppm, 75.22 ppm, d, J_{CF} = 20.6 Hz; 88.46 ppm, d, J_{CF} = 194.9 Hz; 127.18 ppm; 128.42 ppm; 128.52 ppm; 131.10 ppm; 131.15 ppm; 135.30 ppm; 135.38 ppm; 173.41 ppm, d, J_{CF} = 23.68 Hz. Anal. Calcd: C, 70.82; H, 5.94; F, 6.59. Found: C, 70.59; H, 6.13.

X-ray Experimental Data. 2h data: a = 7.8371(6) Å, b = 9.0799(7) Å, c = 0.1826(7) Å, α = 66.681(1)°, β = 72.712(1)°, γ = 84.537(1)°, V = 572.76(8) Å^3, Z = 2, triclinic P-1, T = 173 K. **2k** data: a = 9.9547(5) Å, b = 10.4166(5) Å, c = 15.0323(7) Å, β = 94.239(1)°, V = 1554.5(1) Å^3, Z = 4, monoclinic $P2(1)/n$, T = 173 K.

The structures were solved by the direct methods in SHELXTL5 and refined using full-matrix least-squares methods.[25] The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms, except the hydroxy proton in **2k** which was obtained from a difference Fourier map and refined freely. The H2 and F1 on C2 were found to be disordered and were refined in two parts, thus allowing for a 95:5 ratio of the diastereomers. Their site occupation factors were dependently refined to 0.95(1) for the major part and, consequently, 0.05(1) for the minor part. The minor group was constrained to maintain a geometry similar to the major part. For **2h**, a total of 156 parameters were refined in the final cycle of refinement using 2335 reflections with $I > 2\sigma(I)$ to yield R_1 and wR_2 of 3.70% and 9.55%, respectively. For **2k**, a total of 205 parameters were refined in the final cycle of refinement using 2999 reflections with $I > 2\sigma(I)$ to yield R_1 and wR_2 of 4.45% and 12.00%, respectively. Refinement was done using F^2.

Acknowledgment. We gratefully acknowledge the Instituto Colombiano para el Fomento de la Ciencia y la Tecnología "Francisco José de Caldas" COLCIENCIAS (Grant No. 1106-05-038-99), Vice-Rectoría de Investigaciones y Postgrados from Universidad de Caldas, Vice-Rectoría de Investigaciones from Universidad del Valle. Support of this research in part by the National Science Foundation (W.R.D.) is acknowledged with thanks, and K.A.A. also acknowledges the National Science Foundation and the University of Florida for funding of the purchase of the X-ray equipment.

Supporting Information Available: ORTEP drawings and X-ray crystal reports for compounds **2h** and **2k** and pertinent ROE data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015778X

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