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β,β-Difluoro analogs of α-oxo-β-phenylpropionic acid and phenylalanine

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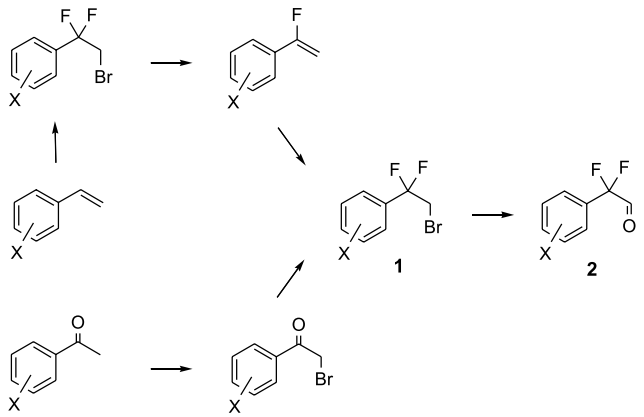
To Dieter Seebach with congratulations and best wishes

Abstract—A simple three-step procedure converted the readily accessible (2-bromo-1,1-difluoroethyl)arenes (**2**) into α-aryl-α,α-difluoroacetaldehydes (**1**). Subsequent hydrocyanation, hydrolysis, oxidation and again hydrolysis afforded β-aryl-β,β-difluoro-α-oxopropionic acids (**3**). Reductive amination transformed the oxoacids **3** into a separable mixture of α-hydroxyacids **11** and racemic β,β-difluoro-β-phenylalanine derivatives (**4**). Enantiomerically pure β,β-difluorophenylalanine (L-**4a**) was obtained when α,α-difluoro-α-phenylacet-aldehyde (**1a**) was condensed with homochiral 1-phenylethylamine, hydrogen cyanide added to the resulting imine, the diastereomeric mixture thus produced hydrolyzed to the carboxamides (**15**) which were found to be separable by fractional crystallization or chromatography. The pK_a values of the β-aryl-β,β-difluoroalanines (**4**) were measured and biological profile of the latter probed. 3-(4-Chlorophenyl)-3,3-difluoro-2-oxopropionic acid (**4c**) proved to be a potent (K_i 27 μM) and selective inhibitor of arogenate dehydratase, a key enzyme catalyzing the last step of the phenylalanine biosynthesis.

1. Introduction

Years ago, we have disclosed a convenient access to aryldifluoroacetaldehydes (**2**). If not commercial, the starting material, a styrene or a ring-substituted congener, was usually made by Wittig methylenation of the corresponding benzaldehyde. It was then consecutively subjected to a *vic*-bromofluorination, a base-promoted dehydrobromination and a second *vic*-bromofluorination. The resulting (2-bromo-1,1-difluoroethyl)arene[1] (**1**) was eventually oxidized by applying the Pummerer method.[1] As we have recognized in the meantime, the bromo compounds **1** are also readily obtained by the bromination of the corresponding acetophenone and the subsequent treatment of the α-bromoketone with diethylaminosulfur trifluoride ('DAST') or sulfur tetrafluoride (see Section 6) (Scheme 1).

We wanted to explore now how the aldehydes **2** might be converted into the 3,3-difluoro analogs of 3-aryl-2-oxopropionic acids (3-arylpyruvic acids, 2-hydroxycinnamic acids; **3**) and 3-arylalanines (**4**). Both types of compounds are physiologically relevant intermediates (Scheme 2).



Scheme 1.

The *erythro*- and *threo*-β-fluorophenylalanines have been extensively investigated in the past.[2–6] β,β-Difluoro-β-phenylalanine, one of the few difluorinated amino acids known so far, was synthesized by R. Guedj et al. in a fairly laborious multistep sequence.[7,8] Biological studies accomplished with this compound have not been reported. We felt, suitably *para* substituted derivatives of β,β-difluorophenylalanine might exhibit a potential as inhibitors of tyrosine hydroxylase,[9] decarboxylase[9] and ammonia lyase.[10] We decided to investigate the ring-unsubstituted parent

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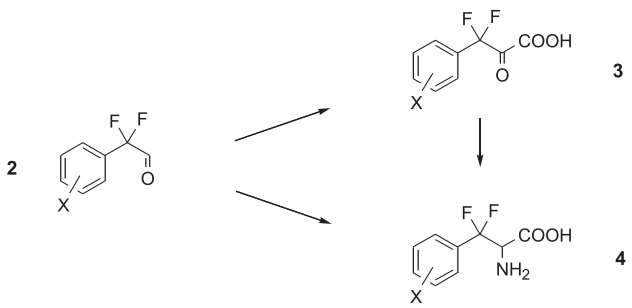
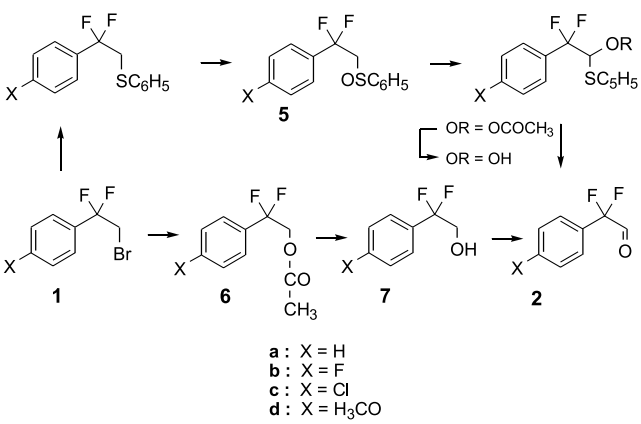


Scheme 2.

structure, along with three analogs carrying fluorine, chlorine and methoxy at the *para* position.

2. 2-Aryl-2,2-difluoroacetaldehydes

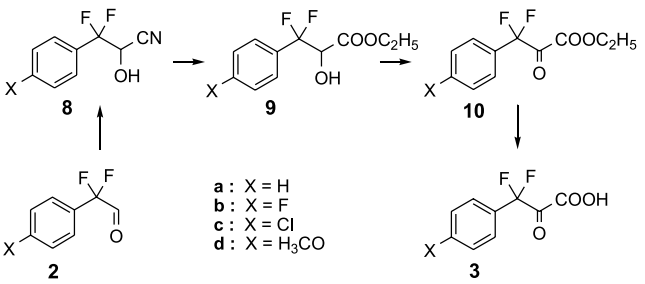
The (2-bromo-1,1-difluoroethyl)arenes (**1**) were prepared in the standard way described above.[1] However, their transformation into the α-aryl-α,α-difluoroacetaldehydes (**2**) no longer relied on the Pummerer isomerization of the sulfoxide **5** but was based on a simplified sequence consisting of a nucleophilic acetate/bromide displacement, hydrolysis of the resulting ester **6** to the alcohol **7** and treatment of the latter with the Swern[11,12] or Dess–Martin[13,14] reagent. Under such conditions the aldehydes **2** could be isolated in almost quantitative yield although they showed a pronounced tendency to form the hydrate or to polymerize (Scheme 3).



Scheme 3.

3. 3-Aryl-3,3-difluoro-2-oxopropionic acids

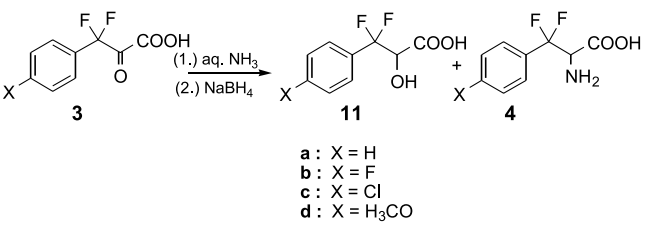
The cyanhydrines **8** were obtained in satisfactory yield (62–74%) when the hydrogen sulfite adducts of the aldehydes **2** were dissolved in an aqueous solution of sodium cyanide. The hydrolysis was accomplished by passing gaseous hydrogen chloride into an ethanolic solution of the cyanhydrines **8** before pouring the mixture into water. The resulting ethyl 3-aryl-3,3-difluoro-2-hydroxypropionates (**9**; 77–78%) were oxidized to the ethyl 3-aryl-3,3-difluoro-2-oxopropionates (**10**; 89–98%) using the Dess–Martin reagent.[13,14] Saponification of the esters **10** with sodium hydrogen carbonate in aqueous isopropanol eventually gave the oxoacids **3** (87–96%) (Scheme 4).



Scheme 4.

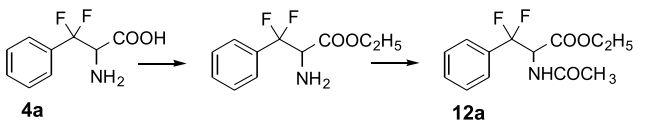
4. 3-Aryl-3,3-difluoroalanines

The consecutive treatment of an oxoacid **3** with 25% aqueous ammonia and sodium borohydride invariably led to a mixture of the α-hydroxyacid **11** and the α-aminoacid **4**. The product separation required the use of an ion exchange column. The product ratios 11:4 depend critically on the imine generating step. For example, 62% of the α-hydroxyacid **11a** and only 1% of the α-aminoacid **4a** were formed when the oxo precursor **3a** was exposed to 25% aqueous ammonia at 100 °C under atmospheric pressure, whereas the product composition changed to 29% of **11a** and 67% of **4a** when the treatment with ammonia was performed at 60 °C in a hermetically closed pressure vessel under otherwise identical conditions. In contrast, to shorten the standard reaction time of 5–3 h or to extend it to 19 h had little effect on the combined yields of products, nor on the product ratios (Scheme 5).



Scheme 5.

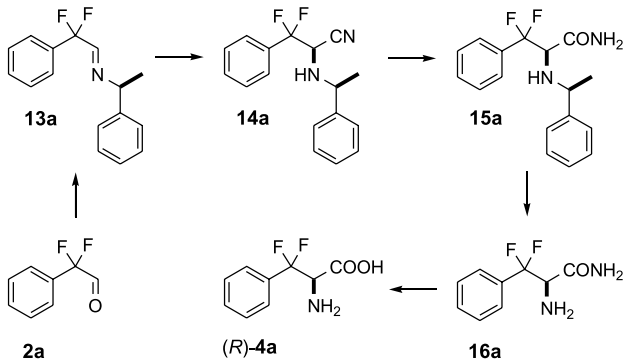
Both the α-aminoacids **4** and their chlorohydrates decompose upon heating above 150 °C. In order to record at least one reproducible melting range, compound **4a** was converted into the *N*-acetyl ethyl ester **12a** (mp 92–93 °C) (Scheme 6).



Scheme 6.

It was never a main objective of the present work to make enantiomerically pure fluoro analogs of α-aminoacids available, the more as the kinetic racemate resolution by enzymatic hydrolysis of methyl phenylalaninates[8] appears to be a generally applicable method. Thus, it was merely for curiosity if we wanted to explore a new approach. The aldehyde **2a** was condensed with (*S*)-1-phenylethylamine and the resulting imine **13a** was heated with trimethylsilyl cyanide in the presence of zinc iodide.[15,16] The aminonitrile

14a, existing as a roughly 1:1 diastereomeric mixture, was immediately hydrolyzed to provide the carboxamide **15a**, one component of which crystallized readily. Removal of the chiral auxiliary by catalytic hydrogenation to afford **16a** and acid-mediated hydrolysis of the carboxamide **16a** to the free amino acid (L)- or (*R*)-β,β-difluoroalanine (**4a**), concluded the reaction sequence. Unfortunately, the hydrolysis was accompanied by extensive racemization. We should have searched for a milder amide cleavage method but ran out of time (Scheme 7).



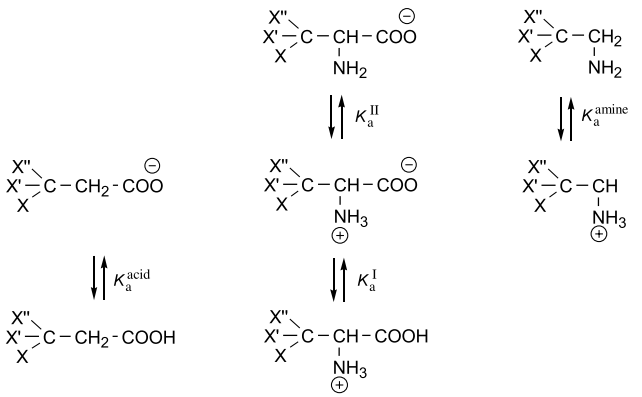
Scheme 7.

5. Physical and biological properties

The introduction of fluorine atoms into organic lead compounds is a favorite tool for the modulation of molecular properties in the life science arena.[17,18] The change of the pK_a value caused by such a halogen substituent is of course a key issue in this respect. It is plausible to expect the inductive effect to level off with distance, decreasing for example to one third of the former magnitude with each additional methylene group inserted between the substituent-produced perturbation and the monitoring functional group. One might further suppose fluorine effects to be cumulative, in other words to increase proportionally if there are two or three halogen atoms in the same chemical environment rather than a single one. At least the last assumption is naive and invalid, as we shall see in a minute.

β-Fluoroamino acids are particularly instructive model compounds to test the additivity or non-additivity of substituent effects on acidity.[19] Ideally, they would behave as a super-position of 3-fluorinated propanoic acids and 2-fluorinated ethylamines. This means, the first dissociation constant of the amino acid (K_a^I) should approximate that of the corresponding propanoic acid (K_a^{acid}) and the second one (K_a^{II}) should mirror that of the corresponding promoted amine (K_a^{amine}) (Scheme 8).

This view is oversimplified and not supported by the reality. Due to cross-interactions between the two functional groups, the pK_a values of amino acids deviate considerably from that of their structural subcomponents (Tables 1–3). More importantly, the acidity does not increase monotonously with the number of fluorine substituents. In fact, the first one does little or even may slightly raise the pK_a value. In this context, it should be recalled that halogen effects on the acidity of acetic acids in aqueous solution,[20,21] but not in the gas phase,[22,23] are rather entropy than enthalpy



Scheme 8.

dictated. The introduction of a geminal pair of fluorine atoms into the β-position of alanine lowers the pK_a^I and pK_a^{II} values by 0.8 and 1.5 units, whereas the same structural modification of phenylalanine does hardly affect the pK_a^I value (+0.1), but decreases the pK_a^{II} number by 2.4 units (Table 3), as potentiometric measurement have now revealed. The acidity differences between the *p*-chloro and *p*-methoxy substituted phenylalanines and their β,β-difluoro congeners are quite similar (ΔpK_a^I +0.2 to +0.3; ΔpK_a^I −2.3 to −2.5).

A preliminary screening of the β-aryl-β,β-difluoroalanines **5** as inhibitors of the tyrosine metabolism ended disappointingly. No binding appeared to occur at low concentrations.

Table 1. Negative logarithmic of dissociation constants (pK_a^{acid}) of propanoic acid and its 3-fluoro substituted derivatives[24–29] X″X′XC–CH_2–COOH

X″	X′	X	(pK_a^{acid})
H	H	H	4.8
F	H	H	2.6
F	F	H	1.3
F	F	F	0.2

Table 2. Negative logarithmic of dissociation dissociation constants (pK_a^{amine}) of the *N*-protonated ethylamine and 2-fluoro substituted derivatives[30–33] X″X′XC–CH_2–NH_2

X″	X′	X	(pK_a^{amine})
H	H	H	10.7
F	H	H	8.8
F	F	H	7.1
F	F	F	5.6

Table 3. Negative logarithmic of dissociation constants (pK_a^I and pK_a^{II}) of alanine, phenylalanine and its β-fluoro substituted derivatives[24,30,34–36] X″X′XC–CH(NH_2)–COOH

X″	X′	X	pK_a^I	pK_a^{II}
H	H	H	2.3	9.9
F	H	H	2.4	9.8
F	F	H	1.5	8.4
F	F	F	1.2	5.3
H_5C_6	H	H	2.2	9.2
H_5C_6	F	H	n.r	n.r
H_5C_6	F	F	2.3	6.8

n.r., not yet reported.

On the other hand, the 3-aryl-3,3-difluoro-2-oxopropionic acids display all the structural features of a successful 'transition state analog'.[37–39] The keto group being flanked by two electron-withdrawing entities, the carboxy function and the difluoromethylene unit, is exceptionally electrophilic. If water is not rigorously excluded, the oxo compound spontaneously metamorphoses to the corresponding hydrate. This held the promise of 3-aryl-3,3-difluoro-2-oxopropionic acids to act as potential inhibitors of plant metabolism. Its structure suggesting possible interference with the biosynthesis of phenylalanine, the oxoacid **3c** was considered to be particularly attractive and was, therefore, selected for a series of tests. Only bacteria, fungi and plants are capable of synthesizing the three proteinogenic aromatic amino acids, that is, phenylalanine, tyrosine, and tryptophan, along the shikimate pathway,[40] and phenylalanine in particular is the biosynthetic precursor of a large number of aromatic natural plant products, such as flavonoids, lignins, coumarins, etc. En route to these compounds, phenylalanine is deaminated by phenylalanine ammonia-lyase (PAL) to yield (*E*)-cinnamic acid. Among the flavonoids, anthocyanins are coloured intensely red or blue, and inhibitors of the synthesis of phenylalanine and cinnamic acid can be easily identified by their interference with anthocyanin pigment formation in vivo. When testing the effect of oxoacid **3c** on light-induced anthocyanin synthesis in buckwheat hypocotyls,[41] we found inhibition with an IC_{50} value of ca. 200 μM. Unlike known inhibitors of PAL, oxoacid **3c** did not cause an increase, but rather a decrease in the concentration of the endogenous soluble phenylalanine, suggesting an interference of oxoacid **3c** with phenylalanine biosynthesis. The number of potential sites of interference of oxoacid **3c** with phenylalanine biosynthesis was narrowed down by experiments in which oxoacid **3c** was applied simultaneously with the herbicidal compound glyphosate (*N*-[phosphonomethyl]-glycine), which is known to inhibit the shikimate pathway at the level of the enzyme 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, thereby causing the accumulation of large amounts of shikimate in planta. As oxoacid **3c** did not affect glyphosate-induced shikimate accumulation in buckwheat hypocotyls, we suspected one of the enzymes catalyzing a step between EPSP and phenylalanine as the target of oxoacid **3c**. As we had, for the first time, succeeded in the cloning and heterologous expression of the ultimate enzyme in phenylalanine biosynthesis, that is, arogenate dehydratase, from the higher plant *Arabidopsis thaliana*, we tested oxoacid **3c** as a potential inhibitor of this enzyme and found it to be strongly inhibitory (K_i=27 μM, mixed-type inhibition). Reduction of the 2-oxo group of oxoacid **3c** led to the loss of the inhibitory action on arogenate dehydratase. Thus, a presumably specific inhibitor of this poorly characterized plant enzyme has been uncovered and may serve as a lead in the identification of more potent compounds with possible herbicidal activity.

6. Experimental

6.1. Generalities

Details regarding standard operations and abbreviations can be found in previous publications from this laboratory.[42–44] ^{1}H, (^{1}H-decoupled) ^{13}C and ^{19}F NMR spectra were recorded at 400, 101 and 376 MHz, respectively, chemical shifts being given relative to tetramethylsilane and trichlorofluoromethane as the internal standards. The samples were dissolved in deuterochloroform or, if marked by an asterisk, in hexadeuteroacetone unless stated otherwise. Mass spectra were obtained at 70 eV ionization potential while a source temperature of 200 °C was applied. Whenever no molecular peak was observed under such conditions, chemical ionization ('c.i.') in an ammonia atmosphere at 100 °C source temperature was applied. To avoid redundant information, only the [^{35}Cl] and [^{79}Br] containing fragments, and not the [^{37}Cl] or [^{81}Br] isotopomers, are listed. For the pK_a measurements, an automatic titrator model PCA101 (Sirius Analytical Instruments Ltd, East Sussex, UK) was employed.

6.2. (2-Bromo-1-fluoroethyl)benzenes

6.2.1. (2-Bromo-1-fluoroethyl)benzene. At 0 °C, triethylamine tris(hydrofluoride) (46 mL, 45 g, 0.28 mol) was added dropwise over 30 min to a solution of styrene (28 mL, 25 g, 0.24 mol) and *N*-bromosuccinimide (50 g, 0.28 mol) in dichloromethane (0.15 L). The mixture was stirred for 15 h at 25 °C before being washed with water (3×50 mL), a saturated aqueous solution of sodium hydrogen carbonate (3×50 mL) and brine (2×50 mL). Distillation afforded a colorless oil; bp 69–72 °C/2 mm Hg; (Ref. 45: bp 53 °C/0.05 mm Hg); n_D^{20} 1.5433; d_4^{20} 1.473; yield: 39.5 g (81%). ^{1}H NMR: δ 7.5 (5H, m), 5.60 (1H, ddd, *J*=47.1, 7.8, 4.1 Hz), 3.66 (1H, ddd, *J*=15.3, 11.3, 7.8 Hz), 3.58 (1H, ddd, *J*=26.0, 11.3, 4.2 Hz). ^{13}C NMR: δ 137.1 (d, *J*=20 Hz), 129.2 (s), 128.7 (s), 125.7 (d, *J*=6 Hz), 92.7 (d, *J*=126 Hz), 34.3 (d, *J*=28 Hz). ^{19}F NMR: δ −175.0 (ddd, *J*=47.0, 26.0, 15.4 Hz). MS: 202 (3%, M^+), 127 (3%), 109 (100%), 89 (1%).

6.2.2. 1-(2-Bromo-1-fluoroethyl)-4-fluorobenzene. Analogously from 4-fluorostyrene (29 mL, 29 g, 0.24 mol); colorless oil; bp 70–72 °C/2 mm Hg; mp 11–13 °C; n_D^{20} 1.5223; d_4^{20} 1.552; yield: 44.0 g (83%). ^{1}H NMR: δ 7.33 (2H, dd, *J*=8.4, 5.7 Hz), 7.09 (2H, t, *J*=8.4 Hz), 5.60 (1H, ddd, *J*=46.5, 7.5, 4.5 Hz), 3.67 (1H, ddd, *J*=15.2, 11.3, 7.5 Hz), 3.58 (1H, ddd, *J*=24.2, 11.3, 4.5 Hz). ^{13}C NMR: δ 163.1 (d, *J*=248 Hz), 133.0 (dd, *J*=21, 3 Hz), 127.8 (t, *J*=7 Hz), 115.8 (d, *J*=22 Hz), 92.1 (d, *J*=178 Hz), 34.0 (d, *J*=29 Hz). ^{19}F NMR: δ −112.4 (symm. m), −172.2 (ddd, *J*=46.3, 24.2, 15.3 Hz). MS: 220 (10%, M^+), 201 (3%), 140 (9%), 127 (100%). Anal. Calcd for $C_8H_7BrF_2$ (221.04) C 43.47, H 3.19; found C 43.64, H 2.88%.

6.2.3. 1-(2-Bromo-1-fluoroethyl)-4-chlorobenzene. Analogously from 4-chlorostyrene (31 mL, 33 g, 0.24 mol); slightly yellow oil; bp 92–98 °C/2 mm Hg; mp 9–11 °C; n_D^{20} 1.5564; d_4^{20} 1.576; yield: 45.7 g (80%). ^{1}H NMR: δ 7.41 (2H, dm, *J*=7.3 Hz), 7.32 (2H, dm, *J*=7.3 Hz), 5.62 (1H, ddd, *J*=46.6, 7.3, 4.5 Hz), 3.68 (1H, ddd, *J*=16.2, 11.3, 7.3 Hz), 3.61 (1H, ddd, *J*=24.4, 11.3, 4.4 Hz). ^{13}C NMR: δ 135.5 (d, *J*=21 Hz), 135.1 (s), 128.9 (s), 127.1 (d, *J*=6 Hz), 91.9 (d, *J*=179 Hz), 33.9 (d, *J*=29 Hz). ^{19}F NMR: δ −174.5 (1 F, ddd, *J*=46.6, 23.8, 15.8 Hz). MS: 236 (42%, M^+), 219 (2%), 157 (3%), 143 (100%). Anal. Calcd for C_8H_7BrClF (237.50) C 40.46, H 2.97; found C 40.43, H 2.84%.

6.3. (1-Fluorovinyl)benzenes

6.3.1. 1-(Fluorovinyl)benzene. 1-(2-Bromo-1-fluoroethyl)-benzene (26 mL, 39 g, 0.19 mol) was added to a solution of potassium *tert*-butoxide (21 g, 0.19 mol) in tetrahydrofuran (80 mL). The mixture was stirred 2 h at 25 °C and filtered. The solvent was evaporated and the residue distilled; colorless liquid; bp 61–64 °C/40 mm Hg (Ref. 46: bp 45.0–45.4 °C/14 mm Hg); mp −29 to −27 °C; n_D^{20} 1.5223; d_4^{20} 1.026; yield: 18.9 g (81%). ^{1}H NMR: δ 7.6 (5H, m), 5.02 (1H, dd, *J*=49.8, 3.4 Hz), 4.84 (1H, dd, *J*=17.9, 3.4 Hz). ^{13}C NMR: δ 163.0 (d, *J*=250 Hz), 132.0 (d, *J*=29 Hz), 129.4 (s), 128.5 (s), 124.6 (d, *J*=7 Hz), 89.5 (d, *J*=26 Hz). ^{19}F NMR: δ −108.5 (1 F, dd, *J*=49.8, 17.8 Hz). MS: 122 (100%, M^+), 109 (50%), 96 (20%).

6.3.2. 1-Fluoro-4-(1-fluorovinyl)benzene. Analogously from 1-(2-bromo-1-fluoroethyl)-4-fluoro-benzene (27 mL, 42 g, 0.19 mol); colorless liquid; bp 144–146 °C; mp −30 to −28 °C; n_D^{20} 1.4976; d_4^{20} 1.126; yield: 21.3 g (80%). ^{1}H NMR: δ 7.52 (2H, dd, *J*=8.9, 5.2 Hz), 7.05 (2H, t, *J*=8.9 Hz), 4.95 (1H, dd, *J*=49.6, 3.6 Hz), 4.82 (1H, dd, *J*=17.9, 3.6 Hz). ^{13}C NMR: δ 163.4 (d, *J*=249 Hz), 162.2 (d, *J*=250 Hz), 128.53 (dd, *J*=30, 3 Hz), 126.6 (t, *J*=8 Hz), 115.6 (d, *J*=22 Hz), 89.3 (d, *J*=23 Hz). ^{19}F NMR: δ −107.5 (1F, dd, *J*=49.6, 17.9 Hz), −119.9 (1F, symm. m). MS: 140 (100%, M^+), 120 (17%), 114 (18%), 96 (11%). Anal. Calcd for $C_8H_6F_2$ (140.13) C 68.57, H 4.32; found C 68.60, H 4.40%.

6.3.3. 1-Chloro-4-(1-fluorovinyl)benzene. Analogously from 1-(2-chloro-1-fluoroethyl)-4-chloro-benzene (29 mL, 45 g, 0.19 mol); colorless liquid; bp 72–73 °C/12 mm Hg; mp −29 to −28 °C; n_D^{20} 1.5442; d_4^{20} 1.189; yield: 25.0 g (84%). ^{1}H NMR: δ 7.42 (2H, dm, *J*=8.7 Hz), 7.33 (2H, dm, *J*=8.7 Hz), 5.00 (1H, dd, *J*=49.4, 3.7 Hz), 4.86 (1H, dd, *J*=17.8 Hz, 3.7).^{13}C NMR: δ 162.0 (d, *J*=250 Hz), 135.3 (s), 130.5 (d, *J*=30 Hz), 128.7 (s), 125.9 (d, *J*=7 Hz), 90.1 (d, *J*=22 Hz). ^{19}F NMR: δ −108.6 (1F, dd, *J*=49.4 Hz, 17.6). MS: 156 (100%, M^+), 136 (2%), 121 (39%), 101 (28%), 91 (8%). Anal. Calcd for C_8H_6ClF (156.59) C 61.36, H 3.86; found C 61.49, H 3.99%.

6.4. (2-Bromo-1,1-difluoroethyl)benzenes

The (2-bromo-1,1-difluoroethyl)benzenes were made from (1-fluorovinyl)benzenes following exactly the same protocol as described for the preparation of (2-bromo-1-fluoroethyl)-benzenes from styrenes. Due to the chemical lability of 1-(2,bromo-1-fluoroethyl)-4-methoxy-benzene, the *p*-methoxy derivative **1d** was prepared on a different route (see below).

6.4.1. (2-Bromo-1,1-difluoroethyl)benzene (1a). From (1-fluorovinyl)benzene (18 mL, 18 g, 0.15 mol) using *N*-bromosuccinimide (32 g, 0.18 mol) and triethylamine tris(hydrofluoride) (49 mL, 48 g, 0.30 mol) in dichloromethane (0.12 L). Upon distillation a faintly yellow oil was collected; bp 55–56 °C/2 mm Hg (Ref. 1: bp 62–63 °C/5 mm Hg); mp −26 to −24 °C; n_D^{20} 1.5131; d_4^{20} 1.534; yield: 30.2 g (91%). ^{1}H NMR: δ 7.5 (5H, m), 3.75 (2H, t, *J*=13.9 Hz). ^{13}C NMR: δ 134.4 (t, *J*=26 Hz), 130.6 (s), 128.6 (s), 125.4 (t, *J*=6 Hz), 118.5 (t, *J*=244 Hz), 33.8 (t, *J*=35 Hz). ^{19}F NMR: δ −98.2 (2F, t, *J*=13.8 Hz). MS: 220 (45%, M^+), 169 (19%), 127 (100%), 109 (37%), 77 (25%).

6.4.2. 1-(2-Bromo-1,1-difluoroethyl)-4-fluorobenzene (1b). Analogously from 1-fluoro-4-(1-fluorovinyl)benzene (19 mL, 21 g, 0.15 mol); slightly yellow liquid; bp 82–84 °C/15 mm Hg; mp −5 to −3 °C; n_D^{20} 1.4943; d_4^{20} 1.602; yield: 27.9 g (78%). ^{1}H NMR: δ 7.50 (2H, dd, *J*=8.6, 5.1 Hz), 7.13 (2H, t, *J*=8.5 Hz), 3.74 (2H, t, *J*=13.5 Hz). ^{13}C NMR: δ 164.0 (d, *J*=251 Hz), 130.4 (td, *J*=27, 3 Hz), 127.7 (q, *J*=6 Hz), 118.4 (t, *J*=245 Hz), 115.8 (d, *J*=22 Hz), 33.6 (t, *J*=36 Hz). ^{19}F NMR: δ −96.9 (2F, t, *J*=13.4 Hz), −110.2 (1F, symm. m). MS: 238 (13%, M^+), 220 (2%), 145 (100%), 125 (2%), 109 (9%), 95 (4%). Anal. Calcd for $C_8H_6BrClF_2$ (255.49) C 40.20, H 2.53; found C 40.12, H 2.89%.

6.4.3. 1-(2-Bromo-1,1-difluoroethyl)-4-chlorobenzene (1c). Analogously from 1-chloro-4-(1-fluorovinyl)benzene (20 mL, 24 g, 0.15 mol); colorless liquid; bp 82–84 °C/2 mm Hg; mp −4 to −2 °C; n_D^{20} 1.5287; d_4^{20} 1.621; yield: 31.8 g (83%). ^{1}H NMR: δ 7.44 (4H, s), 3.74 (2H, t, *J*=13.5 Hz). ^{13}C NMR: δ 136.8 (s), 132.8 (t, *J*=26 Hz), 128.9 (s), 126.9 (t, *J*=6 Hz), 118.4 (t, *J*=245 Hz), 33.4 (t, *J*=35 Hz). ^{19}F NMR: δ −97.7 (2F, t, *J*=13.6 Hz). MS: 254 (34%, M^+), 237 (4%), 161 (100%), 125 (15%), 111 (9%). Anal. Calcd for $C_8H_6BrClF_2$ (255.49) C 37.61, H 2.37; found C 37.59, H 2.14%.

6.4.4. 1-(2-Bromo-1,1-difluoroethyl)-4-methoxybenzene (1d). A solution of 2-bromo-1-(4-methoxyphenyl)ethanone (80 g, 0.35 mol) and diethylaminosulfur trifluoride (46 mL, 56 g, 0.35 mol) in dichloromethane (0.35 L) was heated under reflux for 50 h. The mixture was cautiously poured onto ice (0.10 L) and the organic phase washed with a saturated aqueous solution of sodium hydrogen carbonate (3×0.10 L), water (2×0.10 L) and brine (0.10 L). Distillation in the presence of some potassium carbonate (0.1 g) gave a yellow oil; bp 92–94 °C/2 mm Hg; mp 15–17 °C; n_D^{20} 1.5253; d_4^{20} 1.516; yield: 33.2 g (38%). ^{1}H NMR: δ 7.42 (2H, d, *J*=7.7 Hz), 6.94 (2H, d, *J*=7.7 Hz), 3.73 (2H, t, *J*=13.8 Hz). ^{13}C NMR: δ 161.2 (s), 126.9 (t, *J*=6 Hz), 126.4 (t, *J*=27 Hz), 118.4 (t, *J*=244 Hz), 113.9 (s), 55.4 (s), 34.0 (t, *J*=36 Hz). ^{19}F NMR: δ −96.7 (2F, t, *J*=13.8 Hz). MS: 250 (75%, M^+), 233 (53%), 157 (100%), 135 (62%). Anal. Calcd for $C_9H_9BrF_2O$ (251.07) C 43.06, H 3.61; found C 43.11, H 3.63%.

6.5. 2-Aryl-2,2-difluoroethyl acetates

6.5.1. 2,2-Difluoro-2-phenylethyl acetate (6a). A mixture containing (2-bromo-1,1-difluoroethyl)benzene (**1a**; 17 mL, 27 g, 0.12 mol), anhydrous potassium acetate (47 g, 0.48 mol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (3.2 g, 12 mmol) in anhydrous *N*,*N*-dimethylformamide (0.12 L) was heated to 150 °C for 15 h. The mixture was diluted with water (0.10 L) and extracted with diethyl ether (3×50 mL). The combined organic layers were evaporated and the product was isolated by distillation as a colorless liquid; bp 57–59 °C/1 mm Hg; mp −32 to −30 °C; n_D^{20} 1.4655; d_4^{20} 1.188; yield: 20.6 g (86%). ^{1}H NMR: δ 7.5 (5H, m), 4.50 (2H, t, *J*=13.3 Hz), 2.09 (3H, s). ^{13}C NMR: δ 169.9

(s), 134.1 (t, J=25 Hz), 130.5 (s), 128.6 (s), 125.4 (t, J=6 Hz), 119.2 (t, J=244 Hz), 65.1 (t, J=33 Hz), 20.5 (s). ^{19}F NMR: δ −105.0 (2F, t, J=13.4 Hz). MS: 200 (13%, M^+), 158 (2%), 140 (6%), 127 (100%), 109 (6%). Anal. Calcd for $C_{10}H_{10}F_2O_2$ (200.19) C 60.00, H 5.04; found C 59.89, H 4.93%.

6.5.2. 2,2-Difluoro-2-(4-fluorophenyl)ethyl acetate (6b). Analogously from 1-(2-bromo-1,1-difluoroethyl)-4-fluorobenzene (**1b**; 18 mL, 29 g, 0.12 mol); colorless liquid; bp 40–42 °C/0.5 mm Hg; mp 8–9 °C; n_D^{20} 1.4529; d_4^{20} 1.260; yield: 21.2 g (81%). ^{1}H NMR: δ 7.51 (2H, dd, J=8.8, 5.1 Hz), 7.13 (2H, t, J=8.8 Hz), 4.47 (2H, t, J=13.1 Hz), 2.07 (3H, s). ^{13}C NMR: δ 169.8 (s), 164.0 (d, J=250 Hz), 130.2 (td, J=26, 3 Hz), 127.8 (q, J=7 Hz), 119.0 (t, J=244 Hz), 115.8 (d, J=22 Hz), 65.0 (t, J=34 Hz), 20.5 (s). ^{19}F NMR: δ −103.8 (2F, t, J=13.0 Hz), −110.4 (1F, symm. m). MS: 218 (28%, M^+), 215 (7%), 199 (5%), 158 (16%), 145 (100%), 109 (8%). Anal. Calcd for $C_{10}H_9F_3O_2$ (218.17) C 55.05, H 4.16; found C 55.37, H 3.91%.

6.5.3. 2-(4-Chlorophenyl)-2,2-difluoroethyl acetate (6c). Analogously from 1-(2-bromo-1,1-difluoroethyl)-4-chlorobenzene (**1c**; 19 mL, 31 g, 0.12 mol); colorless liquid; bp 90–92 °C/2 mm Hg; mp −7 to −5 °C; n_D^{20} 1.4851; d_4^{20} 1.298; yield: 22.1 g (78%). ^{1}H NMR: δ 7.42 (4H, symm. m), 4.47 (2H, t, J=13.0 Hz), 2.08 (3H, s). ^{13}C NMR: δ 169.6 (s), 136.7 (s), 132.6 (t, J=26 Hz), 128.8 (s), 127.0 (t, J=6 Hz), 118.9 (t, J=244 Hz), 64.8 (t, J=34 Hz), 20.3 (s). ^{19}F NMR: δ −104.7 (2F, t, J=13.0 Hz). MS: 234 (100%, M^+), 215 (7%), 174 (7%), 161 (70%), 125 (14%), 111 (7%). Anal. Calcd for $C_{10}H_9ClF_2O_2$ (234.63) C 51.19, H 3.87; found C 51.13, H 3.97%.

6.5.4. 2,2-Difluoro-2-(4-methoxyphenyl)ethyl acetate (6d). Analogously from 1-(2-bromo-1,1-difluoroethyl)-4-methoxybenzene (**1d**, 20 mL, 30 g, 0.12 mol); bp 102–104 °C/1 mm Hg; mp 11–13 °C; n_D^{20} 1.4914, d_4^{20} 1.226; yield: 22.3 g (81%). ^{1}H NMR: δ 7.43 (2H, d, J=7.7 Hz), 6.94 (2H, d, J=7.7 Hz), 4.46 (2H, t, J=13.2 Hz), 3.82 (3H, s), 2.08 (3H, s). ^{13}C NMR: δ 169.6 (s), 161.2 (s), 127.0 (t, J=6 Hz), 126.2 (t, J=26 Hz), 119.4 (t, J=244 Hz), 113.9 (s), 65.1 (t, J=34 Hz), 55.3 (s), 20.5 (s). ^{19}F NMR: δ −103.3 (2F, t, J=13.2 Hz). MS: 230 (83%, M^+), 211 (17%), 157 (100%), 114 (38%). Anal. Calcd for $C_{11}H_{12}F_2O_3$ (230.21) C 57.39, H 5.25; found C 57.35, H 5.30%.

6.6. 2-Aryl-2,2-difluoroethanol

6.6.1. 2,2-Difluoro-2-phenylethanol (7a). A solution of 2,2-difluoro-2-phenylethyl acetate (**6a**; 15 mL, 28 g, 90 mmol) and sodium hydroxide (7.2 g, 0.18 mol) in 80% aqueous ethanol (0.10 L) was left for 2 h at 25 °C. The mixture was diluted with water and the product extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (3×50 mL) and evaporated. The product was isolated by distillation; colorless liquid; bp 69–72 °C/2 mm Hg; mp 19–21 °C; n_D^{20} 1.4890; d_4^{20} 1.232; yield: 13.8 g (97%). ^{1}H NMR: δ 7.5 (5H, m), 3.98 (2H, t, J=13.6 Hz), 2.68 (1H, broad s). ^{13}C NMR: δ 134.5 (t, J=26 Hz), 130.3 (s), 128.5 (s), 125.5 (t, J=6 Hz), 120.7 (t, J=244 Hz), 65.7 (t, J=32 Hz). ^{19}F NMR: δ −107.9 (t, J=13.6 Hz). MS: 158 (7%, M^+), 127 (100%), 109 (2%), 91 (10%), 77 (28%). Anal. Calcd for $C_8H_8F_2O$ (158.15) C 60.76, H 5.10; found C 60.61, H 5.11%.

6.6.2. 2,2-Difluoro-2-(4-fluorophenyl)ethanol (7b). Analogously from 2,2-difluoro-2-(4-fluorophenyl)ethyl acetate (**6b**; 16 mL, 20 g, 90 mmol); the product was purified by crystallization rather than distillation; colorless needles (from diethyl ether and hexanes); mp 41–42 °C; yield: 14.7 g (93%). ^{1}H NMR: δ 7.50 (2H, dd, J=8.8, 5.4 Hz), 7.12 (2H, t, J=8.8 Hz), 3.93 (2H, t, J=13.3 Hz), 2.40 (1H, broad s). ^{13}C NMR: δ 163.9 (d, J=250 Hz), 130.5 (t, J=25 Hz), 127.8 (q, J=7 Hz), 120.3 (t, J=244 Hz), 115.7 (d, J=22 Hz), 65.9 (t, J=33 Hz). ^{19}F NMR: δ −106.5 (2F, t, J=13.0 Hz), −110.9 (1F, symm. m). MS: 176 (9%, M^+), 157 (1%), 145 (100%), 125 (4%), 109 (7%), 95 (6%). Anal. Calcd for $C_8H_7F_3O$ (176.14) C 54.55, H 4.01; found C 54.42, H 3.87%.

6.6.3. 2-(4-Chlorophenyl)-2,2-difluoroethanol (7c). Analogously from 2-(4-chlorophenyl)-2,2-di-fluoroethyl acetate (**6c**; 16 mL, 21 g, 90 mmol); colorless needles (from chloroform and hexanes); mp 38–39 °C; yield: 16.2 g (94%). ^{1}H NMR: δ 7.42 (4H, symm. m), 3.92 (2H, t, J=13.4 Hz), 2.48 (1H, broad s). ^{13}C NMR: δ 136.5 (s), 132.9 (t, J=26 Hz), 128.9 (s), 127.1 (t, J=6 Hz), 120.3 (t, J=244 Hz), 65.7 (t, J=33 Hz). ^{19}F NMR: δ −107.5 (t, J=13.4 Hz). MS: 192 (45%, M^+), 161 (100%), 125 (21%), 111 (10%). Anal. Calcd for $C_8H_7ClF_2O$ (192.59) C 49.89, H 3.66; found C 49.60, H 3.90%.

6.6.4. 2,2-Difluoro-2-(4-methoxyphenyl)ethanol (7d). Analogously from 2,2-difluoro-2-(4-methoxyphenyl)ethyl acetate (**6d**; 17 mL, 21 g, 90 mmol); colorless needles (from diethyl ether and hexanes); mp 57–58 °C; bp 122–125 °C/4 mm Hg; yield: 16.1 g (95%). H NMR: δ 7.44 (2H, d, J=7.7 Hz), 6.95 (2H, d, J=7.7 Hz), 3.94 (2H, td, J=13.4, 6.5 Hz), 3.83 (3H, s), 2.09 (1H, broad t, J=6.1 Hz). ^{13}C NMR: δ 161.0 (s), 127.0 (t, J=6 Hz), 126.6 (t, J=26 Hz), 120.8 (t, J=243 Hz), 113.9 (s), 66.0 (t, J=33 Hz), 55.4 (s). ^{19}F NMR: δ −106.1 (2F, t, J=13.4 Hz). MS: 188 (21%, M^+), 169 (1%), 157 (100%), 142 (4%), 114 (16%). Anal. Calcd for $C_9H_{10}F_2O_2$ (188.18) C 57.45, H 5.36; found C 57.96, H 5.32%.

6.7. 2-Aryl-2,2-difluoroacetaldehydes

6.7.1. 2,2-Difluoro-2-phenylethanal (2a). At −75 °C, anhydrous dimethyl sulfoxide (13 mL, 14 g, 0.18 mol) was added to a solution of oxalyl chloride (7.6 mL, 11 g, 88 mmol) in dichloromethane (0.30 L). The mixture was kept at −60 °C for 30 min, before 2,2-difluoro-2-phenylethanol (**7a**; 10 mL, 13 g, 80 mmol) in dichloromethane (0.10 mL) was added, then stirred vigorously at −60 °C for 30 min, before triethylamine was added (50 mL, 36 g, 0.36 mol). After having waited 6 h at 25 °C, the mixture was washed with water (5×0.10 L), dried and evaporated. The residue cannot be stored for a longer period of time, undergoing polymerization or decomposition; yellow oil; bp 60–64 °C/5 mm Hg (Ref. 1: bp 66–69 °C/5 mm Hg); yield: 12.4 g (99%). ^{1}H NMR: δ 9.55 (1H, t, J=3.2 Hz), 7.4 (5H, m). ^{19}F NMR: δ −111.7 (2F, t, J=3.1 Hz), −113.0 (2F, t, J=5.5 Hz).

6.7.2. 2,2-Difluoro-2-(4-fluorophenyl)ethanal (2b). Analogously from 2,2-difluoro-2-(4-fluoro-phenyl)ethanol (**7b**; 14 g, 80 mmol); yellowish oil; bp 49–54 °C/1 mm Hg; n_D^{20} 1.4668; d_4^{20} 1.276; unstable compound; yield: 23.8 g (99%). ^{1}H NMR: δ 7.56 (2H, dd, *J*=8.6, 5.1 Hz), 7.17 (2H, t, *J*=8.5 Hz), 4.79 (1H, t, *J*=8.4 Hz), 3.67 (1H, broad s). ^{13}C NMR: δ 165.5 (d, *J*=252 Hz), 128.5 (q, *J*=7 Hz), 127.1 (t, *J*=26 Hz), 117.7 (t, *J*=251 Hz), 116.0 (t, *J*=22 Hz), 115.2 (s), 65.7 (t, *J*=38 Hz). ^{19}F NMR: δ −104.7 (1F, dd, *J*=253.5, 7.5 Hz), −106.4 (1F, dd, *J*=253.5, 8.5 Hz), −108.8 (1F, symm. m). MS: 201 (1%, M^+), 155 (1%), 145 (100%), 127 (3%), 95 (4%). Anal. Calcd for $C_8H_5F_3O$ (174.12) C 55.19, H 2.89; found C 55.87, H 3.09%.

6.7.3. 2-(4-Chlorophenyl)-2,2-difluoroethanal (2c). Analogously from 2-(4-chlorophenyl)-2,2-difluoroethanol (**7c**; 15 g, 80 mmol); yellow oil; bp 49–51 °C/1 mm Hg; n_D^{20} 1.4995; yield: 15.0 (99%). ^{1}H NMR: δ 9.56 (1H, t, *J*=2.7 Hz), 7.44 (4H, s). ^{13}C NMR: δ 188.0 (t, *J*=40 Hz), 137.9 (s), 129.4 (s), 128.6 (t, *J*=25 Hz), 127.4 (t, *J*=6 Hz), 114.3 (t, *J*=251 Hz). ^{19}F NMR: δ −110.8 (2F, t, *J*=2.7 Hz). MS: 190 (8%, M^+), 171 (2%), 161 (100%), 143 (5%), 125 (13%), 111 (10%). Anal. Calcd for $C_8H_5ClF_2O$ (190.58) C 50.42, H 2.64; found C 50.02, H 2.92%.

6.7.4. 2,2-Difluoro-2-(4-methoxyphenyl)ethanal (2d). A solution containing 2,2-difluoro-2-(4-methoxyphenyl)-ethanol (**7d**; 15 g, 80 mmol) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one[13,14] ('Dess–Martin reagent'; 34 g, 80 mmol) in dichloromethane (0.16 L) was kept at 25 °C for 4 h. The suspension formed was diluted with diethyl ether (0.60 L) before being slowly poured into a saturated solution of sodium hydrogen carbonate (0.60 L) in which beforehand sodium thiosulfate pentahydrate (40 g, 0.16 mol) had been dissolved. After 15 min of vigorous stirring, the organic phase was collected and the aqueous one extracted with diethyl ether (3×0.10 L). The combined organic layers were dried and evaporated. Distillation of the residue provided an unstable colorless oil; bp 49–51 °C/1 mm Hg; n_D^{20} 1.4995; d_4^{20} 1.280; yield: 11.0 g (74%). ^{1}H NMR: δ 9.52 (1H, t, *J*=3.4 Hz), 7.45 (2H, d, *J*=8.7 Hz), 6.97 (2H, d, *J*=8.7 Hz), 3.82 (3H, s). ^{13}C NMR: δ 188.2 (t, *J*=41 Hz), 162.0 (s), 127.6 (t, *J*=6 Hz), 122.0 (t, *J*=26 Hz), 115.0 (t, *J*=251 Hz), 114.5 (s), 55.4 (s). ^{19}F NMR: δ −110.6 (2F, s). MS (c.i.): 204 (5%, M^++NH_4), 186 (29%, M^+), 167 (53%), 157 (100%), 114 (62%). Anal. Calcd for $C_9H_8ClF_2O_2$ (186.16) C 58.07, H 4.33; found C 58.07, H 4.24%.

6.8. Cyanhydrines

6.8.1. 3,3-Difluoro-2-hydroxy-3-phenylpropionitrile (8a). 2,2-Difluoro-2-phenylethanal (**2a**; 9.4 g, 60 mmol) was added to a solution of sodium metabisulfite (11 g, 60 mmol) in water. The mixture was vigorously stirred for 2 h at 25 °C and, after the addition of a solution of sodium cyanide (5.9 g, 0.12 mol) in water (25 mL), again for 1 h. The mixture was extracted with diethyl ether (3×50 mL). The product was absorbed on silica gel (30 mL) and eluted from a column filled with more silica (0.35 L) with a 1:4 (v/v) mixture of diethyl ether and hexanes to afford a yellowish oil, bp 99–100 °C/1 mm Hg (Ref. 47: bp 109–110 °C/1.3 mm Hg); n_D^{20} 1.4875; d_4^{20} 1.312; yield: 7.82 g (71%). ^{1}H NMR: δ 7.5 (5H, m), 4.81 (1H, dd, *J*=9.6, 8.0 Hz), 3.87 (1H, broad s). ^{13}C NMR: δ 131.4 (s), 131.2 (t, *J*=25 Hz), 128.7 (s), 126.1 (t, *J*=6 Hz), 118.0 (t, *J*=251 Hz), 115.2 (s), 65.6 (t, *J*=37 Hz). ^{19}F NMR: δ −105.7 (1F, dd, *J*=252.2, 7.8 Hz), −107.7 (1F, dd, *J*=252.2, 9.6 Hz). MS: 183 (1%, M^+), 127 (100%), 109 (5%), 77 (18%). Anal. Calcd for $C_9H_7F_2NO$ (183.16) C 59.02, H 3.85; found C 58.96, H 4.00%.

6.8.2. 3,3-Difluoro-3-(4-fluorophenyl)-2-hydroxypropionitrile (8b). Analogously from 2,2-difluoro-2-(4-fluorophenyl)ethanal (**2b**; 10.4 g, 60 mmol); yellow oil; bp 99–102 °C/2 mm Hg; n_D^{20} 1.4769; d_4^{20} 1.388; yield: 7.51 g (62%). ^{1}H NMR: δ 7.56 (2H, dd, *J*=8.6, 5.1 Hz), 7.17 (2H, t, *J*=8.5 Hz), 4.79 (1H, t, *J*=8.4 Hz), 3.67 (1H, broad s). ^{13}C NMR: δ 165.5 (d, *J*=252 Hz), 128.5 (q, *J*=7 Hz), 127.1 (t, *J*=26 Hz), 117.7 (t, *J*=251 Hz), 116.0 (t, *J*=22 Hz), 115.2 (s), 65.7 (t, *J*=38 Hz). ^{19}F NMR: δ −104.7 (1F, dd, *J*=253.5, 7.5 Hz), −106.4 (1F, dd, *J*=253.5, 8.5 Hz), −108.8 (1F, symm. m). MS: 201 (1%, M^+), 155 (1%), 145 (100%), 127 (3%), 95 (4%). Anal. Calcd for $C_9H_6F_3NO$ (201.15) C 53.74, H 3.01; found C 53.76, H 2.94%.

6.8.3. 3-(4-Chlorophenyl)-3,3-difluoro-2-hydroxypropionitrile (8c). Analogously from 2-(4-chlorophenyl)-2,2-difluoroethanal (**2c**; 11.4 g, 60 mmol); yellow oil; bp 99–102 °C/2 mm Hg; n_D^{20} 1.5055, d_4^{20} 1.595; yield: 8.55 g (69%). ^{1}H NMR: δ 7.49 (4H, symm. m), 4.79 (1H, dd, *J*=8.9, 7.9 Hz), 3.70 (1H, broad s). ^{13}C NMR: δ 137.8 (s), 129.5 (t, *J*=25 Hz), 129.1 (s), 127.7 (t, *J*=6 Hz), 117.6 (t, *J*=251 Hz), 114.8 (s), 65.5 (t, *J*=37 Hz). ^{19}F NMR: δ −105.4 (1F, dd, *J*=253.8, 7.6 Hz), −107.4 (1F, dd, *J*=253.8, 9.0 Hz). MS: 217 (1%, M^+), 190 (2%), 161 (100%), 143 (5%), 125 (10%), 111 (6%). Anal. Calcd for $C_9H_6ClF_2NO$ (206.62) C 49.68, H 2.78; found C 49.40, H 3.09%.

6.8.4. 3,3-Difluoro-2-hydroxy-3-(4-methoxyphenyl)propionitrile (8d). Analogously from 2,2-difluoro-2-(4-methoxyphenyl)ethanal (**2d**; 11.2 g, 60 mmol); yellow oil; bp 99–102 °C/2 mm Hg; n_D^{20} 1.5043, d_4^{20} 1.272; yield: 9.46 g (74%). ^{1}H NMR: δ 7.48 (2H, d, *J*=8.6 Hz), 6.97 (2H, d, *J*=8.6 Hz), 4.76 (1H, t, *J*=8.3 Hz), 3.83 (3H, s), 4.7 (1H, broad m). ^{13}C NMR: δ 161.8 (s), 127.7 (t, *J*=6 Hz), 123.1 (t, *J*=25 Hz), 118.2 (t, *J*=250 Hz), 115.2 (s,), 114.2 (s), 65.9 (t, *J*=38 Hz), 55.5 (s). ^{19}F NMR: δ −104.8 (1F, dd, *J*=250.4, 8.6 Hz), −105.9 (1F, dm, *J*=250 Hz). MS (c.i.): 231 (4%, M^++NH_4), 213 (6%, M^+), 186 (6%), 164 (100%), 157 (47%). Anal. Calcd for $C_{10}H_9F_2NO_2$ (213.19) C 56.32, H 4.26; found C 56.31, H 4.27%.

6.9. Ethyl 3-aryl-3,3-difluoro-2-hydroxypropionates

6.9.1. Ethyl 3,3-difluoro-2-hydroxy-3-phenylpropionate (9a). Gaseous hydrogen chloride was slowly bubbled into a mixture of 3,3-difluoro-2-hydroxy-3-phenylpropionitrile (**8a**; 6.4 g, 35 mmol) and ethanol (4.1 mL, 3.2 g, 70 mmol), whereupon a precipitate formed. After 4 h at 25 °C, water (20 mL) was added and the suspension was stirred until it became clear. The product was extracted with diethyl ether (4×25 mL) and, after washing (2×25 mL of brine), drying and evaporation of the combined organic

layers, crystallized from diethyl ether and hexanes; colorless needles; mp 59–60 °C (Ref. 47: mp 59–60 °C); yield: 6.76 g (84%). ^{1}H NMR: δ 7.5 (5H, m), 4.56 (1H, dt, J=12.8, 7.8 Hz), 4.28 (2H, q, J=7.2 Hz), 3.29 (1H, broad d, J=8.2 Hz), 1.27 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 169.5 (s), 133.5 (t, J=25 Hz), 130.5 (s), 128.3 (s), 125.8 (t, J=6 Hz), 119.3 (t, J=251 Hz), 73.7 (t, J=33 Hz), 62.8 (s), 13.9 (s). ^{19}F NMR: δ −104.0 (1F, dd, J=252.8, 7.6 Hz), −108.3 (1F, dd, J=252.8, 13.0 Hz). MS: 230 (3%, M^+), 210 (1%), 149 (3%), 127 (100%), 109 (15%), 91 (12%), 77 (18%).

6.9.2. Ethyl 3,3-difluoro-3-(4-fluorophenyl)-2-hydroxypropionate (9b). Analogously from 3,3-difluoro-3-(4-fluorophenyl)-2-hydroxypropionitrile (**8b**; 7.0 g, 35 mmol); colorless needles; mp 43–44 °C; yield: 7.12 g (82%). ^{1}H NMR: δ 7.49 (2H, dd, J=8.7, 5.2 Hz), 7.11 (2H, t, J=8.6 Hz), 4.51 (1H, dt, J=13.1, 7.5 Hz), 4.27 (2H, q, J=7.1 Hz), 3.37 (1H, broad d, J=7.9 Hz), 1.27 (3H, t, J=7.1 Hz). ^{13}C NMR: δ 169.4 (s), 164.0 (d, J=250 Hz), 129.5 (t, J=25 Hz), 128.1 (q, J=7 Hz), 118.9 (t, J=251 Hz), 115.5 (d, J=22 Hz), 73.6 (t, J=33 Hz), 63.0 (s), 14.0 (s). ^{19}F NMR: δ −102.5 (1F, dd, J=253.5, 7.1 Hz), −107.3 (1F, dd, J=253.4, 13.1 Hz), −110.6 (1F, symm. m). MS: 248 (2%, M^+), 145 (100%), 127 (26%), 107 (4%). Anal. Calcd for $C_{11}H_{11}F_3O_3$ (248.20) C 53.23, H 4.47; found C 53.36, H 4.89%.

6.9.3. Ethyl 3-(4-chlorophenyl)-3,3-difluoro-2-hydroxypropionate (9c). Analogously from 3-(4-chlorophenyl)-3,3-difluoro-2-hydroxypropionitrile (**8c**; 7.2 g, 35 mmol); colorless needles; mp 45–46 °C; yield: 7.14 g (77%). ^{1}H NMR: δ 7.44 (4H, symm. m), 4.51 (1H, dt, J=13.4, 6.8 Hz), 4.29 (2H, q, J=7.1 Hz), 3.75 (1H, broad d, J=6.9 Hz), 1.28 (3H, t, J=7.1 Hz). ^{13}C NMR: δ 169.4 (s), 136.9 (s), 132.1 (t, J=26 Hz), 128.7 (s), 127.5 (t, J=6 Hz), 118.9 (t, J=251 Hz), 73.5 (t, J=33 Hz), 63.0 (s), 14.0 (s). ^{19}F NMR: δ −103.1 (1F, dd, J=253.8 Hz, 6.8), −108.4 (1F, dd, J=253.8 Hz, 13.4). MS: 264 (5%, M^+), 244 (1%), 161 (100%), 143 (10%), 125 (4%), 111 (3%). Anal. Calcd for $C_{11}H_{11}ClF_2O_3$ (264.66) C 49.92, H 4.19; found C 49.81, H 4.30%.

6.9.4. Ethyl 3,3-difluoro-2-hydroxy-3-(4-methoxyphenyl)propionate (9d). Analogously from 3,3-difluoro-2-hydroxy-3-(4-methoxyphenyl)propionitrile (**8d**; 7.5 g, 35 mmol); colorless needles; mp 54–55 °C; yield: 7.93 g (87%). ^{1}H NMR: δ 7.42 (2H, d, J=8.8 Hz), 6.93 (2H, d, J=8.8 Hz), 4.51 (1H, dt, J=12.6 Hz, 7.4), 4.27 (2H, q, J=7.2 Hz), 3.83 (3H, s), 3.25 (1H, broad d, J=8.0 Hz), 1.27 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 169.6 (s), 161.1 (s), 127.4 (t, J=6 Hz), 125.6 (t, J=26 Hz), 119.3 (t, J=251 Hz), 113.7 (s), 73.8 (t, J=33 Hz), 62.8 (s), 55.3 (s), 14.0 (s). ^{19}F NMR: δ −102.0 (1F, dd, J=251.5, 7.1 Hz), −106.8 (1F, dd, J=251.5, 12.6 Hz). MS (c.i.): 278 (100%, M^++NH_4), 260 (12%, M^+), 238 (100%), 157 (75%), 114 (8%). Anal. Calcd for $C_{12}H_{14}F_2O_4$ (260.24) C 55.39, H 5.42; found C 55.49, H 5.36%.

6.10. Ethyl 3-aryl-3,3-difluoro-2-oxopropionates

6.10.1. Ethyl 3,3-difluoro-2-oxo-3-phenylpropionate (10a) hydrate. Ethyl 3,3-difluoro-2-hydroxy-3-phenylpropionate (**9a**; 5.8 g, 25 mmol) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one[13,14] (16 g, 38 mmol) were conjointly dissolved in dichloromethane (0.12 L) and kept at 25 °C for 5 h. After dilution with diethyl ether (0.30 L), the mixture was slowly poured into a concentrated aqueous solution of sodium hydrogen carbonate (0.30 L), which also contained sodium thiosulfate pentahydrate (19 g, 75 mmol). After 15 min of vigorous stirring, the organic phase was collected and the aqueous one extracted with diethyl ether (3×0.10 L). The combined organic layers were evaporated and the residue absorbed on silica gel (30 mL). The product was eluted from a column filled with more silica (0.32 L) using a 1:1 (v/v) mixture of diethyl ether and hexanes. The product was recrystallized from the same mixture; colorless needles; mp 48–50 °C (Ref. 47 mp 55–56 °C); yield: 5.85 g (95%). ^{1}H NMR: δ 7.6 (2H, m), 7.5 (3H, m), 4.37 (2H, q, J=7.2 Hz), 1.37 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 168.9 (s), 131.6 (t, J=25 Hz), 130.7 (s), 128.0 (s), 127.2 (t, J=6 Hz), 118.6 (t, J=254 Hz), 93.0 (t, J=34 Hz), 64.0 (s), 13.9 (s). ^{19}F NMR: δ −110.2 (2F, s). MS: 228 (2%, M^+), 200 (1%), 127 (100%), 109 (6%), 91 (1%), 77 (6%).

6.10.2. Ethyl 3,3-difluoro-3-(4-fluorophenyl)-2-oxopropionate (10b) hydrate. Analogously from ethyl 3,3-difluoro-3-(4-fluorophenyl)-2-hydroxypropionate (**9b**; 6.2 g, 25 mmol); colorless needles; mp 44–45 °C; yield: 6.47 g (98%). ^{1}H NMR: δ 7.57 (2H, dd, J=8.8, 5.2 Hz), 7.09 (2H, t, J=8.6 Hz), 4.37 (2H, s), 4.34 (2H, q, J=7.1 Hz), 1.33 (3H, t, J=7.1 Hz). ^{13}C NMR: δ 168.9 (s), 164.2 (d, J=250 Hz), 129.5 (q, J=7 Hz), 127.8 (t, J=26 Hz), 118.4 (t, J=253 Hz), 115.1 (d, J=22 Hz), 93.0 (t, J=35 Hz), 64.1 (s), 13.9 (s). ^{19}F NMR: δ −109.3 (2F, s), −110.4 (1F, symm. m). MS: 246 (2%, M^+), 218 (3%), 171 (7%), 145 (100%), 125 (11%), 95 (22%). Anal. Calcd for $C_{11}H_{11}F_3O_4$ (264.20) C 50.01, H 4.20; found C 50.24, H 4.31%.

6.10.3. Ethyl 3-(4-chlorophenyl)-3,3-difluoro-2-oxopropionate (10c) hydrate. Analogously from ethyl 3-(4-chlorophenyl)-3,3-difluoro-2-hydroxypropionate (**9c**; 6.6 g, 25 mmol); colorless needles; mp 65–67 °C; yield: 6.26 g (89%). ^{1}H NMR: δ 7.53 (2H, d, J=7.7 Hz), 7.40 (2H, d, J=7.7 Hz), 4.39 (2H, q, J=7.2 Hz), 4.12 (2H, broad m), 1.37 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 168.8 (s), 136.9 (s), 130.2 (t, J=26 Hz), 128.7 (t, J=6 Hz), 128.2 (s), 118.2 (t, J=253 Hz), 92.8 (t, J=33 Hz), 64.1 (s), 13.8 (s). ^{19}F NMR: δ −110.0 (2F, s). MS: 262 (5%, M^+), 234 (4%), 161 (100%), 143 (4%), 125 (8%), 111 (6%). Anal. Calcd for $C_{11}H_{11}ClF_2O_4$ (280.66) C 47.08, H 3.95; found C 47.13, H 4.16%.

6.10.4. Ethyl 3,3-difluoro-2-oxo-3-(4-methoxyphenyl)-propionate (10d) hydrate. Analogously from ethyl 3,3-difluoro-2-hydroxy-3-(4-methoxyphenyl)propionate (**9d**; 6.5 g, 25 mmol); colorless needles; mp 69–70 °C; yield: 6.38 g (92%). ^{1}H NMR: δ 7.50 (2H, d, J=8.9 Hz), 6.91 (2H, d, J=8.9 Hz), 4.34 (2H, q, J=7.2 Hz), 4.25 (2H, s), 3.80 (3H, s), 1.34 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 169.1 (s), 161.3 (s), 128.7 (t, J=6 Hz), 123.8 (t, J=26 Hz), 118.8 (t, J=253 Hz), 113.4 (s), 93.1 (t, J=35 Hz), 64.0 (s), 55.3 (s), 13.9 (s). ^{19}F NMR: δ −109.1 (2F, s). MS (c.i.): 276 (32%, M^++NH_4), 258 (8%, M^+), 239 (72%), 157 (100%), 114 (23%). Anal. Calcd for $C_{11}H_{11}ClF_2O_4$ (280.66) C 52.18, H 5.11; found C 52.20, H 5.10%.

6.11. 3-Aryl-3,3-difluoro-2-oxopropionic acids

Upon heating or even simple storage, these compounds may loose partially or completely hydrate water. Thus melting ranges and analytical data may be a bit fortuitous.

6.11.1. 3,3-Difluoro-2-oxo-3-phenylpropionic acid (3a) hydrate. Ethyl 3,3-difluoro-2-oxo-3-phenylpropionate (**10a**; 4.92 g, 20 mmol) and sodium hydrogen carbonate (5.0 g, 60 mmol) in 50% aqueous isopropanol (40 mL) were heated to 50 °C for 24 h. The solvents were evaporated. The residue was taken up in water (10 mL), washed with diethyl ether and acidified with 1.0 M hydrochloric acid (50 mL), which had beforehand been saturated with sodium chloride. The product was extracted with diethyl ether (3×50 mL) and, after drying and evaporation of the solvent, crystallized from a mixture of ethyl acetate and hexanes; colorless needles; mp 116–118 °C (Ref. 47: mp 90–91 °C); yield: 4.09 g (94%). ^{1}H NMR*: δ 7.62 (2H, dm, J=7.8 Hz), 7.5 (3H, m). ^{13}C NMR*: δ 170.1 (s), 133.4 (t, J=25 Hz), 129.9 (s), 127.4 (s), 127.3 (t, J=7 Hz), 119.3 (t, J=252 Hz), 93.1 (t, J=34 Hz). ^{19}F NMR*: δ −107.9 (2F, s). MS: 199 (2%, M^+), 127 (100%), 109 (5%), 91 (2%).

6.11.2. 3,3-Difluoro-3-(4-fluorophenyl)-2-oxopropionic acid (3b) hydrate. Analogously from ethyl 3,3-difluoro-3-(4-fluorophenyl)-2-oxopropionate (**10b**; 5.3 g, 20 mmol); colorless needles; mp 135–137 °C; yield: 4.52 g (96%). ^{1}H NMR*: δ 7.68 (2H, dd, J=9.0, 5.4 Hz), 7.21 (2H, t, J=9.0 Hz), 6.23 (2H, broad s). ^{13}C NMR*: δ 170.7 (s), 164.7 (d, J=247 Hz), 130.7 (q, J=7 Hz), 130.1 (t, J=26 Hz), 119.9 (t, J=252 Hz), 115.3 (d, J=22 Hz), 94.0 (t, J=34 Hz). ^{19}F NMR*: δ −107.4 (2F, s), −111.9 (1F, symm. m). MS: 218 (1%, M^+), 199 (2%), 145 (100%), 125 (20%), 95 (31%). Anal. Calcd for $C_9H_7F_3O_4$ (236.14) C 45.78, H 2.99; found C 45.82, H 3.20%.

6.11.3. 3-(4-Chlorophenyl)-3,3-difluoro-2-oxopropionic acid (3c) hydrate. Analogously from ethyl 3-(4-chlorophenyl)-3,3-difluoro-2-oxopropionate (**10c**; 5.6 g, 20 mmol); colorless needles; mp 156–158 °C (hydrate); mp 167–169 °C (without hydrate water); yield: 4.40 g (87%). ^{1}H NMR*: δ 7.63 (2H, d, J=8.4 Hz), 7.48 (2H, d, J=8.4 Hz), 6.22 (2H, s). ^{13}C NMR*: δ 170.5 (s), 136.5 (s), 132.9 (t, J=26 Hz), 130.0 (t, J=6 Hz), 128.5 (s), 119.8 (t, J=252 Hz), 93.8 (t, J=33 Hz). ^{19}F NMR*: δ −108.2 (2F, s). MS: 234 (1%, M^+), 189 (1%), 161 (100%), 143 (3%), 125 (9%), 111 (6%). Anal. Calcd for $C_9H_7ClF_2O_4$ (252.60) C 42.80, H 2.79; found C 42.92, H 2.73%.

6.11.4. 3,3-Difluoro-2-oxo-3-(4-methoxyphenyl)propionic acid (3d) hydrate. Analogously from ethyl 3,3-difluoro-2-oxo-3-(4-methoxyphenyl)propionate (**10d**; 5.5 g, 20 mmol); colorless needles; mp 122–124 °C; yield: 4.52 g (91%). ^{1}H NMR*: δ 7.54 (2H, d, J=9.0 Hz), 6.97 (2H, d, J=9.0 Hz), 6.09 (2H, broad s), 3.83 (3H, s). ^{13}C NMR*: δ 170.9 (s), 162.0 (s), 129.8 (t, J=6 Hz), 126.2 (t, J=26 Hz), 120.3 (t, J=252 Hz), 113.7 (s), 94.1 (t, J=34 Hz), 55.6 (s). ^{19}F NMR*: δ −106.9 (2F, s). MS: 230 (12%, M^+), 211 (10%), 186 (7%), 157 (100%), 139 (43%). Anal. Calcd for $C_{10}H_{10}F_2O_5$ (248.19) C 48.40, H 4.06; found C 48.60, H 4.16%.

6.12. 3-Aryl-3,3-difluoroalanines

6.12.1. 2-Amino-3,3-difluoro-3-phenylpropionic acid (4a). 3,3-Difluoro-2-oxo-3-phenylpropionic acid (**3a**; 2.2 g, 10 mmol) was dissolved in a 25% aqueous solution of ammonia (20 mL) placed in a pressure-resistant vessel, which was hermetically closed. After heating to 60 °C for 5 h, sodium borohydride (1.1 g, 30 mmol) was added to the mixture through which a gentle current of nitrogen was bubbled for 30 min at 25 °C. At 0 °C, the mixture was acidified with 37% hydrochloric acid (5.0 mL) before being poured into a column filled with an ion exchange resin (Dowex 50W-X8, acid form, 50–100 mesh, 110 mL) and which was eluted consecutively with 50% aqueous isopropanol (0.50 L) and neat water (0.50 L). These eluents were combined and evaporated. The residue was suspended in a 2.0 M aqueous solution of sodium hydroxide (50 mL) and washed with diethyl ether (3×25 mL). The aqueous phase was acidified with 5.0 M hydrochloric acid which was beforehand saturated with sodium chloride. Extraction with diethyl ether (3×25 mL) and evaporation of the dried organic phases left a residue behind, the crystallization of which provided the 3,3-difluoro-2-hydroxy-3-phenylpropionic acid **11a** as described below (Section 6.13). Finally the ion exchange column was eluted with a 1.0 M aqueous solution of ammonia. Evaporation of the solvents afforded the aminoacid **4a**; colorless needles crystallized as the chlorhydrate from hydrogen chloride-containing ethanol; mp 176–177 °C (decomp.; Ref. 8: mp 178–179 °C); yield: 1.34 g (67%). ^{1}H NMR (CD_3OD): δ 7.6 (5H, m), 4.95 (1H, dd, J=20.7, 5.4 Hz). ^{13}C NMR (CD_3OD): δ 165.8 (s), 133.6 (t, J=24 Hz), 132.4 (s), 129.8 (s), 126.9 (t, J=6 Hz), 120.1 (t, J=250 Hz), 59.6 (t, J=29 Hz). ^{19}F NMR (CD_3OD): δ −90.4 (1F, dd, J=250.3, 4.8 Hz), −109.3 (1F, dd, J=250.3, 21.1 Hz). MS: 202 (4%, M^++1), 156 (4%), 137 (24%), 127 (100%), 109 (24%), 91 (4%). Anal. Calcd for $C_9H_{10}ClF_2NO_2$ (237.64) C 45.49, H 4.24; found C 45.81, H 4.10%.

6.12.2. 2-Amino-3,3-difluoro-3-(4-fluorophenyl)propionic acid (4b). Analogously from 3,3-difluoro-3-(4-fluorophenyl)-2-oxopropionic acid (**3b**; 2.4 g, 10 mmol); colorless needles; mp 174–176 °C (decomp.); yield: 0.46 g (21%). ^{1}H NMR (CD_3OD): δ 7.67 (2H, dd, J=8.6, 5.1 Hz), 7.27 (3H, t, J=8.6 Hz), 5.01 (1H, dd, J=21.6, 5.0 Hz). ^{13}C NMR (CD_3OD): δ 165.9 (d, J=250 Hz), 165.7 (s), 129.9 (t, J=25 Hz), 129.6 (q, J=7 Hz), 119.9 (t, J=250 Hz), 116.9 (d, J=23 Hz), 59.5 (t, J=29 Hz). ^{19}F NMR (CD_3OD): δ −89.1 (1F, d, J=250.8 Hz), −108.4 (1F, dd, J=250.8, 21.6 Hz), −109.3 (1F, symm. m). MS (c.i.): 237 (8%, M^++NH_4), 220 (100%, M^++1), 176 (14%), 156 (41%), 145 (49%), 127 (17%), 95 (6%). Anal. Calcd for $C_9H_{10}ClF_2NO_2$ (237.64) C 42.29, H 3.55; found C 42.82, H 4.16%.

6.12.3. 2-Amino-3-(4-chlorophenyl)-3,3-difluoropropionic acid (4c). Analogously from 3-(4-chlorophenyl)-3,3-difluoro-2-oxopropionic acid (**3c**; 2.5 g, 10 mmol); colorless needles; mp 186–188 °C (decomp.); yield: 0.76 g (32%). ^{1}H NMR (CD_3OD): δ 7.61 (2H, d, J=8.3 Hz), 7.56 (2H, d, J=8.3 Hz), 5.03 (1H, dd, J=22.0, 4.8 Hz). ^{13}C NMR (CD_3OD): δ 165.6 (s), 138.7 (s), 132.4 (t, J=25 Hz), 130.1 (s), 128.8 (t, J=6 Hz), 119.8 (t, J=250 Hz), 59.3 (t, J=28 Hz). ^{19}F NMR (CD_3OD): δ

−89.7 (1F, d, *J*=252.0 Hz), −109.3 (1F, dd, *J*=252.0, 22.0 Hz). MS (c.i.): 253 (6%, M^++NH_4), 238 (6%, M^++1), 183 (79%), 166 (100%). Anal. Calcd for $C_9H_9Cl_2F_2NO_2$ (272.08) C 39.73, H 3.33; found C 40.10, H 3.06%.

6.12.4. 2-Amino-3,3-difluoro-3-(4-methoxyphenyl)propionic acid (4d). Analogously from 3,3-difluoro-2-oxo-3-(4-methoxyphenyl)propionic acid (**3d**; 2.5 g, 10 mmol); colorless platelets; mp 168–170 °C (decomp.); yield: 1.11 g (48%). ^{1}H NMR (CD_3OD): δ 7.52 (2H, d, *J*=8.9 Hz), 7.05 (2H, d, *J*=8.9 Hz), 4.89 (1H, dd, *J*=20.5, 5.5 Hz), 3.85 (3H, s). ^{13}C NMR (CD_3OD): δ 167.6 (s), 164.5 (s), 130.0 (t, *J*=6 Hz), 127.0 (t, *J*=25 Hz), 121.8 (t, *J*=249 Hz), 116.6 (s), 61.2 (t, *J*=30 Hz), 57.5 (s). ^{19}F NMR (CD_3OD): δ −88.8 (1F, dd, *J*=248.8, 5.1 Hz), −107.4 (1F, dd, *J*=248.8, 20.5 Hz). MS (c.i.): 249 (22%, M^++NH_4), 232 (100%, M^++1), 188 (20%), 168 (86%), 157 (53%), 114 (10%). Anal. Calcd for $C_{10}H_{12}ClF_2NO_3$ (267.66) C 44.87, H 4.52; found C 44.61, H 4.74%.

6.13. 3-Aryl-3,3-difluoro-2-hydroxypropionic acids

The 3-aryl-3,3-difluoro-2-hydroxypropionic acids **11** were the first components to be eluted from the ion exchange column as described in the preceding section. They were purified by crystallization from diethyl ether and hexanes.

6.13.1. 3,3-Difluoro-2-hydroxy-3-phenylpropionic acid (11a). Colorless needles; mp 100–102 °C; yield: 0.59 g (29%). ^{1}H NMR*: δ 7.5 (5H, m), 5.17 (1H, broad s), 4.64 (1H, dd, *J*=13.7, 6.6 Hz). ^{13}C NMR*: δ 170.3 (s), 135.1 (t, *J*=25 Hz), 131.1 (s), 129.0 (s), 126.9 (t, *J*=6 Hz), 120.7 (t, *J*=249 Hz), 74.2 (t, *J*=32 Hz). ^{19}F NMR*: δ −102.7 (1F, dd, *J*=253.6, 6.4 Hz), −108.7 (1F, dd, *J*=253.6, 13.6 Hz). MS: 202 (1%, M^+), 138 (4%), 127 (100%), 109 (17%), 91 (3%). Anal. Calcd for $C_9H_8F_2O_3$ (202.16) C 53.57, H 3.99; found C 53.27, H 4.04%.

6.13.2. 3,3-Difluoro-3-(4-fluorophenyl)-2-hydroxypropionic acid (11b). Colorless needles; mp 109–110 °C; yield: 1.49 g (68%). ^{1}H NMR*: δ 7.65 (2H, dd, *J*=9.0, 5.3 Hz), 7.24 (2H, t, *J*=9.0 Hz), 4.72 (1H, dd, *J*=14.0 Hz, 7.8). ^{13}C NMR*: δ 170.2 (s), 164.6 (d, *J*=248 Hz), 131.1 (t, *J*=26 Hz), 129.4 (q, *J*=26 Hz), 120.4 (t, *J*=249 Hz), 115.9 (d, *J*=22 Hz), 74.1 (t, *J*=32 Hz). ^{19}F NMR*: δ −99.7 (1F, dd, *J*=252.5, 7.4 Hz), −105.5 (1F, dd, *J*=252.5, 14.0 Hz), −111.3 (1F, symm. m). MS: 220 (1%, M^++1), 201 (1%), 156 (2%), 145 (100%), 127 (14%), 95 (7%). Anal. Calcd for $C_9H_7F_3O_3$ (220.15) C 49.10, H 3.21; found C 49.32, H 2.85%.

6.13.3. 3-(4-Chlorophenyl)-3,3-difluoro-2-hydroxypropionic acid (11c). Colorless needles; mp 128–129 °C; yield: 1.51 g (64%). ^{1}H NMR*: δ 7.60 (2H, d, *J*=8.5 Hz), 7.52 (2H, d, *J*=8.5 Hz), 4.71 (1H, dd, *J*=14.0, 7.9 Hz). ^{13}C NMR*: δ 170.1 (s), 136.7 (s), 134.0 (t, *J*=26 Hz), 128.9 (s), 128.8 (t, *J*=6 Hz), 120.4 (t, *J*=249 Hz), 74.0 (t, *J*=32 Hz). ^{19}F NMR*: δ −100.5 (1F, dd, *J*=252.8, 7.8 Hz), −106.4 (1F, dd, *J*=252.8, 14.0 Hz). MS (c.i.): 254 (11%, M^++NH_4), 236 (6%, M^+), 216 (1%), 161 (100%), 143 (11%), 111 (10%). Anal. Calcd for $C_9H_7ClF_2O_3$ (236.60) C 45.69, H 2.98; found C 45.78, H 3.03%.

6.13.4. 3,3-Difluoro-2-hydroxy-3-(4-methoxyphenyl)propionic acid (11d). Colorless needles; mp 104–105 °C; yield: 0.74 g (32%). ^{1}H NMR*: δ 7.50 (2H, d, *J*=8.9 Hz), 7.00 (2H, d, *J*=8.9 Hz), 4,65 (1H, dd, *J*=13.7, 7.7 Hz), 3.83 (3H, s). ^{13}C NMR*: δ 170.4 (s), 162.0 (s), 128.4 (t, *J*=6 Hz), 127.2 (t, *J*=26 Hz), 120.9 (t, *J*=249 Hz), 114.3 (s), 74.3 (t, *J*=33 Hz), 55.7 (s). ^{19}F NMR*: δ −99.1 (1F, dd, *J*=250.9, 7.7 Hz), −104.8 (1F, dd, *J*=250.9, 13.7 Hz). MS: 232 (9%, M^+), 213 (9%), 168 (14%), 157 (100%), 139 (22%), 114 (14%). Anal. Calcd for $C_{10}H_{10}F_2O_4$ (232.19) C 51.73, H 4.34; found C 52.08, H 4.30%.

6.14. 3,3-Difluorophenylalanine derivatives

6.14.1. Ethyl 2-amino-3,3-difluoro-3-phenylpropionate hydrochloride. A solution of 2-amino-3,3-difluoro-3-phenylpropionic acid (**4a**; 1.0 g, 5.0 mmol) and concentrated sulfuric acid (1.0 mL) in ethanol (10 mL) was heated under reflux for 24 h. The mixture was concentrated by evaporation and, after addition of a 2.0 M solution of sodium hydroxide (20 mL), was extracted with diethyl ether (3×25 mL). The combined organic layers were dried and evaporated. The residue was crystallized from ethanol saturated with hydrogen chloride; colorless needles; mp 158–160 °C; yield: 0.73 g (55%). ^{1}H NMR (CD_3OD): δ 7.6 (5H, m), 5.08 (1H, dd, *J*=21.2, 5.0 Hz), 4.09 (2H, q, *J*=7.1 Hz), 0.99 (3H, t, *J*=7.1 Hz). ^{13}C NMR (CD_3OD): δ 164.8 (s), 133.4 (t, *J*=24 Hz), 132.7 (s), 130.0 (s), 126.8 (t, *J*=6 Hz), 119.9 (t, *J*=250 Hz), 64.3 (s), 59.6 (t, *J*=28 Hz), 13.9 (s). ^{19}F NMR (CD_3OD): δ −90.6 (1F, dd, *J*=248.4, 4.6 Hz), −110.2 (1F, dd, *J*=248.4, 21.2 Hz). MS: 230 (7%, M^++1), 210 (4%), 189 (6%), 156 (5%), 127 (15%), 102 (100%). Anal. Calcd for $C_{11}H_{14}ClF_2NO_2$ (265.69) C 49.79, H 5.31; found C 49.57, H 5.36%.

6.14.2. Ethyl 2-acetamido-3,3-difluoro-3-phenylpropionate (12a). Ethyl 2-amino-3,3-difluoro-3-phenylpropionate hydrochloride (see preceding paragraph; 0.73 g, 2.8 mmol), acetic anhydride (5.0 mL) and pyridine (5.0 mL) were combined and stored at 25 °C for 24 h. The mixture was absorbed on silica gel (5 mL) and eluted with diethyl ether from a column filled with more silica (0.10 L); colorless needles (from diethyl ether and hexanes); mp 92–93 °C; yield: 0.24 g (32%). ^{1}H NMR: δ 7.5 (5H, m), 6.44 (1H, d, *J*=9.3 Hz), 5.36 (1H, ddd, *J*=13.6, 12.5, 9.5 Hz), 4.10 (2H, q, *J*=7.2 Hz), 2.01 (3H, s), 1.10 (3H, t, *J*=7.2 Hz). ^{13}C NMR: δ 169.7 (s), 167.0 (s), 133.7 (t, *J*=25 Hz), 130.6 (s), 128.4 (s), 125.5 (t, *J*=6 Hz), 119.5 (t, *J*=251 Hz), 62.2 (s), 57.4 (t, *J*=30 Hz), 23.0 (s), 13.7 (s). ^{19}F NMR: δ −101.2 (1F, dd, *J*=247.4, 12.4 Hz), −105.2 (1F, dd, *J*=247.4, 13.7 Hz). MS: 271 (11%, M^+), 231 (3%), 198 (6%), 156 (18%), 127 (76%), 102 (100%). Anal. Calcd for $C_{13}H_{15}F_2NO_3$ (271.26) C 57.56, H 5.57; found C 56.83, H 5.42%.

6.15. Resolution of the 3,3-difluorophenylalanine racemate

6.15.1. *N*-[(*S*)-1-Phenylethyl]-2,2-difluoro-2-phenylethylideneamine (13a). A solution of 2,2-difluoro-2-phenylethanal (**2a**; 9.4 g, 60 mmol) and *N*-[(*S*)-1-phenylethyl]amine (9.2 mL, 8.7 g, 72 mmol) in toluene (20 mL) was heated under reflux for 4 h and the water formed was collected in a

Dean-Stark trap. Fractional distillation afforded the product as a colorless oil; bp 116–118 °C/1 mm Hg; mp 14–16 °C; n_D^{20} 1.5318, d_4^{20} 1.115; yield: 8.57 g (55%). ^{1}H NMR: δ 7.83 (1H, t, J=5.2 Hz), 7.5 (2H, m), 7.4 (3H, m), 7.2 (5H, m), 4.51 (1H, q, J=6.3 Hz), 1.51 (3H, d, J=6.3 Hz). ^{13}C NMR: δ 155.6 (t, J=33 Hz), 143.5 (s), 134.4 (t, J=29 Hz), 130.4 (s), 128.5 (s), 128.4 (s), 127.3 (s), 126.7 (s), 125.8 (t, J=6 Hz), 116.7 (t, J=239 Hz), 69.0 (s), 24.1 (s). ^{19}F NMR: δ −100.1 (2F, dd, J=13.9 Hz, 5.0). MS: 260 (61%, M^++1), 232 (4%), 169 (3%), 127 (9%), 105 (100%). Anal. Calcd for $C_{16}H_{15}F_2N$ (259.30) C 74.11, H 5.83; found C 74.09, H 6.29%.

6.15.2. 3,3-Difluoro-3-phenyl-2-[(*S*)-1-phenylethylamino]-propionitrile (14a). *N*-[(*S*)-1-Phenyl-ethyl]-2,2-difluoro-2-phenylethylideneamine (**13a**; 7.0 mL, 7.8 g, 30 mmol), cyanotrimethylsilane (4.0 mL, 3.0 g, 30 mmol) and zinc diiodide (0.96 g, 3.0 mmol) were heated in a closed vessel at 50 °C for 3 days. The mixture was absorbed on silica gel (30 mL) and eluted from a column filled with more silica (0.30 L) using a 1:9 (v/v) mixture of diethyl ether and hexanes; faintly yellow oil; n_D^{20} 1.5301, d_4^{20} 1.145; yield: 7.90 g (92%). ^{1}H NMR: δ 7.5 (5H, m), 7.3 (4H, m), 7.0 (1H, m), 4.05 (0.5H, dd, J=10.5 Hz, 8.2), 4.03 (0.5H, q, J=6.5 Hz), 3.94 (0.5H, q, J=6.5 Hz), 3.72 (0.5H, dd, J=14.7, 6.0 Hz), 1.79 (1H, broad s), 1.32 (1.5H, d, J=6.5 Hz), 1.27 (1.5H, d, J=6.5 Hz). ^{13}C NMR: δ 143.2 (s), 141.9 (s), 132.6 (t, J=25 Hz), 132.5 (t, J=25 Hz), 131.0 (s), 130.8 (s), 128.8 (s), 128.6 (s), 128.4 (s), 127.9 (s), 126.7 (s), 125.9 (t, J=6 Hz), 119.0 (t, J=250 Hz), 118.5 (t, J=250 Hz), 115.8 (s), 56.5 (s), 56.2 (s), 55.2 (t, J=34 Hz), 55.0 (t, J=34 Hz), 24.9 (s), 22.6 (s). ^{19}F NMR: δ −98.6 (0.5F, dd, J=250.3 Hz, 6.0), −101.1 (0.5F, dd, J=248.1, 8.1 Hz), −103.6 (0.5F, dd, J=248.0, 10.4 Hz), −107.2 (0.5F, dd, J=250.4, 14.6 Hz). MS: 286 (1%, M^+), 271 (5%), 159 (12%), 127 (9%), 105 (100%), 91 (1%). Anal. Calcd for $C_{17}H_{16}F_2N_2$ (286.32) C 71.31, H 5.63; found C 71.19, H 5.80%.

6.15.3. 3,3-Difluoro-3-phenyl-2-[(*S*)-1-phenylethylamino]-propionamide (15a). At 0 °C, the mixture of 3,3-difluoro-3-phenyl-2-[(*S*)-1-phenylethylamino]propionitrile (**14a**; 6.3 mL, 7.2 g, 25 mmol) in dichloromethane (25 mL) and 97% sulfuric acid (40 mL) were stirred for 3 h. The mixture was poured on ice (0.10 L) and a 25% solution of ammonia (0.10 L) was cautiously added. The organic layer was collected and the aqueous one was extracted with dichloromethane (3×50 mL). The combined organic layers were evaporated and the residue was absorbed on silica gel (30 mL). Elution with a 1:1 (v/v) mixture of diethyl ether and hexanes provided first a small amount of unconsumed starting material **14a** (0.22 g, 3%) and then the product **15a** as a colorless oil; yield: 4.87 g (64%). ^{1}H NMR: δ 7.4 (5H, m), 7.2 (4H, m), 7.0 (1H, m), 6.36 (0.5H, broad s), 6.27 (0.5H, broad s), 6.16 (0.5H, broad s), 5.95 (0.5H, broad s), 3.65 (0.5H, q, J=6.7 Hz), 3.60 (0.5H, q, J=6.8 Hz), 3.59 (0.5H, dd, J=13.2, 10.2 Hz), 3.39 (0.5H, dd, J=16.3, 8.4 Hz), 2.12 (1H, broad s), 1.28 (3H, d, J=6.6 Hz), 1.25 (3H, d, J=6.6 Hz). ^{13}C NMR: δ 170.7 (s), 170.2 (s), 144.4 (s), 143.7 (s), 134.4 (t, J=26 Hz), 130.2 (s), 130.1 (s), 128.6 (s), 128.5 (s), 128.1 (s), 127.3 (s), 127.2 (s), 126.7 (s), 126.6 (s), 126.0 (t, J=6 Hz), 125.9 (t, J=6 Hz), 121.6 (t, J=250 Hz), 120.6 (t, J=249 Hz), 65.3 (t, J=29 Hz), 64.7 (t, J=29 Hz), 57.3 (s), 56.7 (s), 24.8 (s), 23.8 (s). ^{19}F NMR: δ −98.4 (0.5F, dd, J=248.3, 8.2 Hz), −99.6 (0.5F, dd, J=246.8, 10.1 Hz), −101.9 (0.5F, dd, J=246.8, 13.0 Hz), −106.9 (0.5F, dd, J=248.3, 16.2 Hz). MS: 305 (4%, M^++1), 260 (7%), 177 (18%), 127 (5%), 120 (40%), 105 (100%), 91 (3%). Anal. Calcd for $C_{17}H_{18}F_2N_2O$ (304.34) C 67.09, H 5.96; found C 67.04, H 5.82%.

This oil crystallized from a mixture of diethyl ether and hexanes at −20 °C; colorless needles; mp 75–78 °C; $[\alpha]_D^{20}$=−6.9 (dichloromethane; c=0.51); yield: 1.67 g (34%). ^{1}H NMR: δ 7.5 (5H, m), 7.2 (3H, m), 7.0 (2H, m), 6.26 (1H, broad s), 5.97 (1H, broad s), 3.68 (1H, q, J=6.6 Hz), 3.42 (1H, dd, J=16.2, 8.6 Hz), 2.22 (1H, broad s), 1.31 (3H, d, J=6.6 Hz). ^{13}C NMR: δ 170.5 (s), 143.6 (s), 134.3 (t, J=26 Hz), 130.1 (s), 128.5 (s), 128.1 (s), 127.2 (s), 126.7 (s), 125.9 (t, J=6 Hz), 120.6 (t, J=249 Hz), 65.3 (t, J=29 Hz), 56.7 (s), 24.8 (s). ^{19}F NMR: δ −98.3 (1F, dd, J=248.4, 8.4 Hz), −106.9 (1F, dd, J=248.4, 16.3 Hz).

6.15.4. (*R*)-2-Amino-3,3-difluoro-3-phenylpropionamide (16a). A slurry containing the crystallized 3,3-difluoro-3-phenyl-2-[(*S*)-1-phenylethylamino]propionamide (see above; **15a**; 4.6 g, 15 mmol) and 10% palladium on charcoal (0.69 g) in ethanol (50 mL) was stirred at 25 °C for 2 h under a blanket of hydrogen (1 atm.). The solvent was evaporated and the product absorbed on silica gel (20 mL). Elution from a column filled with more silica (0.23 L) with diethyl ether gave a yellowish oil which crystallized from a mixture of chloroform and hexanes; colorless prisms; mp 77–78 °C; $[\alpha]_D^{20}$=+17.1 (dichloromethane; c=0.52); yield: 2.91 g (91%). ^{1}H NMR: δ 7.5 (5H, m), 6.41 (1H, broad s), 6.06 (1H, broad s), 3.97 (1H, t, J=11.6 Hz), 1.84 (2H, broad s). ^{13}C NMR: δ 170.6 (s), 133.8 (t, J=26 Hz), 130.4 (s), 128.4 (s), 125.8 (t, J=6 Hz), 120.9 (t, J=248 Hz), 60.9 (t, J=29 Hz). ^{19}F NMR: δ −102.3 (1F, dd, J=248.0, 11.2 Hz), −103.1 (1F, dd, J=248.0, 11.8 Hz). MS: 201 (100%, M^++1), 181 (24%), 156 (14%), 136 (13%), 127 (16%), 109 (21%). Anal. Calcd for $C_9H_{10}F_2N_2O$ (200.19) C 54.00, H 5.04; found C 54.14, H 5.13%.

6.15.5. (*R*)-2-Amino-3,3-difluoro-3-phenylpropionic acid (L-3,3-difluorophenylalanine) (*R*-4a) hydrochloride. (*R*)-2-Amino-3,3-difluoro-3-phenylpropionamide (**16a**; 2.4 g, 10 mmol) and 20% aqueous sulfuric acid (10 mL) were heated under reflux for 4 h. After addition of a 5.0 M aqueous solution of sodium hydroxide (50 mL), the mixture was extracted with diethyl ether (3×50 mL). In this way a major amount of the starting material **16a** (1.54 g, 65%) was recovered. The aqueous phase was acidified with 37% hydrochloric acid (10 mL) before being loaded in a column filled with an ion exchange resin (Dowex 50W-X8, acid form, 50–100 mesh, 0.11 L). The column was washed consecutively with 50% aqueous isopropanol (0.50 L) and water (0.50 L). The product was eluted with a 1.0 M aqueous solution of ammonia and isolated, after evaporation of the solvent and crystallization from ethanol saturated with hydrogen chloride, as colorless needles; mp 176–177 °C (decomp.); $[\alpha]_D^{20}$=+1.0 (HCl 1.2 N; c=0.52) (Ref. 8: $[\alpha]_D^{20}$=+14.5 (HCl 1.2 N; c=0.15)); yield: 0.44 g (22%).

6.16. Determination of the acidity constants

The samples were dissolved in a 0.10 M aqueous solution of

potassium chloride and the pH of the solution was adjusted to 2.5 by addition of 0.50 M hydrochloric acid. The sample concentrations fell in the range between 5×10^{-4} and 2×10^{-3} M. Using a automatic titrator equipment (model PCA 101) and working under argon, the sample was titrated with a 0.50 M solution of potassium hydroxide until pH 10 was attained, the change in pH being monitored with a glass electrode.[48,49] This electrode was calibrated in the pH range of 1.8–12.2 by means of a 0.10 M aqueous solution of potassium chloride following the instructions of the supplier. The pK_a value was calculated as a function of the change in shape of the titration curve in comparison with a blank titration carried out without any sample present. The data were processed with the *pKaLOGP* software.[48] To check the reproducibility, all measurements were performed three-fold.

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