Preparation and Reaction of Difluorinated Malonaldehydic Acid Derivatives: a New Route to Functionalized α,α-Difluorinated Esters and Amides

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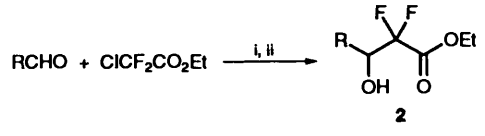
Formylation of difluorinated Reformatsky reagents derived from chlorodifluoroacetic acid derivatives provided β,β-difluorinated *N,O*-acetals, which were easily converted into the corresponding ethyl hemiacetals. These compounds were found to be effective aldehyde equivalents and reacted with active methylene compounds, nitromethane, or phosphonoacetate to afford α,α-difluoro-functionalized esters and amides in good yields.

In recent years, the difluoromethylene group has attracted much attention largely due to a multitude of studies on compounds containing such moiety that exhibit excellent biological activities.[1] This moiety has a steric profile similar to that of the methylene group but has a very different polarity and a drastically altered reactivity. In addition, it has been argued that the difluoromethylene functionality could be regarded as an isopolar and isosteric replacement for ether oxygen[2] and that exchange of the oxygen at the biochemically labile position for the difluoromethylene unit may enhance its stability with retention of biological activities shown by the parent compound.[3]

A Reformatsky reaction of halogenodifluoroacetates with electrophiles has been widely used as a method for the introduction of difluromethylene groups into compounds,[4–9] and has been applied to the synthesis of gem-difluorinated analogues of natural products, such as deoxy sugars,[5] β-lactams,[6] malic acid[7] and pepstatin.[8] Lang and Schaub reported the preparation of α,α-difluoro-β-hydroxy esters **2** by the addition of a Reformatsky reagent derived from ethyl chlorodifluoroacetate **1a** with various aldehydes in DMF (Scheme 1).[9]



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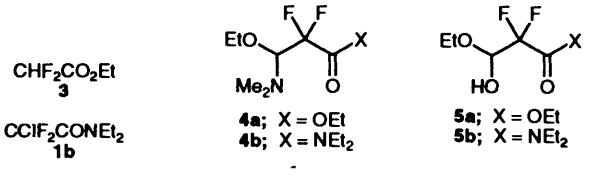
Scheme 1 *Reagents and conditions:* i, zinc, DMF, 70 °C; ii, H_3O^+

Although somewhat less reactive, this reagent seems to be the most attractive CF_2 source, since **1a** is readily available and inexpensive.

The above reaction when performed in the absence of aldehyde, gave ethyl difluoroacetate **3** quantitatively after aqueous work-up. However, use of only 0.5 equiv. of zinc gave a Vilsmeier-type formylation of the Reformatsky reagent and formation of the gem-difluorinated *N,O*-acetal **4a** as the main product. The acetal thus obtained was readily converted into the corresponding ethyl hemiacetal **5a**, which shows promise as



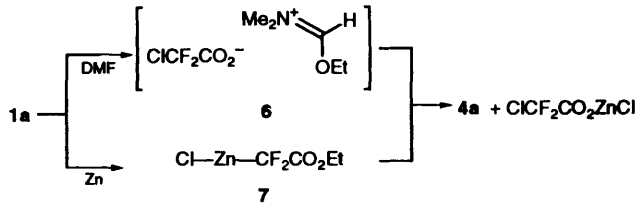
a versatile building block for the synthesis of α,α-difluoro-functionalized esters. We report here the experimental details for formylation of the Reformatsky reagents derived from ethyl chlorodifluoroacetate **1a** and *N,N*-diethylchlorodifluoroacetamide **1b**, and the synthetic use of the corresponding ethyl hemiacetals **5a** and **5b** as aldehyde equivalents.[10]

Table 1 Preparation of the *N,O*-acetal **4a**

Entry	DMF activator	Yield (%)
1	$ClCF_2CO_2Et$	36
2	CF_3CO_2Et	42
3	$EtOCO_2Et$	no reaction
4	$ClCO_2Et$	49
5	$PhSO_3Et$	81
6	p-$Me_6C_6H_4SO_3Et$	64
7	$EtOSO_3Et$	84

Results and Discussion

Treatment of ethyl chlorodifluoroacetate **1a** with activated zinc (0.5 equiv.) in DMF at 80 °C for 5 h gave ethyl 3-(dimethylamino)-3-ethoxy-2,2-difluoropropionate **4a** (36% yield; based on 0.5 equiv. of **1a**) after aqueous work-up followed by distillation. From a mechanistic point of view, this seems similar to the Vilsmeier reaction reported by Lang,[11] and involves initial generation of ethyl *N,N*-dimethylformimidate **6** from DMF and ethyl chlorodifluoroacetate, which is attacked by the difluorinated Reformatsky reagent **7** derived from a second ethyl chlorodifluoroacetate and zinc (Scheme 2). The low yield of the product is presumably due to the formation of a self Claisen condensation product **8** as a by-product.



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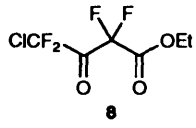
Scheme 2 Reaction mechanism for formylation of the difluorinated Reformatsky reagent



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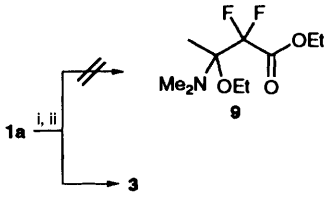
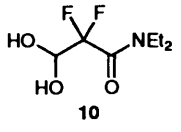
We expected that the side-reaction would be retarded by using an excess of zinc and the reagent which is not so electrophilic as to be attacked by the Reformatsky reagent but has the ability to form a formylating agent with DMF,

thereby improving the yield of **4a**. Table 1 summarizes the results of the formylation reactions using 3.0 equiv. of zinc and various DMF activators. Because of the above side reaction, ethyl trifluoroacetate gave a low yield of the desired product. Ethyl benzenesulfonate–DMF complex afforded **4a** in 81% yield, but the remaining sulfonate could not be removed by simple distillation. The best result was obtained by using diethyl sulfate to give pure **4a** in 84% yield. Attempts to prepare the *N,O*-ketal **9** by employing DMAC as a solvent was unsuccessful giving ethyl difluoroacetate **3** exclusively (Scheme 3). The difluorinated Reformatsky reagent derived

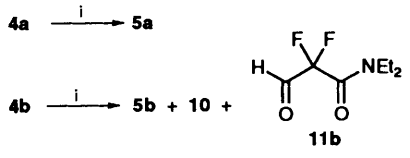


Scheme 3 *Reagents and conditions:* i, zinc, diethyl sulfate, DMAC, 70 °C; ii, H_3O^+

from *N,N*-diethylchlorodifluoroacetamide **1b** was also successfully formylated by the present reaction to afford the corresponding *N,O*-acetal **4b** (54%). The low yield of **4b**, compared with that of **4a**, is due to partial hydrolysis of its relatively less stable tetrahedral acetal function upon aqueous work-up which worked well in the case of **4a**. Indeed, ^{19}F NMR analysis of the aqueous layer revealed a considerable amount of the resulting hydrate **10** (δ − 114.4, d, J 7.6 Hz).



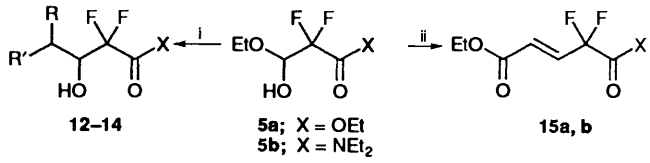
The *N,O*-acetals thus obtained were readily converted into the corresponding ethyl hemiacetals **5** by treatment with sulfuric acid in ethanol (Scheme 4). The ethyl ester derivative **5a** was



Scheme 4 *Reagents and conditions:* i, H_2SO_4, EtOH, room temp., 10 min, then distillation

distilled to give pure material (96%) while the distillate of the amide **5b** contained detectable quantities of the corresponding hydrate **10** and aldehyde **11b** (87% ^{19}F NMR yield). This result was not unexpected in view of the low stability of the acetal function of the *N,O*-acetal **4b** observed on aqueous work-up following formylation of **1b**.

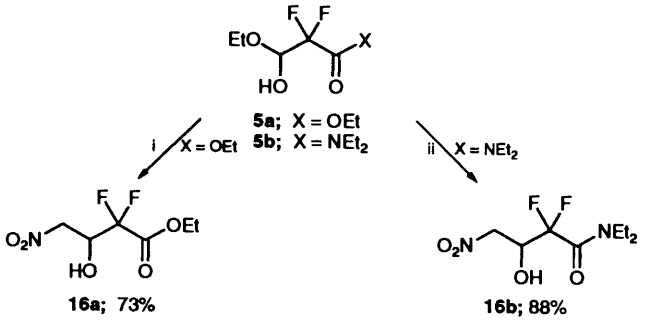
To demonstrate the synthetic utilities of ethyl hemiacetals, their reactions with a variety of nucleophiles were examined. Since the α,α-difluorinated esters are sensitive to strong bases and undergo hydrolysis even under conditions where water has been carefully excluded, the reactions of **5a** with nucleophiles were performed using a Lewis acid or relatively weak bases. As shown in Scheme 5, in the presence of zinc iodide, **5a** reacts with 1,3-dicarbonyl compounds to give α,α-difluoro-β-hydroxy esters **12–14** (61–76%). Owing to the accompanying hydrolysis of the α,α-difluorinated ester, the Horner–Wadsworth–Emmons reaction using a common base (butyllithium or sodium hydride) resulted in low yields of the product; however, **7a** was successfully converted into the difluorinated glutaconate **15**



12a; R = R' = CO_2Et, X = OEt	76%	**15a**; X = OEt	83%
13; R = R' = C(O)Me, X = OEt	61%	**15b**; X = NEt_2	76%
14; R = CO_2Et, R' = C(O)Me, X = OEt	63%		
12b; R = R' = CO_2Et, X = NEt_2	76%		

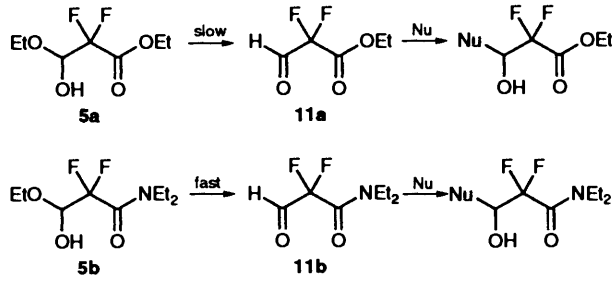
Scheme 5 *Reagents and conditions:* i, RCH_2R', ZnI_2, 1,4-dioxane, reflux. 4–8 h; ii, $(EtO)_2POCH_2CO_2Et$, Et_3N, LiBr, THF, room temp., 2 h

(83%) using triethylamine in the presence of lithium bromide.[12] The amide **5b** was also an effective electrophile and reacted similarly with diethyl malonate or phosphonoacetate to afford **12b** or **15b**, respectively. Interestingly, the nitro aldol reaction of **5b** with nitromethane under basic conditions proceeded smoothly at room temperature to give **16b** (88%) while that of **5a** required higher temperature to afford **16a** (73%) (Scheme 6).



Scheme 6 *Reagents and conditions:* i, CH_3NO_2, K_2CO_3, THF, 3 h, reflux; ii, Me_3NO_2, K_2CO_3, THF, room temp., 2 h

Since nucleophilic substitution of an ethoxy group is retarded by the presence of the electron withdrawing difluoromethylene moiety, the above reaction is considered to proceed by way of *in situ* generation of the aldehydes **11** which then undergo attack by the nitromethane carbanion. However, PM3 calculation which we performed indicates that electrophilicity of **11a** (LUMO energy −0.33 eV) is higher than that of **11b** (LUMO energy −0.21 eV).[13] As mentioned above, the hemiacetal function of **5b** is less stable than that of **5a**, and hence more easily converted into the corresponding aldehyde **11b**. Consequently, the observed difference in reactivity suggests that the rate-determining step is the conversion of the ethyl hemiacetals **5** into the aldehydes **11** and that the electrophilicity of the aldehydes **11** themselves has little effect on the rate of the reaction (Scheme 7).



Scheme 7

In conclusion, the ethyl hemiacetals **5** prepared by formylation of difluorinated Reformatsky reagents were found to be effective α,α-difluorinated aldehyde equivalents, which reacted

with a variety of nucleophiles to provide an alternative route to the functionalized α,α-difluoro esters and amides.

Experimental

General.—IR Spectra were obtained on a JASCO A-102 spectrometer. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on either a Varian VXR-500 or Varian Gemini-200 spectrometer. Chemical shifts are in ppm downfield from tetramethylsilane as internal standard for ^1H and ^{13}C nuclei, while hexafluorobenzene was used as internal standard (δ_F −162.90) for ^{19}F nuclei. *J* Values are given in Hz. M.p.s were obtained on a capillary apparatus and are uncorrected. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl in a recirculating still. *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride and stored over molecular sieves 4 Å (MS 4 Å). Zinc powder (Kanto Chemical Co., Inc.) was freshly activated by the acid treatment[14] and used within a few hours. Ethyl chlorodifluoroacetate and chlorodifluoroacetic anhydride were obtained from PCR, Inc. Column chromatography was performed with silica gel (E. Merck, Art. 7734, 70–230 mesh) by using hexane–ethyl acetate (v/v) as the eluent. All products have a >95% purity based on ^1H and ^{19}F NMR except for **5b** and **13**.

Computational Methods.—Geometry optimization was initially carried out by molecular mechanics calculations using the entire set of potential functions with a block diagonal conjugate gradient minimization procedure. The geometries for each compound were then fully optimized by PM3 calculations (MOPAC version 6.1 run on a Sony Tektronix CAChe® molecular modelling workstation).

Chloro-N,N-*diethyldifluoroacetamide* **1b**—Diethylamine (3.66 g, 50.0 mmol) was added to a solution of chlorodifluoroacetic anhydride (12.15 g, 50.0 mmol) in dry ether (50 cm^3) at 0 °C. After being stirred at ambient temperature for 6 h, the reaction mixture was diluted with ether (100 cm^3) and poured into aqueous sodium hydrogen carbonate (150 cm^3). The organic layer was separated, and the aqueous layer was extracted with ether (150 cm^3 × 2). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residual oil was distilled to give **1b** (8.54 g, 92%), b.p. 86 °C/30 mmHg (Found: M^+, 185.0430. $C_6H_{10}ClF_2NO$ requires *M*, 185.0419); ν_{max}(neat)/cm^{-1} 2984 and 1688; δ_H(500 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7.1, CH_3), 1.25 (3 H, t, *J* 7.1, CH_3), 3.44 (2 H, q, *J* 7.1, NCH_2), 3.52 (2 H, tq, *J* 1.4 and 7.1, NCH_2); δ_C(50 MHz; $CDCl_3$) 12.1 (CH_3), 14.0 (CH_3), 42.2 (NCH_2), 42.7 (t, *J* 3.9, NCH_2), 119.3 (t, *J* 302, CF_2) and 158.7 (t, *J* 29.1, CO); δ_F(470 MHz; $CDCl_3$) −58.3 (s).

Ethyl 3-(*Dimethylamino*)-3-*ethoxy*-2,2-*difluoropropionate* **4a**.—A solution of diethyl sulfate (2.31 g, 15.0 mmol) in DMF (4 cm^3) was stirred at 90 °C for 2 h. To that solution were added zinc powder (1.31 g, 20.0 mmol) and ethyl chlorodifluoroacetate (1.585 g, 10.0 mmol) at 70 °C, and the mixture was stirred at that temperature for 4 h. The mixture was filtered to remove the excess of zinc, diluted with pentane (30 cm^3) and poured into aqueous ammonium chloride (30 cm^3). The organic layer was separated, and the aqueous layer was extracted with pentane (30 cm^3 × 2). The combined organic extracts were washed with aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$), and evaporated. The residual oil was distilled to give **4a** (1.884 g, 84%), b.p. 90–92 °C/12 mmHg (Found: M^+, 225.1178. $C_9H_{17}F_2NO_3$ requires *M*, 225.1177); ν_{max}(neat)/cm^{-1} 3000, 1780 and 1760; δ_H(500 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.0, CH_3), 1.34 (3 H, t, *J* 7.1, CH_3), 2.49 [6 H, s, $N(CH_3)_2$], 3.63 (1 H, dq, *J* 9.5 and 7.0, OCH_AH_B), 3.73 (1 H, dq, *J* 9.5 and 7.0, OCH_AH_B), 4.33 (2 H, q, *J* 7.1, OCH_2) and 4.36 (1 H, dd, *J* 10.7 and 12.4, CF_2CH); δ_C(50 MHz; $CDCl_3$) 14.0 (CH_3), 15.2 (CH_3), 40.2 (2 C, 5, *J* 2.6, NMe_2), 62.8 (OCH_2), 66.9 (OCH_2), 92.0 (t, *J* 25.0, CF_2CH), 115.4 (dd, *J* 259 and 261, CF_2) and 164.3 (t, *J* 31.3, CF_2CO); δ_F(470 MHz; $CDCl_3$) −118.2 (1 F, dd, *J* 9.9 and 258) and −116.6 (1 F, dd, *J* 12.2 and 258).

3-(*Dimethylamino*)-3-*ethoxy*-N,N-*diethyl*-2,2-*difluoropropionamide* **4b**.—This compound was prepared similarly from **2b** (52%), 92–94 °C/3 mmHg (Found: M^+, 252.1651. $C_{11}H_{22}F_2N_2O_2$ requires *M*, 252.1649); ν_{max}(neat)/cm^{-1} 2900 and 1660; δ_H(500 MHz; $CDCl_3$) 1.15 (3 H, t, *J* 7.1, CH_3), 1.18 (3 H, t, *J* 7.1, CH_3), 1.20 (3 H, t, *J* 7.1, CH_3), 2.55 (6 H, s, NMe_2), 3.24–3.38 (2 H, m, NCH_2), 3.45–3.51 (1 H, m, NCH_2), 3.55 (1 H, dq, *J* 9.4, 7.1, $CHCOCH_2$), 3.60–3.70 (1 H, m, NCH_2), 3.72 (1 H, dq, *J* 9.4, 7.1, $CHCOCH_2$) and 4.49 (1 H, dd, *J* 5.3, 17.0, CF_2CH); δ_C(50 MHz; $CDCl_3$) 12.1 (CH_3), 14.6 (CH_3), 15.2 (CH_3), 40.1 (2 C, t, *J* 2.4, NMe_2), 42.1 (NCH_2), 42.2 (dd, *J* 3.6 and 10.3, NCH_2), 65.9 (OCH_2), 91.4 (dd, *J* 20.7 and 28.5, CF_2CH), 117.8 (dd, *J* 254, 270, CF_2) and 163.2 (t, *J* 27.1, CF_2CO); δ_F(470 MHz; $CDCl_3$) −116.0 (1 F, dd, *J* 16.8, 265) and −107.4 (1 F, dd, *J* 5.3, 265).

Ethyl 3-*Ethoxy*-2,2-*difluoro*-3-*hydroxypropionate* **5a**.—To a solution of **4a** (0.450 g, 2.0 mmol) in ethanol (2.5 cm^3) and water (0.5 cm^3) was added a drop of conc. sulfuric acid, and the mixture was stirred at ambient temperature for 30 min. After dilution with diethyl ether (30 cm^3), the reaction mixture was poured into water (30 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (30 cm^3 × 2). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residual oil was bulb-to-bulb distilled at 140 °C (bath temp.) < 1 mmHg to give **5a** (0.380 g, 96%) (Found: M^+, 252.1651. $C_7H_{12}F_2O_4$ requires *M*, 198.0704); ν_{max}(neat)/cm^{-1} 3480, 3000, 1780 and 1760; δ_H(500 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.1, CH_3), 1.37 (3 H, t, *J* 7.1, CH_3), 2.90 (1 H, s, OH), 3.65 (1 H, dq, *J* 9.8 and 7.1, $CHOCH_2$), 3.92 (1 H, dq, *J* 9.8 and 7.1, $CHOCH_2$), 4.37 (2 H, q, *J* 7.1, OCH_2) and 4.91 (1 H, dd, *J* 5.6 and 7.0, CF_2CH); δ_C(50 MHz; $CDCl_3$) 13.9 (CH_3), 14.9 (CH_3), 63.2 (OCH_2), 64.7 (OCH_2), 94.0 (dd, *J* 26.4 and 31.5, CF_2CH), 111.3 (t, *J* 256, CF_2) and 163.0 (t, *J* 31.1, CF_2CO); δ_F(470 MHz; $CDCl_3$) −125.1 (1 F, dd, *J* 6.9 and 266) and −120.0 (1 F, dd, *J* 6.1 and 266).

3-*Ethoxy*-N,N-*diethyl*-2,2-*difluoro*-3-*hydroxypropionamide* **5b**.—This compound was prepared similarly from **4b** and contained a detectable amount of the corresponding aldehyde **11b** and hydrate **10** (87% ^{19}F NMR yield). The mixture was used for the reaction with nucleophiles without further purification; δ_F(470 MHz; $CDCl_3$) ethyl hemiacetal **5b** −111.5 (1 F, dd, *J* 4.6 and 284), −113.6 (1 F, d, *J* 284); aldehyde **11b** −115.1 (2 F, d, *J* 4.6); hydrate **10** −112.3 (2 F, d, *J* 4.6).

Triethyl 3,3-*Difluoro*-2-*hydroxypropane*-1,1,3-*tricarboxylate* **12a**.—To a suspension of zinc iodide (0.638 g, 2.0 mmol) in dry dioxane (5 cm^3) were added **5a** (0.396 g, 2.0 mmol) and diethyl malonate (0.481 g, 3.0 mmol) at 0 °C, and the mixture was refluxed for 3 h. After dilution with ether (15 cm^3), the reaction mixture was poured into 0.5 mol dm^{-3} HCl (15 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (15 cm^3 × 2). The combined organic extracts were washed with saturated brine (30 cm^3), dried ($MgSO_4$) and evaporated to dryness. Chromatography of the residue on silica gel with hexane–ethyl acetate (4:1) as the eluent yielded **12a** (0.475 g, 76%) (Found: M^+, 312.0998. $C_{12}H_{18}F_2O_7$ requires *M*, 312.1012); ν_{max}(neat)/cm^{-1} 3500, 3000 and 1760; δ_H(500 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.1, CH_3), 1.32 (3 H, t, *J*

7.1, CH_3), 1.37 (3 H, t, *J* 7.1, CH_3), 3.78 [1 H, d, *J* 3.7, $CH(CO_2Et)_2$], 4.27 (2 H, q, *J* 7.1, OCH_2), 4.30 (2 H, q, *J* 7.1, OCH_2), 4.38 (2 H, q, *J* 7.1, OCH_2), 4.62 (1 H, d, *J* 9.2, OH) and 4.79 (1 H, ddt, *J* 9.2, 20.4 and 3.8, CF_2CH); δ_C(50 MHz; $CDCl_3$) 13.9 (3 C, CH_3), 49.4 [$CH(CO_2Et)_2$], 62.5 (OCH_2), 62.6 (OCH_2), 63.4 (OCH_2), 71.1 (dd, *J* 23.1 and 30.2, CHOH), 114.1 (dd, *J* 254.9 and 260.3, CF_2), 162.5 (dd, *J* 29.2 and 33.1, CF_2CO), 166.2 (CO_2Et) and 168.8 (CO_2Et); δ_F(470 MHz; $CDCl_3$) −124.7 (1 F, dd, *J* 21.4 and 261) and −110.9 (1 F, dd, *J* 3.1 and 261).

Ethyl 4,4-*Diacetyl*-2,2-*difluoro*-3-*hydroxypropionate* **13**.—This compound was prepared similarly from pentane-2,4-dione in 61% yield (^{19}F NMR yield of the crude product). Attempted purification using silica gel chromatography led to a retro-aldol reaction; ν_{max}(neat)/cm^{-1} 3500, 3000, 1770 and 1710; δ_H(500 MHz; $CDCl_3$) 1.37 (3 H, t, *J* 7.2, CH_3), 2.33 (6 H, s, $COCH_3$), 3.0–3.3 (1 H, br, OH), 4.18 [1 H, d, *J* 6.0, $CH(COMe)_2$], 4.37 (2 H, q, *J* 7.2, OCH_2) and 4.56 (1 H, ddd, *J* 5.1, 6.2 and 18.2, CF_2CH); δ_C(50 MHz; $CDCl_3$) 13.9 (CH_3), 30.1 ($COCH_3$), 31.0 ($COCH_3$), 63.6 (OCH_2), 65.2 [$CH(COMe)_2$], 71.1 (dd, *J* 23.9 and 29.4, CHOH), 114.2 (dd, *J* 255 and 259, CF_2), 162.7 (dd, *J* 30.0 and 32.6, COOEt), 200.3 (COMe) and 203.8 (COMe); δ_F(470 MHz; $CDCl_3$) −121.9 (1 F, dd, *J* 18.3 and 262) and −112.0 (1 F, dd, *J* 5.3 and 262).

Diethyl 1-*Acetyl*-3,3-*difluoro*-2-*hydroxypropane*-1,3-*dicarboxylate* **14**.—This compound was prepared similarly from ethyl acetoacetate as a mixture of diastereoisomers (56:44) in 63% yield (Found: M^+, 282.0906. $C_{11}H_{16}F_2O_6$ requires *M*, 282.0915); ν_{max}(neat)/cm^{-1} 3500, 3000, 1780, 1760 and 1720; δ_H(500 MHz; $CDCl_3$) major 1.30 (3 H, t, *J* 7.1, CH_3), 1.37 (3 H, t, *J* 7.1, CH_3), 2.37 (3 H, s, $COCH_3$), 3.97 (1 H, d, *J* 5.3, CHCO), 4.26 (2 H, q, *J* 7.1, OCH_2), 4.37 (2 H, q, *J* 7.1, OCH_2), 4.4 (1 H, br, OH) and 4.8–4.9 (1 H, m, CF_2CH); minor 1.32 (3 H, t, *J* 7.1, CH_3), 1.37 (3 H, t, *J* 7.1, CH_3), 2.35 (3 H, s, $COCH_3$), 3.89 (1 H, d, *J* 5.3, CHCO), 4.29 (2 H, q, *J* 7.1, OCH_2), 4.3 (1 H, br, OH), 4.37 (2 H, q, *J* 7.1, OCH_2) and 4.7–4.8 (1 H, m, CF_2CH); δ_C(50 MHz; $CDCl_3$) major 13.9 (2 C, CH_3), 31.3 ($COCH_3$), 57.0 (CHCOMe), 62.5 (OCH_2), 63.4 (OCH_2), 71.4 (dd, *J* 23.5 and 29.6, CHOH), 114.3 (dd, *J* 254 and 260, CF_2), 162.7 (dd, *J* 29.5 and 32.8, CF_2CO), 168.9 ($CHCO_2Et$) and 204.1 (CHCOMe); minor 13.9 (2 C, CH_3), 29.6 ($COCH_3$), 55.8 (CHOCOMe), 62.5 (OCH_2), 63.5 (OCH_2), 70.4 (dd, *J* 23.5 and 29.9, CHOH), 114.2 (dd, *J* 255 and 260, CF_2), 162.6 (dd, *J* 29.6 and 32.8, CF_2CO), 166.3 ($CHCO_2Et$) and 199.3 (CHCOMe); δ_F(470 MHz; $CDCl_3$) major −122.3 (1 F, dd, *J* 19.8 and 261) and −112.1 (1 F, dd, *J* 4.6 and 261); minor −123.6 (1 F, dd, *J* 19.1 and 261) and −111.9 (1 F, dd, *J* 4.6 and 261).

Diethyl (2-N,N-*Dimethylcarbamoyl*-2,2-*difluoro*-1-*hydroxyethyl*)*malonate* **12b**.—This compound was prepared similarly (stirred at 80 °C) from diethyl malonate and **5b** in 76% yield (Found: M^+, 339.1468. $C_{14}H_{23}F_2NO_6$ requires *M*, 339.1493); ν_{max}(neat)/cm^{-1} 3470, 3000, 1740 and 1660; δ_H(500 MHz; $CDCl_3$) 1.17 (3 H, t, *J* 7.1, CH_3), 1.21 (3 H, t, *J* 7.1, CH_3), 1.28 (3 H, t, *J* 7.1, CH_3), 1.30 (3 H, t, *J* 7.1, CH_3), 3.35–3.46 (2 H, m, NCH_2), 3.47–3.57 (2 H, m, NCH_2), 3.89 [1 H, d, *J* 6.6, $CH(CO_2Et)_2$], 4.23 (2 H, q, *J* 7.1, OCH_2), 4.27 (1 H, dq, *J* 10.7 and 7.1, OCH_2), 4.28 (1 H, dq, *J* 10.7 and 7.1, OCH_2), 4.32 (1 H, d, *J* 7.0, OH) and 4.95 (1 H, dq, *J* 16.6 and 6.7, CF_2CH); δ_C(50 MHz; $CDCl_3$) 12.2 (CH_3), 14.0 (2 C, CH_3), 14.2 (CH_3), 41.7 (NCH_2), 42.0 (dd, *J* 5.4 and 7.1, NCH_2), 51.6 [t, *J* 2.1, $CH(CO_2Et)_2$], 62.0 (OCH_2), 62.1 (OCH_2), 71.0 (dd, *J* 24.2 and 28.2, CHOH), 115.8 (dd, *J* 260 and 266, CF_2), 162.0 (t, *J* 27.7, CF_2CO), 166.4 (CO_2Et) and 167.5 (CO_2Et); δ_F(470 MHz; $CDCl_3$) −115.9 (1 F, dd, *J* 16.8 and 285) and −107.5 (1 F, dd, *J* 6.1 and 285).

Diethyl 3,3-*Difluoroprop*-1-*ene*-1,3-*dicarboxylate* **15a**.—To a suspension of lithium bromide (0.217 g, 2.5 mmol) in THF (5 cm^3) was added triethyl phosphonoacetate (0.493 g, 2.2 mmol) and triethylamine (0.243 g, 2.4 mmol) at 0 °C and the mixture was stirred at ambient temperature for 10 min. Compound **5a** (0.396 g, 2.0 mmol) was then added dropwise and the mixture was stirred at ambient temperature for 2 h. After dilution with ether (15 cm^3), the reaction mixture was poured into 0.5 mol dm^{-3} HCl (20 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (20 cm^3 × 2). The combined organic extracts were washed with saturated brine (50 cm^3), dried ($MgSO_4$) and evaporated to dryness. Chromatography of the residue on silica gel with hexane–ethyl acetate (6:1) as the eluent yielded **15a** (0.369 g, 83%) (Found: M^+, 222.0708. $C_9H_{12}F_2O_4$ requires *M*, 222.0704); ν_{max}(neat)/cm^{-1} 3000, 1780 and 1730; δ_H(500 MHz; $CDCl_3$) 1.33 (3 H, t, *J* 7.1, CH_3), 1.37 (3 H, t, *J* 7.1, CH_3), 4.27 (2 H, q, *J* 7.1, OCH_2), 4.36 (2 H, q, *J* 7.1, OCH_2), 6.44 (1 H, dt, *J* 15.8 and 2.3, CHCO) and 6.90 (1 H, dt, *J* 15.8 and 11.5, $CHCF_2$); δ_C(50 MHz; $CDCl_3$) 13.9 (CH_3), 14.1 (CH_3), 61.5 (OCH_2), 63.7 (OCH_2), 111.4 (t, *J* 250, CF_2), 128.0 (t, *J* 8.5, CHCO), 135.0 (t, *J* 25.7, CF_2CH), 162.6 (t, *J* 33.4, CF_2CO) and 164.4 (CHCO); δ_F(470 MHz; $CDCl_3$) −106.8 (dd, *J* 3.1 and 11.5).

trans-*Ethyl* 4-(*Diethylcarbamoyl*)-4,4-*difluorobut*-2-*enoate* **15b**.—This compound was prepared similarly from **5b** in 76% yield (Found: M^+, 249.1201. $C_{11}H_{17}F_2NO_3$ requires *M*, 249.1177); ν_{max}(neat)/cm^{-1} 2900, 1740 and 1670; δ_H(500 MHz; $CDCl_3$) 1.17 (3 H, t, *J* 7.1, CH_3), 1.23 (3 H, t, *J* 7.1, CH_3), 1.31 (3 H, t, *J* 7.1, CH_3), 3.40 (2 H, q, *J* 7.1, NCH_2), 3.50 (2 H, tq, *J* 1.3 and 7.1, NCH_2), 4.25 (2 H, q, *J* 7.1, OCH_2), 6.34 (1 H, dt, *J* 15.9 and 2.3, CHCO) and 7.07 (1 H, dt, *J* 15.9 and 11.7, CF_2CH); δ_C(50 MHz; $CDCl_3$) 12.3 (CH_3), 14.1 (CH_3), 14.3 (CH_3), 41.6 (NCH_2), 41.9 (t, *J* 5.4, NCH_2), 61.3 (OCH_2), 114.4 (t, *J* 254, CF_2), 125.6 (t, *J* 8.9, CHCO), 136.8 (t, *J* 25.2, $CHCF_2$), 161.7 (t, *J* 29.0, CON) and 164.7 (CHCO); δ_F(470 MHz; $CDCl_3$) −100.9 (d, *J* 11.4).

Ethyl 2,2-*Difluoro*-3-*hydroxy*-4-*nitrobutyrate* **16a**.—To a suspension of potassium carbonate (0.829 g, 6.0 mmol) in dry THF (15 cm^3) were added **5a** (0.793 g, 4.0 mmol) and nitromethane (0.366 g, 6.0 mmol) at 0 °C, and the mixture was refluxed for 3 h. After dilution with ether (40 cm^3), the reaction mixture was poured into 0.5 mol dm^{-3} HCl (40 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (40 cm^3 × 2). The combined organic extracts were washed with saturated brine (100 cm^3), dried ($MgSO_4$), and evaporated to dryness. Chromatography of the residue on silica gel with hexane–ethyl acetate (4:1) as the eluent yielded **16a** (0.622 g, 73%) (Found: M^+, 213.0453. $C_6H_9F_2NO_5$ requires *M*, 213.0449); ν_{max}(neat)/cm^{-1} 3510, 3000, 1760 and 1570; δ_H(500 MHz; $CDCl_3$) 1.40 (3 H, t, *J* 7.1, CH_3), 3.24 (1 H, d, *J* 5.7, OH), 4.41 (2 H, q, *J* 7.1, OCH_2), 4.67 (1 H, dd, *J* 8.3 and 14.3, O_2NCH_2), 4.73 (1 H, dd, *J* 3.6 and 14.3, O_2NCH_2) and 4.9–5.1 (1 H, m, $CHCF_2$); δ_C(50 MHz; $CDCl_3$) 13.9 (CH_3), 64.0 (OCH_2), 68.9 (dd, *J* 24.9 and 30.0, CHOH), 74.6 (t, *J* 3.0, O_2NCH_2), 113.1 (dd, *J* 256 and 260, CF_2) and 162.3 (dd, *J* 30.1 and 31.8, CO); δ_F(470 MHz; $CDCl_3$) −122.0 (1 F, dd, *J* 14.5 and 272) and −113.0 (1 F, dd, *J* 6.1 and 272).

N,N-*Diethyl*-2,2-*difluoro*-3-*hydroxy*-4-*nitrobutanamide* **16b**.—This compound was prepared similarly (stirred at room temperature for 2 h) from **5b** in 88% yield, m.p. 85–86 °C (Found: M^+, 240.0949. $C_8H_{14}F_2N_2O_4$ requires *M*, 240.0922); ν_{max}(KBr)/cm^{-1} 3400, 3000, 1640 and 1560; δ_H(500 MHz; $CDCl_3$) 1.19 (3 H, t, *J* 7.1, NCH_2CH_3), 1.24 (3 H, t, *J* 7.1, NCH_2CH_3), 3.4–3.6 (4 H, m, NCH_2CH_3), 3.98 (1 H, d, *J* 5.1, OH), 4.6–4.7 (2 H, m, O_2NCH_2) and 5.0–5.1 (1 H, m, $CHCF_2$);

δ_C(50 MHz; $CDCl_3$) 12.2 (CH_3), 14.1 (CH_3), 41.6 (NCH_2), 41.9 (dd, *J* 5.5, 6.3, NCH_2), 69.8 (dd, *J* 24.2 and 29.4, CHOH), 74.8 (dd, *J* 3.0 and 4.1, O_2NCH_2), 115.1 (dd, *J* 262 and 268, CF_2), 161.7 (t, *J* 27.6, CO); δ_F(470 MHz; $CDCl_3$) −117.3 (1 F, dd, *J* 18.3 and 291) and −108.0 (1 F, dd, *J* 5.3 and 291).

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