Conversion of α-Keto Esters into β,β-Difluoro-α-keto Esters and Corresponding Acids: A Simple Route to a Novel Class of Serine Protease Inhibitors

Melchiorre F. Parisi,* Giuseppe Gattuso, Anna Notti, and Françisco M. Raymo

Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, 98166 Vill. S. Agata Messina, Italy

Robert H. Abeles

Graduate Department of Biochemistry, Brandeis University, 415 South Street, Waltham, Massachusetts 02254

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The preparation of a series of β,β-difluoro-α-keto esters and corresponding acids RCF_2COCO_2R' (R = Me, Et, *i*-Pr, Bn, and Ph; R' = Et and H), designed as potential inhibitors of serine proteases, is described. The standard procedure developed consists in the initial formation of an α,α-difluoro ester from an α-keto ester, followed by a simple four-step sequence involving the synthesis of hemiacetal, cyanohydrin, and α-hydroxy ester difluorinated intermediates. This method provides an easy route to β,β-difluoro-α-keto esters and corresponding acids, via "formal" insertion of a difluoromethylene group between the R substituent and the α-carbonyl group of a generic α-keto ester.

Introduction

Many reversible inhibitors of proteolytic enzymes[1] consist of a substrate-like peptidic or peptidomimetic structure, bearing at the P_1 position[2] an electrophilic carbonyl group in place of the scissile amide bond. Examples of reactive carbonyl moieties used as serine protease inhibitors include fluorinated ketones (difluoro[3] and trifluoro[4]), α-keto esters,[5] α-keto acids,[5a,6] α-diketones,[5b,7] α,α-difluoro-β-keto amides,[8] and α-keto-benzoxazolones.[9] The mechanism of action of these inhibitors most likely involves nucleophilic addition of the active site serine hydroxyl group of the protease to the carbonyl group of the inhibitor, with formation of a metastable hemiketal adduct which mimics the tetrahedral species involved in the enzymatic cleavage of peptide bonds (transition-state analogue inhibitors).[10] Formation of enzyme–inhibitor hemiketal adducts has been demonstrated by a number of X-ray[8,9,11] and ^{13}C NMR[12] studies.

Since the effectiveness of such inhibitors is highly dependent on the electrophilicity of their carbonyl group, we decided to investigate the inhibitory properties of compounds with a carbonyl flanked by two electron-withdrawing groups. We focused our attention on β,β-difluoro-α-keto esters, as an attractive synthetic target combining the reactive functionalities characteristic of two known classes of serine protease inhibitors (fluorinated ketones and α-keto esters) within one molecule. This approach proved to be successful, and we have recently shown that ethyl 3,3-difluoro-2-oxo-4-phenylbutanoate (**6d**) and ethyl 3,3-difluoro-2-oxo-3-phenylpropanoate (**6e**) are reversible competitive inhibitors of α-chymotrypsin.[13] The ester **6d**, in particular, was found to be more active than trifluoromethyl ketone (*N*-Ac-D,L-Phe-CF_3)[3a] and α-keto ester (*N*-Bz-D,L-Phe-CO_2Et)[5a] inhibitors of comparable size. Furthermore, when its ethoxy group was replaced with an appropriate amino acid chain (e.g., alanyl-leucyl-arginine methyl ester), the resultant peptide inhibited α-chymotrypsin more effectively, and in a slow-binding manner.[14]

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(1) For a general review on protease inhibitors, see: Rich, D. H. In *Comprehensive Medicinal Chemistry, The Rational Design, Mechanistic Study and Therapeutic Application of Chemical Compounds*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: New York, 1990; pp 391–439.

(2) The "P" and "S" terminology was originally introduced by Schechter and Berger to describe the interaction between a protease and a peptide. The individual amino acid residues of a peptide substrate (or inhibitor) are numbered P_1, P_2, etc. in the N-terminal direction and P_1', P_2', etc. in the C-terminal direction from the scissile peptide bond (P_1–P_1'). The corresponding subsites of the enzyme are described as S_1, S_2, etc. and S_1', S_2', etc. See: Schechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157.

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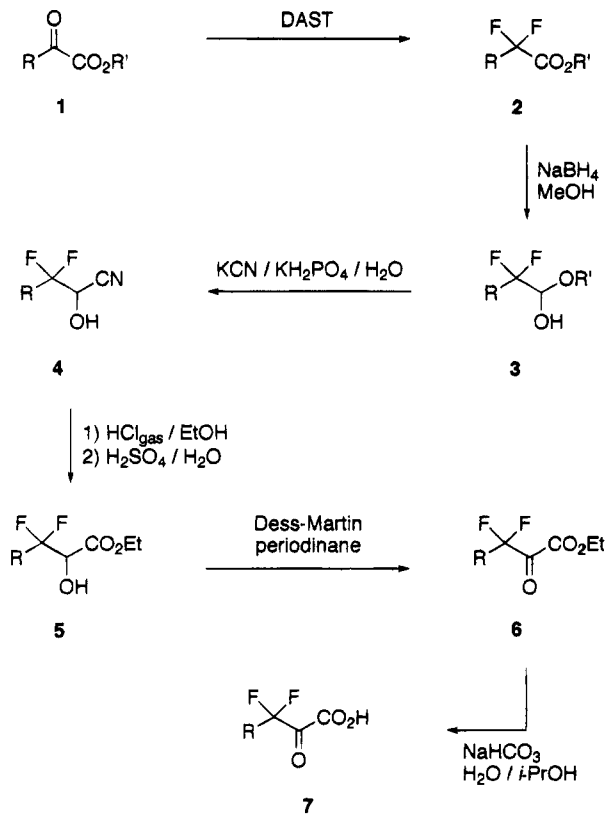
Scheme 1



1-3	R	R'
a	CH_3	Et
b	CH_3CH_2	Me
c	$(CH_3)_2CH$	Et
d	$PhCH_2$	Me
e	Ph	Me

4-7	R
a	CH_3
b	CH_3CH_2
c	$(CH_3)_2CH$
d	$PhCH_2$
e	Ph

The potential of β,β-difluoro-α-keto esters as inhibitors of serine proteases has not yet been fully investigated, possibly because of the lack of a general method for their preparation. Bartlett[15] has recently prepared methyl difluoropyruvate from diethyl difluorooxaloacetate[16] via hydrolysis/decarboxylation/methylation. This synthetic approach, however, is clearly unsuitable for the preparation of higher homologs of difluoropyruvates (the C-2 atom of a difluorooxaloacetate is already fully substituted). In this report, we describe a convenient standard procedure which we have developed for the conversion of α-keto esters (or acids) into β,β-difluoro-α-keto esters and corresponding acids (Scheme 1). In addition to the phenyl- and benzyl-substituted β,β-difluoro-α-keto esters and acids, briefly described in our previous studies,[13] we have now synthesized, via this method, a number of alkyl-substituted analogues designed as potential inhibitors of elastases.[17]

Results and Discussion

The procedure developed for the synthesis of β,β-difluoro-α-keto esters **6a–e** and their corresponding acids **7a–e** is outlined in Scheme 1, and the yields of conversions are reported in Table 1. This method involves the initial fluorination of an α-keto ester to form an α,α-difluoro ester, followed by a simple four-step sequence to transform its alkoxycarbonyl group into the required ethoxalyl moiety present in the target β,β-difluoro-α-keto ester.

Table 1. Yields[a] (%) of Conversions (Scheme 1)

	R	1→2	2→4	4→5	5→6	6→7
a	CH_3	52	64	62	75	62
b	CH_3CH_2	50	61	63	78	76
c	$(CH_3)_2CH$	39	58	60	77	75
d	$PhCH_2$	43	64	73	89	87
e	Ph	70	71	66	81	84

[a] Isolated yields.

The α-keto esters used as starting materials for our studies were commercially available or easily obtained (**1b** and **1d**), in quantitative yield, by treatment of the corresponding α-keto acid with diazomethane. A number of methods have recently been developed to prepare α,α-difluoro esters,[18] and in particular the syntheses of ethyl 2,2-difluoropropanoate[19] (**2a**), methyl 2,2-difluoro-3-phenylpropanoate[20] (**2d**), and methyl difluorophenylethanoate[20a,21] (**2e**) have already been described. In the present work, all α,α-difluoro esters **2a–e** were conveniently prepared by direct fluorination of α-keto esters **1a–e** with (diethylamido)sulfur trifluoride (DAST), using the procedure previously reported by Middleton[21a] for α,α-difluoroarylacetates. Aliphatic difluoro esters **2a–c** are stable but extremely volatile, and severe loss of product inevitably occurred during solvent removal or just on handling. Consequently, although conversion of **1a–c** into product(s) was quantitative, their isolated yields were generally lower (39–52%) than those reported[21a] for aryl substrates (65–92%). Furthermore, in the case of **2c** yield was also depleted by the formation of two fluorinated byproducts.[22] Fluorination of methyl phenylpyruvate (**1d**) gave a complex mixture, from which methyl 2,2-difluoro-3-phenylpropanoate (**2d**) was isolated as the major product (43%). The known[23] tendency of **1d** to tautomerize to the corresponding enol ester accounts for moderate yield and explains the concomitant formation of several byproducts (not characterized). This tautomeric equilibrium reduces the concentration of α-keto ester available for *gem*-difluorination, while the enol formed is likely to undergo side reactions with DAST.

The success of our synthetic strategy relies on the partial reduction of difluoro esters **2a–e** to difluoro hemiacetals **3a–e**. This crucial step was carried out by using sodium borohydride in methanol at −50/−45 °C,

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with subsequent quenching of the reaction (1 N HCl) at low temperature. Under such controlled conditions selectivity was high, with over-reduction byproduct (difluoro alcohol) kept to less than 5%. The reduction of ethyl difluoro esters **2a** and **2c** afforded the ethyl hemiacetals **3a** and **3c** along with the corresponding methyl hemiacetals, as a result of partial alkoxy-exchange during workup. However, product separation was unnecessary since for the purpose of the synthesis both hemiacetals behave as carbonyl equivalents in the following reaction with potassium cyanide. Routinely, all hemiacetals were reacted with potassium cyanide in aqueous KH_2PO_4 without prior purification. Traces of difluoro alcohol, carried over from the previous reduction step, were then removed by column chromatography or distillation, and cyanohydrins **4a–e** were recovered in 58–71% overall yields from the corresponding difluoro esters **2a–e**. Cyanohydrins **4a–e** were treated with dry HCl and absolute ethanol in a Pinner reaction[24] to afford, after hydrolysis of the intermediate imino ester hydrochlorides (not isolated), the corresponding hydroxy esters **5a–e**.[25] Oxidation of **5a–e** was readily accomplished, in good yield, by using Dess–Martin periodinane[26] under Linderman[27] conditions, and the resulting α-keto esters **6a–e** were then hydrolyzed, under alkaline conditions, to the final α-keto acids **7a–e**.

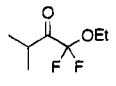
The ^1H, ^{19}F, and ^{13}C NMR spectral data of all compounds in this work were in agreement with the proposed structures. Distinctive ^{19}F NMR spectra were observed for compounds **3–5**, fully consistent with the presence of a CF_2 group next to a chiral carbon atom. The geminal fluorines were always anisochronous, and gave rise to a typical AB pattern further split by hydrogen(s) present on the adjacent carbon atom(s). The ^1H NMR spectra of the crude hemiacetals showed a doublet of doublets for the C(1)-hydrogen and either a singlet for the OMe group (**3b**, **3d**, and **3e**) or an ABX_3 pattern for the OEt group (**3a** and **3c**). Pure samples of **4–5** gave ^1H NMR spectra in which the signal due to the C(2)-hydrogen was always (except in the case of **4e**)[28] present as a doublet of doublet of doublets, showing a $J_{H,H}$ with the hydroxyl hydrogen and two different $^3J_{H,F}$ with the geminal fluorines at C-3. By NMR analysis both β,β-difluoro-α-keto acids **7a–e** and their esters **6a–e** were found to exist as a mixture of keto and hydrated (*gem*-diol) forms.[29] In agreement with the marked electrophilic character of their α-carbonyl group, the hydrate was always highly predominant (>94%).

In conclusion, we have developed a convenient procedure which allows the synthesis of a series of β,β-difluoro-α-keto esters and corresponding acids via "formal" insertion of a difluoromethylene group between the R substituent (R = alkyl, benzyl, and phenyl) and the α-carbonyl group of an α-keto ester. Moreover, during our studies we have prepared a series of stable intermediates bearing a variety of synthetically useful functional group(s) adjacent to a difluoromethylene unit. We expect several of them to be versatile precursors for the synthesis of selectively difluorinated molecules by means of standard transformations. Particularly interesting in this respect are the difluoro hemiacetals **3a–e**, readily available with our synthesis in two steps. Kitazume[30] has, very recently, reported that difluoroacetaldehyde ethyl hemiacetal reacts with a wide range of nucleophiles to yield difluoromethylated carbinols, lactones, amino sugars, imines, amino acids, and β-lactams.

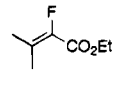
Experimental Section

General Methods. Melting points and boiling points are uncorrected. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 300, 75, and 282 MHz, respectively, using $CDCl_3$ as solvent unless otherwise stated. All chemical shifts are reported in ppm and are relative to TMS for ^1H and ^{13}C NMR, and to $CFCl_3$ for ^{19}F NMR. Unless otherwise indicated, J values refer to H–H coupling constants. Mass spectra were measured in the electron impact (EI) at 70 eV or in the chemical ionization (CI) mode. Elemental analyses were carried out by Redox s.n.c., Cologno Monzese, Italy. Thin-layer chromatography was performed on glass plates precoated with silica gel 60 SIF_{254}, and compounds were visualized by exposure to UV light or with phosphomolybdic acid. Column chromatographic separations were carried out on silica gel 60, 230–400 mesh. Anhydrous CH_2Cl_2 and Et_2O were dried and freshly distilled from CaH_2. Petroleum ether refers to the 30–45 °C fraction. Other solvents and chemicals were of reagent grade and were used as supplied from the manufacturers. Starting α-keto esters were commercially available except for methyl 2-oxobutanoate (**1b**) and methyl phenylpyruvate (**1d**), which were prepared from the corresponding α-keto acids by treatment, at −15 °C, with an alcohol-free ethereal solution of diazomethane.[31] Due to poor shelf life,[32] phenylpyruvic acid when required was obtained by ether extraction from a 0.5 N HCl solution of its more stable monohydrate sodium salt (purchased from Aldrich Chemical Co.). Organic extracts were routinely dried over anhydrous $MgSO_4$ and concentrated under reduced

(22) The two byproducts were identified as 1-ethoxy-1,1-difluoro-3-methyl-2-butanone (**A**) and ethyl 2-fluoro-3-methyl-2-butenoate (**B**) on the basis of distinctive ^1H, ^{13}C, and ^{19}F NMR spectral patterns. For **A**: ^1H NMR δ 1.17 (d, J = 6.9 Hz, 6 H), 1.33 (t, J = 7.1 Hz, 3 H), 3.08 (septet, J = 6.9 Hz, 1 H), 4.05 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 14.9, 18.2, 35.2 , 60.4 (t, $^3J_{C,F}$ = 7 Hz), 116.2 (t, $^1J_{C,F}$ = 274 Hz), 198.8 (t, $^2J_{C,F}$ = 34 Hz); ^{19}F NMR δ −83.3 (s). For **B**: ^1H NMR δ 1.34 (t, J = 7.1 Hz, 3 H), 1.87 (d, $^4J_{H,F}$ = 4.1 Hz, 3 H), 2.11 (d, $^4J_{H,F}$ = 3.3 Hz, 3 H), 4.27 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 14.2, 18.5 (d, $^3J_{C,F}$ = 5 Hz), 18.6 (d, $^3J_{C,F}$ = 2 Hz), 60.9, 129.5 (d, $^2J_{C,F}$ = 14 Hz), 143.7 (d, $^1J_{C,F}$ = 250 Hz), 161.3 (d, $^2J_{C,F}$ = 35 Hz); ^{19}F NMR δ −128.6 (m). ^{19}F NMR analysis of the reaction mixture, prior to solvent removal, indicated the following product ratio **2c**:**A**:**B** = 69:12:19. The formation of **B** is presumably the result of a side reaction similar to the one leading to vinyl fluoride in the fluorination of ketones with DAST. The isolation of compound **A**, on the other hand, is unusual, considering that ester groups do not react with DAST. For a review on the reactivity of DAST, see: Hudlicky, M. *Org. React.* **1988**, *35*, 513.



A



B

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(25) Although β,β-difluoro-α-hydroxy esters **5a–e** could also be obtained by direct treatment of cyanohydrins **4a–e** with ethanol and concentrated sulfuric acid at 100 °C, the Pinner procedure was preferred because higher yields and cleaner reaction crudes were obtained.

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(28) An overlapping doublet of triplets was observed in the case of **4e** (see Experimental Section).

(29) The ^{19}F NMR (acetone-d_6) spectrum of each of these compounds showed two signals: one of low intensity at low field (keto form) and the other of much greater intensity, always shifted 2–7.4 ppm to higher field (hydrated form). Unambiguous assignment of the high-field peak to the hydrated ketones was deduced from the corresponding ^{13}C NMR (acetone-d_6) spectra. These showed the presence, in the expected region, of a triplet (δ 93.4–94.7 ppm) consistent with a quaternary *gem*-diol carbon atom, with diagnostic carbon–fluorine coupling ($^2J_{C,F}$ = 31–33 Hz) and, in contrast, the absence of a low-field resonance characteristic of a ketone carbonyl group (no resonances above 172 ppm).

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pressure below 40 °C using a rotary evaporator unless noted otherwise.

General Procedure for the Preparation of α,α-Difluoro Esters 2a–e. α-Keto esters **1a–e** were fluorinated according to the method of Middleton[21a] (using 0.2 molar excess of DAST). Routinely, reaction mixtures were taken up in CH_2Cl_2, and products were purified by distillation or chromatography. Owing to the high volatility of alkyl-substituted α,α-difluoro esters **2a–c**, solvent removal was carried out under controlled conditions (200 mmHg at 0 °C) and distillations were performed with the collecting flask cooled in liquid nitrogen to minimize product loss.

Ethyl 2,2-Difluoropropanoate (2a). Reaction time 30 min at 0 °C. Distillation at atmospheric pressure gave **2a** (52%) as a colorless oil: bp 108–109 °C (lit.[19b] 103–104 °C); ^{1}H NMR δ 1.36 (t, J = 7.1 Hz, 3 H), 1.81 (t, $^3J_{H,F}$ = 18.8 Hz, 3 H), 4.33 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 13.9, 21.4 (t, $^2J_{C,F}$ = 25 Hz), 62.8, 115.1 (t, $^1J_{C,F}$ = 247 Hz), 164.3 (t, $^2J_{C,F}$ = 33 Hz); ^{19}F NMR δ −99.6 (q, $^3J_{H,F}$ = 19.0 Hz); IR (neat) 1769 cm^{-1}; MS (CI, CH_4) m/z 139 (MH^+, 100), 119 (14), 111 (59), 91 (16).

Methyl 2,2-Difluorobutanoate (2b). Reaction time 1 h at 25 °C. Distillation under reduced pressure gave **2b** (50%) as a colorless oil: bp 67–68 °C/140 mmHg; ^{1}H NMR δ 1.04 (t, J = 7.5 Hz, 3 H), 2.09 (tq, $^3J_{H,F}$ = 16.7 Hz, J = 7.5 Hz, 2 H), 3.88 (s, 3 H); ^{13}C NMR δ 5.7 (t, $^3J_{C,F}$ = 5 Hz), 28.0 (t, $^2J_{C,F}$ = 24 Hz), 53.2, 116.7 (t, $^1J_{C,F}$ = 250 Hz), 164.8 (t, $^2J_{C,F}$ = 33 Hz); ^{19}F NMR δ −108.1 (t, $^3J_{H,F}$ = 17.0 Hz); IR (neat) 1772 cm^{-1}; MS (CI, CH_4) m/z 139 (MH^+, 100), 119 (73), 99 (18). Anal. Calcd for $C_5H_8F_2O_2$: C, 43.48; H, 5.84; F, 27.51. Found: C, 43.10; H, 5.59; F, 27.16.

Ethyl 2,2-Difluoro-3-methylbutanoate (2c). Reaction time 3 h at 25 °C. Two sequential column chromatography using 95:5 petroleum ether/Et_2O and 75:25 petroleum ether/CH_2Cl_2 as eluent gave **2c** (39%) as a colorless oil: bp 76–77 °C/73 mmHg; ^{1}H NMR δ 1.04 (d, J = 6.9 Hz, 6 H), 1.36 (t, J = 7.1 Hz, 3 H), 2.25–2.49 (m, 1 H), 4.34 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 14.0, 14.7 (t, $^3J_{C,F}$ = 4 Hz), 33.0 (t, $^2J_{C,F}$ = 23 Hz), 62.5, 117.7 (t, $^1J_{C,F}$ = 252 Hz), 164.4 (t, $^2J_{C,F}$ = 33 Hz); ^{19}F NMR δ −115.0 (d, $^3J_{H,F}$ = 15.0 Hz); IR (neat) 1772 cm^{-1}; MS (CI, CH_4) m/z 167 (MH^+, 100), 147 (16), 139 (25), 127 (7), 99 (14). Anal. Calcd for $C_7H_{12}F_2O_2$: C, 50.60; H, 7.28; F, 22.87. Found: C, 50.23; H, 7.16; F, 22.63.

Methyl 2,2-Difluoro-3-phenylpropanoate (2d). Reaction time 1 h at 25 °C. Two sequential column chromatography using 1:1 hexane/$CHCl_3$ and benzene as eluent gave **2d** (43%) as a colorless oil: bp 46–47 °C/0.2 mmHg; ^{1}H NMR δ 3.38 (t, $^3J_{H,F}$ = 16.5 Hz, 2 H), 3.79 (s, 3 H), 7.24–7.35 (m, 5 H); ^{13}C NMR δ 40.9 (t, $^2J_{C,F}$ = 24 Hz), 53.2, 115.4 (t, $^1J_{C,F}$ = 252 Hz), 127.9, 128.6, 130.3, 130.5 (t, $^3J_{C,F}$ = 4 Hz), 164.3 (t, $^2J_{C,F}$ = 33 Hz); ^{19}F NMR δ −105.1 (t, $^3J_{H,F}$ = 16.5 Hz); IR (neat) 1771 cm^{-1}; MS (EI) m/z 200 (M^+, 4), 180 (100), 179 (62), 160 (26), 102 (51), 91 (82).

Methyl Difluorophenylethanoate (2e). Reaction time 2 h at 25 °C. Distillation under reduced pressure gave **2e** (70%) as a colorless oil: bp 83–84 °C/7 mmHg (lit.[21a] 100–101 °C/20 mmHg); ^{1}H NMR δ 3.85 (s, 3 H), 7.43–7.62 (m, 5 H); ^{13}C NMR δ 53.6, 113.4 (t, $^1J_{C,F}$ = 252 Hz), 125.4 (t, $^3J_{C,F}$ = 6 Hz), 128.6, 131.0 (t, $^4J_{C,F}$ = 2 Hz), 132.6 (t, $^2J_{C,F}$ = 25 Hz), 164.6 (t, $^2J_{C,F}$ = 35 Hz); ^{19}F NMR δ −104.3 (s); IR (neat) 1769 cm^{-1}; MS (EI) m/z 186 (M^+, 13), 127 (100), 77 (75).

General Procedure for the Reduction of Difluoro Esters 2a–e to Difluoro Aldehyde Hemiacetals 3a–e. Solid sodium borohydrate (25.0 mmol) was added in four batches (at 15 min intervals) to a solution of difluoro ester (25.0 mmol) in MeOH (25 mL). Just prior to each addition the internal temperature of the reaction was brought to −60 °C and then left to rise to −50/−45 °C. After 1–4 h of vigorous stirring at −50/−45 °C, the slurry was quenched by slow addition of 75 mL of 1 N HCl (at ≤−60 °C) and then allowed to reach room temperature. The reaction mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with water (2 × 50 mL) and dried. Removal of the solvent afforded crude aldehyde hemiacetals, which were used in the next step of the synthesis without further purification.

1-Ethoxy-2,2-difluoro-1-propanol (3a). After 1 h, **2a** yielded a crude mixture containing the ethyl hemiacetal **3a** and the corresponding methyl hemiacetal (73:27). For **3a**: ^{1}H NMR δ 1.25 (t, J = 7.0 Hz, 3 H), 1.63 (t, $^3J_{H,F}$ = 19.0 Hz, 3 H), 1.80–2.45 (hump, 1 H), 3.62 and 3.91 (AB part of ABX_3 system, $J_{AX} = J_{BX}$ = 7.0 Hz, J_{AB} = 9.6 Hz, 2 H), 4.63 (dd, $^3J_{H,F}$ = 4.9, 7.4 Hz, 1 H); ^{19}F NMR δ −105.9 (ddq, $^2J_{F,F}$ = 250.5 Hz, $^3J_{H,F}$ = 5.0, 19.0 Hz, 1 F), −110.6 (ddq, $^2J_{F,F}$ = 250.5 Hz, $^3J_{H,F}$ = 7.5, 19.0 Hz, 1 F). For 2,2-difluoro-1-methoxy-1-propanol: ^{1}H NMR δ 1.62 (t, $^3J_{H,F}$ = 19.0 Hz, 3 H), 1.80–2.45 (hump, 1 H), 3.52 (s, 3 H), 4.54 (dd, $^3J_{H,F}$ = 4.9, 7.3 Hz, 1 H); ^{19}F NMR δ −106.0 (ddq, $^2J_{F,F}$ = 251.5 Hz, $^3J_{H,F}$ = 5.0, 19.0 Hz, 1 F), −110.5 (ddq, $^2J_{F,F}$ = 251.5 Hz, $^3J_{H,F}$ = 7.5, 19.0 Hz, 1 F).

2,2-Difluoro-1-methoxy-1-butanol (3b). After 2 h, **2b** yielded a crude oil of **3b**: ^{1}H NMR δ 1.04 (t, J = 7.5 Hz, 3 H), 1.40–1.75 (hump, 1 H), 1.82–2.08 (m, 2 H), 3.52 (s, 3 H), 4.55 (dd, $^3J_{H,F}$ = 5.2, 8.1 Hz, 1 H); ^{19}F NMR δ −116.5 (dddd, $^2J_{F,F}$ = 250.5 Hz, $^3J_{H,F}$ = 5.0, 14.0, 23.5 Hz, 1 F), −119.8 (dddd, $^2J_{F,F}$ = 250.5 Hz, $^3J_{H,F}$ = 8.0, 11.5, 23.0 Hz, 1 F).

1-Ethoxy-2,2-difluoro-3-methyl-1-butanol (3c). After 4 h, **2c** yielded a crude mixture containing the ethyl hemiacetal **3c** and the corresponding methyl hemiacetal (60:40). For **3c**: ^{1}H NMR δ 1.01 and 1.06 (d each, J = 6.9 Hz, 3 H each), 1.25 (t, J = 7.0 Hz, 3 H), 1.40–1.75 (hump, 1 H), 2.20–2.42 (m, 1 H), 3.60 and 3.93 (AB part of ABX_3 system, $J_{AX} = J_{BX}$ = 7.0 Hz, J_{AB} = 9.7 Hz, 2 H), 4.71 (dd, $^3J_{H,F}$ = 5.7, 9.5 Hz, 1 H); ^{19}F NMR δ −125.1 (ddd, $^2J_{F,F}$ = 251.5 Hz, $^3J_{H,F}$ = 5.5, 20.0 Hz, 1 F), −126.2 (dt, $^2J_{F,F}$ = 251.5 Hz, $^3J_{H,F}$ = 10.0 Hz, 1 F). For 2,2-difluoro-1-methoxy-3-methyl-1-butanol: ^{1}H NMR δ 1.01 and 1.06 (d each, J = 6.9 Hz, 3 H each), 1.40–1.75 (hump, 1 H), 2.20–2.42 (m, 1 H), 3.51 (s, 3 H), 4.61 (dd, $^3J_{H,F}$ = 5.7, 9.2 Hz, 1 H); ^{19}F NMR δ −125.2 (ddd, $^2J_{F,F}$ = 252.0 Hz, $^3J_{H,F}$ = 5.5, 20.0 Hz, 1 F), −126.3 (dt, $^2J_{F,F}$ = 252.0 Hz, $^3J_{H,F}$ = 10.0 Hz, 1 F).

2,2-Difluoro-1-methoxy-3-phenyl-1-propanol (3d). After 1.5 h, **2d** yielded a crude oil of **3d**: ^{1}H NMR δ 2.70–3.05 (hump, 1 H), 3.13–3.47 (m, 2 H), 3.48 (s, 3 H), 4.39 (dd, $^3J_{H,F}$ = 4.8, 8.5 Hz, 1 H), 7.24–7.36 (m, 5 H); ^{19}F NMR δ −112.1 (2 × m, $^2J_{F,F}$ = 252.0 Hz, 1 F), −116.5 (2 × m, $^2J_{F,F}$ = 252.0 Hz, 1 F).

2,2-Difluoro-1-methoxy-2-phenylethanol (3e). After 1 h, **2e** yielded a crude oil of **3e**: ^{1}H NMR δ 2.25–2.70 (hump, 1 H), 3.47 (s, 3 H), 4.77 (dd, $^3J_{H,F}$ = 3.4, 7.1 Hz, 1 H), 7.44–7.55 (m, 5 H); ^{19}F NMR δ −108.4 (dd, $^2J_{F,F}$ = 255.0 Hz, $^3J_{H,F}$ = 3.5 Hz, 1 F), −114.4 (dd, $^2J_{F,F}$ = 255.0 Hz, $^3J_{H,F}$ = 7.0 Hz, 1 F).

General Procedure for the Preparation of Cyanohydrins 4a–e. Potassium cyanide (25.0 mmol) was added to a stirred suspension of crude aldehyde hemiacetal **3a–e** (obtained in the previous step from 25.0 mmol of **2a–e**) and KH_2PO_4 (25.0 mmol) in water (25 mL). After 1.5 h at room temperature, the mixture was diluted with H_2O (30 mL) and the product extracted in Et_2O (3 × 50 mL). The combined organic layers were washed sequentially with 2.0% H_2SO_4 and H_2O (3 × 50 mL of each) and then dried. The solvent was evaporated, and the residual oil was purified either by column chromatography or distillation under reduced pressure.

3,3-Difluoro-2-hydroxybutanenitrile (4a). Distillation at 93–94 °C/16 mmHg yielded 1.94 g of **4a** as a colorless oil (64% overall yield from the corresponding difluoro ester **2a**): ^{1}H NMR δ 1.82 (t, $^3J_{H,F}$ = 18.6 Hz, 3 H), 2.97 (d, J = 8.0 Hz, 1 H), 4.60 (ddd, J = 8.0 Hz, $^3J_{H,F}$ = 7.1, 9.6 Hz, 1 H); ^{13}C NMR δ 19.1 (t, $^2J_{C,F}$ = 25 Hz), 64.5 (dd, $^2J_{C,F}$ = 33, 36 Hz), 115.4 (dd, $^3J_{C,F}$ = 3, 5 Hz), 120.0 (t, $^1J_{C,F}$ = 246 Hz); ^{19}F NMR δ −101.3 (ddq, $^2J_{F,F}$ = 252.0 Hz, $^3J_{H,F}$ = 7.0, 18.5 Hz, 1 F), −102.5 (ddq, $^2J_{F,F}$ = 252.0 Hz, $^3J_{H,F}$ = 10.0, 18.5 Hz, 1 F); IR (neat) 3418, 2263 cm^{-1}; MS (CI, CH_4) m/z 122 (MH^+, 100), 102 (5), 95 (11), 75 (3). Anal. Calcd for $C_4H_5F_2NO$: C, 39.67; H, 4.16; F, 31.38; N, 11.57. Found: C, 39.36; H, 4.20; F, 31.26; N, 11.50.

3,3-Difluoro-2-hydroxypentanenitrile (4b). Distillation at 101–102 °C/16 mmHg yielded 2.06 g of **4b** as a colorless oil

(31) De Boer, T. J.; Backer, H. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 250. With this method, in the case of methyl phenylpyruvate (**1d**) we detected (^{1}H NMR) the formation of 7% of the corresponding enol. To minimize enolization it is important to react **1d** as soon as possible after its preparation.

(32) Sciacovelli, O.; Dell'Atti, A.; De Giglio, A.; Cassidei, L. *Z. Naturforsch.* **1976**, *31c*, 5.

(61% overall yield from the corresponding difluoro ester **2b**): ^{1}H NMR δ 1.12 (t, J = 7.5 Hz, 3 H), 2.00–2.19 (m, 2 H), 3.27 (d, J = 8.2 Hz, 1 H), 4.62 (ddd, J = 8.2 Hz, $^3J_{H,F}$ = 7.1, 11.2 Hz, 1 H); ^{13}C NMR δ 5.4 (t, $^3J_{C,F}$ = 5 Hz), 25.6 (t, $^2J_{C,F}$ = 24 Hz), 63.9 (dd, $^2J_{C,F}$ = 32, 35 Hz), 115.3 (t, $^3J_{C,F}$ = 4 Hz), 120.8 (t, $^1J_{C,F}$ = 249 Hz); ^{19}F NMR δ −110.8 (dddd, $^2J_{F,F}$ = 251.0 Hz, $^3J_{H,F}$ = 7.0, 17.0, 20.0 Hz, 1 F), −112.0 (dddd, $^2J_{F,F}$ = 251.0 Hz, $^3J_{H,F}$ = 11.0, 15.5, 18.0 Hz, 1 F); IR (neat) 3416, 2264 cm^{-1}; MS (CI, CH_4) m/z 136 (MH^+, 100), 116 (2), 109 (28), 96 (2), 89 (15). Anal. Calcd for $C_5H_7F_2NO$: C, 44.44; H, 5.22; F, 28.12; N, 10.37. Found: C, 44.14; H, 5.37; F, 28.08; N, 10.28.

3,3-Difluoro-2-hydroxy-4-methylpentanenitrile (4c). Distillation at 99–100 °C/10 mmHg yielded 2.16 g of **4c** as a colorless oil (58% overall yield from the corresponding difluoro ester **2c**): ^{1}H NMR δ 1.08 and 1.12 (d each, J = 6.9 Hz, 3 H each) 2.28–2.52 (m, 1 H), 3.98 (d, J = 9.0 Hz, 1 H), 4.71 (overlapping ddd, $J_{H,H}$ = $^3J_{H,F}$ = 9.0 Hz, $^3J_{H,F}$ = 11.8 Hz, 1 H); ^{13}C NMR δ 14.7 (t, $^3J_{C,F}$ = 5 Hz), 15.4 (t, $^3J_{C,F}$ = 5 Hz), 31.1 (t, $^2J_{C,F}$ = 22 Hz), 62.9 (t, $^2J_{C,F}$ = 33 Hz), 115.4 (t, $^3J_{C,F}$ = 3 Hz), 121.6 (t, $^1J_{C,F}$ = 251 Hz); ^{19}F NMR δ −117.3 (ddd, $^2J_{F,F}$ = 252.5 Hz, $^3J_{H,F}$ = 9.0, 16.0 Hz, 1 F), −117.6 (ddd, $^2J_{F,F}$ = 252.5 Hz, $^3J_{H,F}$ = 12.0, 14.0 Hz, 1 F); IR (neat) 3407, 2264 cm^{-1}; MS (CI, CH_4) m/z 150 (MH^+, 100), 130 (3), 123 (21), 110 (3), 103 (7). Anal. Calcd for $C_6H_9F_2NO$: C, 48.32; H, 6.08; F, 25.48; N, 9.39. Found: C, 48.08; H, 6.18; F, 25.33; N, 9.34.

3,3-Difluoro-2-hydroxy-4-phenylbutanenitrile (4d). Chromatography (2:1 hexane/EtOAc) yielded 3.15 g of **4d** as a pale yellow oil (64% overall yield from the corresponding difluoro ester **2d**), which was crystallized from $CHCl_3$–hexane: mp 74–76 °C; ^{1}H NMR δ 3.03 (d, J = 9.1 Hz, 1 H), 3.27–3.49 (m, 2 H), 4.47 (ddd, J = 9.1 Hz, $^3J_{H,F}$ = 6.0, 13.2 Hz, 1 H), 7.29–7.38 (m, 5 H); ^{13}C NMR δ 38.8 (dd, $^2J_{C,F}$ = 23, 24 Hz), 63.0 (dd, $^2J_{C,F}$ = 30, 34 Hz), 114.9 (t, $^3J_{C,F}$ = 3 Hz), 119.6 (t, $^1J_{C,F}$ = 251 Hz), 128.2, 128.9, 130.4, 130.6 (dd, $^3J_{C,F}$ = 3, 6 Hz); ^{19}F NMR δ −107.1 (dddd, $^2J_{F,F}$ = 252.5 Hz, $^3J_{H,F}$ = 6.0, 18.0, 19.5 Hz, 1 F), −108.6 (ddt, $^2J_{F,F}$ = 252.5 Hz, $^3J_{H,F}$ = 13.0, 15.0 Hz, 1 F); IR (CCl_4) 3578, 3413, 2256 cm^{-1}; MS (CI, CH_4) m/z 198 (MH^+, 100), 178 (3), 153 (9), 151 (11). Anal. Calcd for $C_{10}H_9F_2NO$: C, 60.91; H, 4.60; F, 19.27; N, 7.10. Found: C, 60.64; H, 4.61; F, 19.35; N, 7.01.

3,3-Difluoro-2-hydroxy-3-phenylpropanenitrile (4e). Distillation at 109–110 °C/1.3 mmHg yielded 3.25 g of **4e** as a colorless oil (71% yield from the corresponding difluoro ester **2e**): ^{1}H NMR δ 2.85 (d, J = 8.9 Hz, 1 H), 4.83 (overlapping dt, J = 8.9 Hz, $^3J_{H,F}$ = 8.7 Hz, 1 H), 7.51–7.61 (m, 5 H); ^{13}C NMR δ 65.8 (t, $^2J_{C,F}$ = 37 Hz), 114.7 (t, $^3J_{C,F}$ = 4 Hz), 117.9 (t, $^1J_{C,F}$ = 251 Hz), 126.1 (t, $^3J_{C,F}$ = 6 Hz), 128.8, 130.9 (t, $^2J_{C,F}$ = 25 Hz), 131.4 (t, $^4J_{C,F}$ = 2 Hz); ^{19}F NMR δ −106.5 (dd, $^2J_{F,F}$ = 252.0 Hz, $^3J_{H,F}$ = 8.5 Hz, 1 F), −107.3 (dd, $^2J_{F,F}$ = 252.0 Hz, $^3J_{H,F}$ = 8.5 Hz, 1 F); IR (neat) 3403, 2264 cm^{-1}; MS (CI, CH_4) m/z 184 (MH^+, 100), 164 (5), 157 (9), 137 (30). Anal. Calcd for $C_9H_7F_2NO$: C, 59.02; H, 3.85; F, 20.75; N, 7.65. Found: C, 58.82; H, 3.90; F, 20.46; N, 7.51.

General Procedure for the Preparation of Hydroxy Esters 5a–e. The appropriate cyanohydrin **4a–e** (14.0 mmol) was dissolved in absolute ethanol (7 mL) and the solution cooled to −15 °C. A gentle stream of HCl gas (dried over P_2O_5 and $CaCl_2$ towers) was bubbled through for 5 h, and the vessel was then sealed and left to stand overnight at 4 °C. Ethanol and HCl in excess were removed from the reaction mixture with a water pump, while the flask was kept in a bath at 40 °C with stirring. The slurry of the imino ester hydrochloride was taken up in ice–water (50 mL) containing Na_2CO_3 (3.0 g), and the solution was extracted with ether (3 × 30 mL). The organic extracts were washed with aqueous 5% NaCl (3 × 50 mL) and then cooled at 0 °C. The chilled ethereal solution was extracted with ice–water (30 mL) containing concentrated H_2SO_4 (1.5 g) in three aliquots, each time shaking the mixture for 15 s and collecting the aqueous layer. The aqueous layers were heated at 50 °C for 30 min, cooled, and extracted with ether (3 × 30 mL). The organic fractions were combined, dried, and concentrated to afford after distillation under reduced pressure or chromatography the hydroxy esters **5a–e** in 60–73% yield.

Ethyl 3,3-Difluoro-2-hydroxybutanoate (5a). Distillation under reduced pressure gave **5a** (62%) as a colorless oil: bp 90–91 °C/38 mmHg; ^{1}H NMR δ 1.34 (t, J = 7.1 Hz, 3 H), 1.70 (t, $^3J_{H,F}$ = 18.8 Hz, 3 H), 3.25 (d, J = 7.5 Hz, 1 H), 4.24 (overlapping ddd, $J_{H,H}$ = $^3J_{H,F}$ = 7.5 Hz, $^3J_{H,F}$ = 15.0 Hz, 1 H), 4.33 and 4.37 (AB part of ABX_3 system, J_{AX} = J_{BX} = 7.1 Hz, J_{AB} = 10.8 Hz, 2 H); ^{13}C NMR δ 14.0, 20.3 (t, $^2J_{C,F}$ = 26 Hz), 62.8, 72.8 (dd, $^2J_{C,F}$ = 29, 31 Hz), 121.3 (t, $^1J_{C,F}$ = 246 Hz), 169.8 (t, $^3J_{C,F}$ = 3 Hz); ^{19}F NMR δ −100.0 (ddq, $^2J_{F,F}$ = 249.0 Hz, $^3J_{H,F}$ = 7.5, 19.0 Hz, 1 F), −103.2 (ddq, $^2J_{F,F}$ = 249.0 Hz, $^3J_{H,F}$ = 15.0, 19.0 Hz, 1 F); IR (neat) 3469, 1738 cm^{-1}; MS (CI, CH_4) m/z 169 (MH^+, 100), 154 (16), 149 (12), 141 (9). Anal. Calcd for $C_6H_{10}F_2O_3$: C, 42.86; H, 5.99; F, 22.60. Found: C, 42.90; H, 6.16; F, 22.41.

Ethyl 3,3-Difluoro-2-hydroxypentanoate (5b). Distillation under reduced pressure gave **5b** (63%) as a colorless oil: bp 91–92 °C/14 mmHg; ^{1}H NMR δ 1.07 (t, J = 7.5 Hz, 3 H), 1.34 (t, J = 7.1 Hz, 3 H), 1.89–2.18 (m, 2 H), 3.21 (d, J = 7.9 Hz, 1 H), 4.27 (ddd, J = 7.9 Hz, $^3J_{H,F}$ = 6.6, 17.1 Hz, 1 H), 4.33 and 4.37 (AB part of ABX_3 system, J_{AX} = J_{BX} = 7.1 Hz, J_{AB} = 10.7 Hz, 2 H); ^{13}C NMR δ 5.8 (dd, $^3J_{C,F}$ = 5, 7 Hz), 14.0, 26.6 (t, $^2J_{C,F}$ = 24 Hz), 62.8, 71.7 (dd, $^2J_{C,F}$ = 29, 32 Hz), 122.3 (t, $^1J_{C,F}$ = 248 Hz), 170.0 (dd, $^3J_{C,F}$ = 1, 3 Hz); ^{19}F NMR δ −110.6 (dddd, $^2J_{F,F}$ = 248.5 Hz, $^3J_{H,F}$ = 6.5, 17.0, 21.5 Hz, 1 F), −112.3 (dddd, $^2J_{F,F}$ = 248.5 Hz, $^3J_{H,F}$ = 12.0, 17.0, 19.5 Hz, 1 F); IR (neat) 3480, 1742 cm^{-1}; MS (CI, CH_4) m/z 183 (MH^+, 46), 163 (12), 155 (73), 154 (34), 127 (40), 117 (100). Anal. Calcd for $C_7H_{12}F_2O_3$: C, 46.15; H, 6.64; F, 20.86. Found: C, 46.05; H, 6.67; F, 20.98.

Ethyl 3,3-Difluoro-2-hydroxy-4-methylpentanoate (5c). Following chromatography (4:1 hexane/EtOAc) **5c** was isolated (60%) as a colorless oil. Crystallization from petroleum ether gave a white solid: mp 29–30 °C; ^{1}H NMR δ 1.07 and 1.08 (d each, J = 6.9 Hz, 3 H each), 1.34 (t, J = 7.1 Hz, 3 H), 2.29–2.53 (m, 1 H), 3.22 (d, J = 8.0 Hz, 1 H), 4.35 (ddd, J = 8.0 Hz, $^3J_{H,F}$ = 4.7, 21.3 Hz, 1 H), 4.33 and 4.37 (AB part of ABX_3 system, J_{AX} = J_{BX} = 7.1 Hz, J_{AB} = 10.8 Hz, 2 H); ^{13}C NMR δ 14.0, 14.3 (t, $^3J_{C,F}$ = 5 Hz) 15.9 (dd, $^3J_{C,F}$ = 3, 7 Hz), 31.5 (t, $^2J_{C,F}$ = 23 Hz), 62.8, 70.6 (dd, $^2J_{C,F}$ = 28, 34 Hz), 123.3 (t, $^1J_{C,F}$ = 251 Hz), 170.3 (d, $^3J_{C,F}$ = 3 Hz); ^{19}F NMR δ −117.1 (ddd, $^2J_{F,F}$ = 249.5 Hz, $^3J_{H,F}$ = 8.5, 21.5 Hz, 1 F), −120.7 (ddd, $^2J_{F,F}$ = 249.5 Hz, $^3J_{H,F}$ = 4.5, 22.5 Hz, 1 F); IR (neat) 3502, 1741 cm^{-1}; MS (CI, CH_4) m/z 197 (MH^+, 100), 177 (3), 169 (1), 159 (4). Anal. Calcd for $C_8H_{14}F_2O_3$: C, 48.98; H, 7.19; F, 19.37. Found: C, 48.78; H, 7.19; F, 19.19.

Ethyl 3,3-Difluoro-2-hydroxy-4-phenylbutanoate (5d). Following chromatography (2:1 EtOAc/petroleum ether) **5d** was isolated (73%) as a colorless oil. Crystallization from $CHCl_3$–petroleum ether gave a white solid: mp 56–58 °C; ^{1}H NMR δ 1.30 (t, J = 7.1 Hz, 3 H), 3.18–3.47 (m, 2 H), 3.33 (d, J = 7.6 Hz, 1 H), 4.14 (ddd, J = 7.6 Hz, $^3J_{H,F}$ = 4.8, 19.4 Hz, 1 H), 4.28 and 4.31 (AB part of ABX_3 system, J_{AX} = J_{BX} = 7.1 Hz, J_{AB} = 10.7 Hz, 2 H), 7.31–7.35 (m, 5 H); ^{13}C NMR δ 14.0, 39.7 (dd, $^2J_{C,F}$ = 23, 25 Hz), 62.9, 70.7 (dd, $^2J_{C,F}$ = 28, 32 Hz), 121.2 (t, $^1J_{C,F}$ = 250 Hz), 127.5, 128.5, 130.7, 132.0 (dd, $^3J_{C,F}$ = 2, 7 Hz), 169.9 (d, $^3J_{C,F}$ = 2 Hz); ^{19}F NMR δ −107.0 (dddd, $^2J_{F,F}$ = 249.5 Hz, $^3J_{H,F}$ = 5.0, 18.5, 21.5 Hz, 1 F), −109.6 (dddd, $^2J_{F,F}$ = 249.5 Hz, $^3J_{H,F}$ = 11.0, 15.0, 19.5 Hz, 1 F); IR (CCl_4) 3511, 1737 cm^{-1}; MS (CI, CH_4) m/z 245 (MH^+, 100), 225 (4), 217 (6), 207 (14), 179 (5). Anal. Calcd for $C_{12}H_{14}F_2O_3$: C, 59.01; H, 5.78; F, 15.56. Found: C, 58.78; H, 5.77; F, 15.59.

Ethyl 3,3-Difluoro-2-hydroxy-3-phenylpropanoate (5e). Following chromatography (1:1 hexane/EtOAc) **5e** was isolated (66%) as a colorless oil. Crystallization from $CHCl_3$–petroleum ether gave a white solid: mp 59–60 °C; ^{1}H NMR δ 1.26 (t, J = 7.1 Hz, 3 H), 3.22 (d, J = 8.1 Hz, 1 H), 4.26 and 4.27 (AB part of ABX_3 system, J_{AX} = J_{BX} = 7.1 Hz, J_{AB} = 10.7 Hz, 2 H), 4.53 (ddd, J = 8.1 Hz, $^3J_{H,F}$ = 7.6, 12.8 Hz, 1 H), 7.40–7.51 (m, 5 H); ^{13}C NMR δ 13.7, 62.6, 73.6 (t, $^2J_{C,F}$ = 32 Hz), 119.1 (t, $^1J_{C,F}$ = 251 Hz), 125.7 (t, $^3J_{C,F}$ = 6 Hz), 128.2, 130.3 (t, $^4J_{C,F}$ = 2 Hz), 133.4 (t, $^2J_{C,F}$ = 26 Hz), 169.3 (t, $^3J_{C,F}$ = 3 Hz); ^{19}F NMR δ −103.8 (dd, $^2J_{F,F}$ = 252.0 Hz, $^3J_{H,F}$ = 7.5 Hz, 1 F), −108.1 (dd, $^2J_{F,F}$ = 252.0 Hz, $^3J_{H,F}$ = 13.0 Hz, 1 F); IR (CCl_4) 3515, 1738 cm^{-1}; MS (CI, CH_4) m/z 231 (MH^+, 43), 211 (100), 191 (13), 183 (45), 163 (37). Anal. Calcd for $C_{11}H_{12}F_2O_3$: C, 57.39; H, 5.25; F, 16.51. Found: C, 57.44; H, 5.33; F, 16.54.

General Procedure for the Oxidation of Difluoro Hydroxy Esters 5a–e to Difluoro Keto Esters 6a–e. A procedure analogous to that reported by Linderman[27] was

employed. Dess–Martin reagent[26] (18.5 mmol) was added to a solution of the hydroxy ester (5.0 mmol) in anhydrous CH_2Cl_2 (30 mL) under an argon atmosphere. The suspension was stirred at room temperature for 3 h, diluted with ether (100 mL) and poured into a saturated aqueous solution of $NaHCO_3$ (150 mL) containing $Na_2S_2O_3 \cdot 5H_2O$ (129.5 mmol). The biphasic mixture was stirred until both layers were clear and then separated. The aqueous phase was saturated with NaCl and extracted with EtOAc (5 × 50 mL). All the organic layers were combined, dried, and evaporated. After chromatographic purification, products were isolated as a mixture of keto ester and corresponding hydrate, and product ratio was determined by integration of the respective ^{19}F NMR signals. ^1H and ^{13}C NMR data reported below are relative to the hydrated form, which is in all instances the highly predominant one.

Ethyl 3,3-Difluoro-2-oxobutanoate (6a). Chromatography (4:1 CH_2Cl_2/Et_2O) gave **6a** (75%) as a colorless oil: bp 64 °C/0.9 mmHg; ^1H NMR δ 1.38 (t, J = 7.1 Hz, 3 H), 1.75 (t, $^3J_{H,F}$ = 19.0 Hz, 3 H), 3.98 (s, 1 H), 4.39 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 13.9, 17.9 (t, $^2J_{C,F}$ = 25 Hz), 63.8, 92.6 (t, $^2J_{C,F}$ = 32 Hz), 121.2 (t, $^1J_{C,F}$ = 248 Hz), 169.1; ^{19}F NMR δ −101.0 (q, $^3J_{H,F}$ = 19.0 Hz, CF_2CO), −106.3 (q, $^3J_{H,F}$ = 19.0 Hz, $CF_2C(OH)_2$), ratio 1:99; IR (neat) 3451, 1740 cm^{-1}; MS (CI, CH_4) m/z 185 (M + H_3O^+, 100), 167 (MH^+, 24), 149 (33). Anal. Calcd for $C_6H_8F_2O_3 \cdot 1.1H_2O$: C, 38.75; H, 5.53; F, 20.44. Found: C, 38.61; H, 5.53; F, 20.29.

Ethyl 3,3-Difluoro-2-oxopentanoate (6b). Chromatography (2:1 CH_2Cl_2/Et_2O) gave **6b** (78%) as a white solid: mp 39–42 °C (from $CHCl_3$–petroleum ether); ^1H NMR δ 1.08 (t, J = 7.5 Hz, 3 H), 1.38 (t, J = 7.1 Hz, 3 H), 2.08 (ddq, $^3J_{H,F}$ = 18.4, 19.3 Hz, J = 7.5 Hz, 2 H), 3.96 (s, 1 H), 4.39 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 5.1 (t, $^3J_{C,F}$ = 5 Hz), 13.9, 23.9 (t, $^2J_{C,F}$ = 24 Hz), 63.8, 92.8 (t, $^2J_{C,F}$ = 33 Hz), 121.6 (t, $^1J_{C,F}$ = 250 Hz), 169.2; ^{19}F NMR δ −109.6 (t, $^3J_{H,F}$ = 17.5 Hz, CF_2CO), −116.8 (dd, $^3J_{H,F}$ = 18.5, 19.5 Hz, $CF_2C(OH)_2$), ratio 2:98; IR (CCl_4) 3593, 3505, 1740 cm^{-1}; MS (CI, CH_4) m/z 199 (M + H_3O^+, 74), 181 (MH^+, 100), 163 (11), 161 (10), 159 (8). Anal. Calcd for $C_7H_{10}F_2O_3 \cdot H_2O$: C, 42.43; H, 6.10; F, 19.17. Found: C, 42.15; H, 6.15; F, 19.07.

Ethyl 3,3-Difluoro-4-methyl-2-oxopentanoate (6c). Chromatography (5:1 CH_2Cl_2/Et_2O) gave **6c** (77%) as a white solid: mp 19–21 °C (from petroleum ether); ^1H NMR δ 1.10 (d, J = 6.9 Hz, 6 H), 1.37 (t, J = 7.1 Hz, 3 H), 2.38–2.57 (m, 1 H), 4.06 (s, 1 H), 4.38 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 13.9, 15.7 (t, $^3J_{C,F}$ = 5 Hz), 30.9 (t, $^2J_{C,F}$ = 23 Hz), 63.8, 93.4 (t, $^2J_{C,F}$ = 34 Hz), 122.0 (t, $^1J_{C,F}$ = 253 Hz), 169.5; ^{19}F NMR δ −115.9 (d, $^3J_{H,F}$ = 15.5 Hz, CF_2CO), −118.1 (d, $^3J_{H,F}$ = 15.0 Hz, $CF_2C(OH)_2$), ratio 3:97; IR (neat) 3468, 1737 cm^{-1}; MS (CI, CH_4) m/z 213 (M + H_3O^+, 35) 195 (MH^+, 100), 177 (9), 175 (10), 173 (10). Anal. Calcd for $C_8H_{12}F_2O_3 \cdot 1.2H_2O$: C, 44.52; H, 6.72; F, 17.61. Found: C, 44.43; H, 6.77; F, 17.28.

Ethyl 3,3-Difluoro-2-oxo-4-phenylbutanoate (6d). Chromatography (2:1 EtOAc/petroleum ether) gave **6d** (89%) as a white solid: mp 60–61 °C (from $CHCl_3$–petroleum ether); ^1H NMR δ 1.33 (t, J = 7.1 Hz), 3.38 (t, $^3J_{H,F}$ = 18.5 Hz, 2 H), 4.04 (s, 1 H), 4.31 (q, J = 7.1 Hz, 2 H), 7.29–7.34 (m, 5 H); ^{13}C NMR δ 13.9, 36.9 (t, $^2J_{C,F}$ = 23 Hz), 63.9, 92.7 (t, $^2J_{C,F}$ = 32 Hz), 120.1 (t, $^1J_{C,F}$ = 252 Hz), 127.5, 128.4, 130.9, 131.5 (t, $^3J_{C,F}$ = 3 Hz), 168.8; ^{19}F NMR δ −106.0 (t, $^3J_{H,F}$ = 17.5 Hz, CF_2CO), −112.3 (t, $^3J_{H,F}$ = 18.5 Hz, $CF_2C(OH)_2$), ratio 5:95; IR (CCl_4) 3590, 3497, 1738 cm^{-1}; MS (EI) m/z 242 (M^+, 2), 222 (62), 141 (98), 91 (100). Anal. Calcd for $C_{12}H_{12}F_2O_3 \cdot H_2O$: C, 55.38; H, 5.42; F, 14.60. Found: C, 55.65; H, 5.46; F, 14.37.

Ethyl 3,3-Difluoro-2-oxo-3-phenylpropanoate (6e). Chromatography (1:1 hexane/EtOAc) gave **6e** (81%) as a white solid: mp 55–56 °C (from hexane); ^1H NMR δ 1.38 (t, J = 7.1 Hz, 3 H), 3.97 (s, 1 H), 4.40 (q, J = 7.1 Hz, 2 H), 7.41–7.61 (m, 5 H); ^{13}C NMR δ 13.7, 63.8, 93.0 (t, $^2J_{C,F}$ = 34 Hz), 118.4 (t, $^1J_{C,F}$ = 253 Hz), 127.0 (t, $^3J_{C,F}$ = 6 Hz), 127.8, 130.4 (t, $^4J_{C,F}$ = 2 Hz), 131.7 (t, $^2J_{C,F}$ = 25 Hz), 168.9; ^{19}F NMR δ −105.6 (s, CF_2CO), −110.2 (s, $CF_2C(OH)_2$), ratio 6:94; IR (CCl_4) 3585, 3487, 1739 cm^{-1}; MS (EI) m/z 228 (M^+, 3), 127 (100), 77 (8). Anal. Calcd for $C_{11}H_{10}F_2O_3 \cdot 1.4H_2O$: C, 52.13; H, 5.09; F, 14.99. Found: C, 51.88; H, 4.97; F, 15.34.

General Procedure for the Preparation of Difluoro Keto Acids 7a–e. A solution of keto ester **6a–e** (2.0 mmol) in water–2-propanol (5 mL, 1:1) containing $NaHCO_3$ (5.0 mmol) was stirred overnight at 40–45 °C. The mixture was concentrated to dryness under reduced pressure, the residue obtained was taken up in water (10 mL) and washed with EtOAc (3 × 10 mL). The aqueous phase was acidified to pH *ca.* 2 with 1 N HCl, saturated with NaCl, and then extracted with EtOAc (5 × 10 mL). The combined organic extracts were dried, and the solvent was removed to yield pure materials as a mixture of keto acid and corresponding hydrate. Product ratio was determined by integration of the respective ^{19}F NMR signals. ^1H and ^{13}C NMR data reported below are relative to the hydrated form, which is in all cases the highly predominant one.

3,3-Difluoro-2-oxobutanoic Acid (7a). Obtained from **6a** in 62% yield: mp 79–82 °C (from Et_2O–petroleum ether); ^1H NMR (acetone-d_6) δ 1.71 (t, $^3J_{H,F}$ = 19.0 Hz, 3 H), 5.80–6.55 (hump, 1 H); ^{13}C NMR (acetone-d_6) δ 18.7 (t, $^2J_{C,F}$ = 26 Hz), 93.4 (t, $^2J_{C,F}$ = 31 Hz), 122.6 (t, $^1J_{C,F}$ = 247 Hz), 170.8; ^{19}F NMR (acetone-d_6) δ −99.9 (q, $^3J_{H,F}$ = 20.0 Hz, CF_2CO), −104.8 (q, $^3J_{H,F}$ = 19.0 Hz, $CF_2C(OH)_2$), ratio 2:98; IR (Nujol) 3186, 1749 cm^{-1}; MS (CI, CH_4) m/z 157 (M + H_3O^+, 10), 139 (MH^+, 100), 121 (8), 119 (7), 111 (9). Anal. Calcd for $C_4H_4F_2O_3 \cdot H_2O$: C, 30.78; H, 3.87; F, 24.34. Found: C, 30.69; H, 3.84; F, 24.14.

3,3-Difluoro-2-oxopentanoic Acid (7b). Obtained from **6b** in 76% yield: mp 89–91 °C (from Et_2O–petroleum ether); ^1H NMR (acetone-d_6) δ 1.01 (t, J = 7.5 Hz, 3 H), 2.12 (ddq, $^3J_{H,F}$ = 18.4, 19.4 Hz, J = 7.5 Hz, 2 H), 5.70–6.25 (hump, 1 H); ^{13}C NMR (acetone-d_6) δ 5.4 (t, $^3J_{C,F}$ = 5 Hz), 24.7 (t, $^2J_{C,F}$ = 24 Hz), 93.7 (t, $^2J_{C,F}$ = 31 Hz), 122.9 (t, $^1J_{C,F}$ = 249 Hz), 170.9; ^{19}F NMR (acetone-d_6) δ −108.9 (t, $^3J_{H,F}$ = 18.0 Hz, CF_2CO), −116.0 (dd, $^3J_{H,F}$ = 18.5, 19.5 Hz, $CF_2C(OH)_2$), ratio 3:97; IR (Nujol) 3286, 1737 cm^{-1}; MS (CI, CH_4) m/z 171 (M + H_3O^+, 12), 153 (MH^+, 100), 133 (31), 105 (15), 87 (45). Anal. Calcd for $C_5H_6F_2O_3 \cdot H_2O$: C, 35.30; H, 4.74; F, 22.34. Found: C, 35.21; H, 4.76; F, 22.43.

3,3-Difluoro-4-methyl-2-oxopentanoic Acid (7c). Obtained from **6c** in 75% yield: mp 68–71 °C (from Et_2O–petroleum ether); ^1H NMR (acetone-d_6) δ 1.08 (d, J = 6.9 Hz, 6 H), 2.40–2.64 (m, 1 H), 5.85–6.20 (hump, 1 H); ^{13}C NMR (acetone-d_6) δ 16.4 (t, $^3J_{C,F}$ = 5 Hz), 31.7 (t, $^2J_{C,F}$ = 23 Hz), 94.4 (t, $^2J_{C,F}$ = 33 Hz), 123.0 (t, $^1J_{C,F}$ = 252 Hz), 171.3; ^{19}F NMR (acetone-d_6) δ −115.3 (d, $^3J_{H,F}$ = 16.0 Hz, CF_2CO), −117.3 (d, $^3J_{H,F}$ = 15.0 Hz, $CF_2C(OH)_2$), ratio 6:94; IR (Nujol) 3252, 1738 cm^{-1}; MS (CI, CH_4) m/z 185 (M + H_3O^+, 3), 167 (MH^+, 100), 147 (38), 127 (22), 99 (40), 83 (60). Anal. Calcd for $C_6H_8F_2O_3 \cdot H_2O$: C, 39.14; H, 5.47; F, 20.63. Found: C, 38.78; H, 5.48; F, 20.59.

3,3-Difluoro-2-oxo-4-phenylbutanoic Acid (7d). Obtained from **6d** in 87% yield: mp 101–103 °C (from $CHCl_3$–petroleum ether); ^1H NMR (acetone-d_6) δ 3.43 (dd, $^3J_{H,F}$ = 18.8, 20.2 Hz, 2 H), 6.05–6.45 (hump, 1 H), 7.26–7.32 (m, 5 H); ^{13}C NMR (acetone-d_6) δ 37.3 (t, $^2J_{C,F}$ = 23 Hz), 93.7 (t, $^2J_{C,F}$ = 31 Hz), 121.5 (t, $^1J_{C,F}$ = 251 Hz), 127.7, 128.8, 131.7, 133.6 (t, $^3J_{C,F}$ = 2 Hz), 170.7; ^{19}F NMR (acetone-d_6) δ −105.5 (t, $^3J_{H,F}$ = 18.0 Hz, CF_2CO), −112.8 (dd, $^3J_{H,F}$ = 19.0, 20.0 Hz, $CF_2C(OH)_2$), ratio 5:95; IR (Nujol) 3291, 1753, 1726 cm^{-1}; MS (EI) m/z 214 (M^+, 12), 194 (34), 149 (21), 141 (40), 91 (100). Anal. Calcd for $C_{10}H_8F_2O_3 \cdot H_2O$: C, 51.73; H, 4.34; F, 16.36. Found: C, 51.81; H, 4.33; F, 16.26.

3,3-Difluoro-2-oxo-3-phenylpropanoic Acid (7e). Obtained from **6e** in 84% yield: mp 90–91 °C (from Et_2O–benzene); ^1H NMR (acetone-d_6) δ 3.20–3.85 (hump, 1 H), 7.38–7.63 (m, 5 H); ^{13}C NMR (acetone-d_6) δ 94.0 (t, $^2J_{C,F}$ = 33 Hz), 120.1 (t, $^1J_{C,F}$ = 252 Hz), 128.2 (t, $^3J_{C,F}$ = 7 Hz), 128.3, 130.8 (t, $^4J_{C,F}$ = 2 Hz), 134.1 (t, $^2J_{C,F}$ = 25 Hz), 170.7; ^{19}F NMR (acetone-d_6) δ −103.9 (s, CF_2CO), −107.9 (s, $CF_2C(OH)_2$), ratio 2:98; IR (Nujol) 3184, 1751, 1736 cm^{-1}; MS (EI) m/z 200 (M^+, 1), 127 (100), 77 (15). Anal. Calcd for $C_9H_8F_2O_3 \cdot H_2O$: C, 49.55; H, 3.70; F, 17.42. Found: C, 49.46; H, 3.65; F, 17.54.

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