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α-Fluoro Analogues of Inflammation Inhibiting α-Arylpropionic Acids

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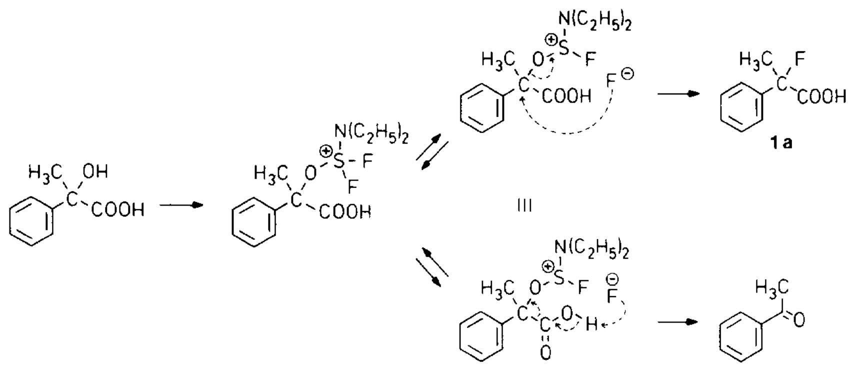
Abstract: 2-Aryl-2-fluoropropionic acids were prepared by treatment of either ethyl α-hydroxy-carboxylates or cyanohydrin *O*-silyl ethers with diethylaminosulfur trifluoride and subsequent hydrolysis. The methyl ester of 2-fluoro-2-(4-isobutylphenyl)propionic acid ("α-fluoroibuprofen") was submitted to an enzymatic racemate resolution. Copyright © 1996 Elsevier Science Ltd

A wide variety of 2-arylpropanoic acids ("profens") are known as powerful non-steroidal antiinflammatory drugs [1, 2]. Most of them exhibit pronounced analgesic and antirheumatic properties. Until now, all profenes, except one (Naproxen), are administered as racemic mixtures although only the (*S*) enantiomers display the desired mode of function, *i.e.* inhibition of the prostaglandin biosynthesis [3]. The use of racemates is justified to some extent since most (*R*) antipodes have been found to undergo an enzymatically controlled *in vivo* racemization, the occurrence [4] and the mechanism [5] of which are well documented.

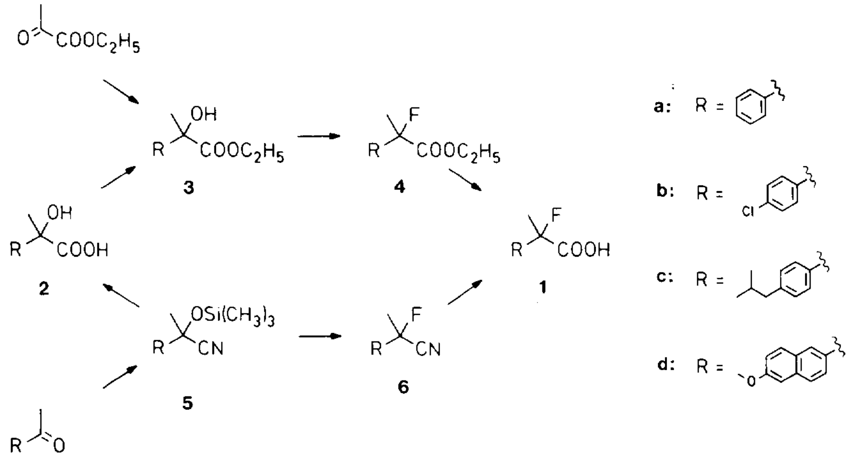
We are intrigued by the idea of introducing a fluorine atom into the α-position of profenes and to examine its effect on the pharmacodynamics of the substance. Of course, no inversion of configuration at the asymmetric center would now be possible. On the other hand, the halogen can be safely assumed to enhance the acidity of the compound and in this way modulate its interactions with receptors, enzymes and coenzyme A [5]. Last but not least, its metabolism could be significantly altered.

2-Fluoro-2-phenylpropanoic acid ("2-fluorohydratropic acid"; **1a**) has previously been prepared by treatment of methyl 2-amino-2-phenylpropionate with sodium nitrite in the presence of hydrogen fluoride and pyridine [6]. Looking for a more general method, we attempted to introduce the halogen atom directly by treatment of 2-hydroxy-2-phenylpropanoic acid (**2a**) with diethylaminosulfur trifluoride ("DAST"). The formation of an acyl fluoride was not considered to be a problem since such kind of conversion is known to occur only at elevated temperatures [7]. The desired compound **1a** was obtained indeed, but in not more than

21% yield. Acetophenone was identified as the main product (45%), having obviously originated from a fragmentation-decarboxylation of the intermediate (diethylamino)alkoxysulfur difluoride.

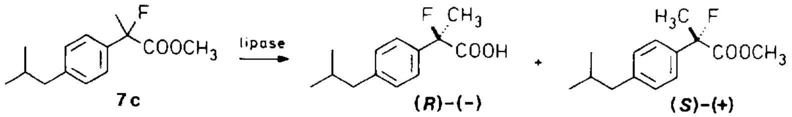


It was nevertheless possible to elaborate a convenient and universally applicable access to α-fluorocarboxylic acids. Ethyl α-fluorocarboxylates **4** could be isolated in high yield when the ethyl esters of the corresponding α-hydroxycarboxylic acids **3** (prepared by the addition of a suitable Grignard reagent onto ethyl pyruvate, or by hydrolysis and subsequent esterification of cyanohydrins **5**) were briefly exposed to the action of DAST at 0 °C, as described in the literature [8] for a few related examples. The hydrolysis of the esters **4** could be accomplished under mild conditions to afford the α-fluoropropionic acids **1a**, **1b**, **1c** and **1d** in 39 - 66% overall yield.



Alternatively, DAST may also be used to replace the trimethylsilyl protected [9] hydroxy group of cyanohydrins **5** by fluorine [10]. The resulting α-fluoronitriles **6** can smoothly be hydrolyzed [11] to give the α-fluoropropionic acid derivative **1**.

As optically active cyanohydrins are readily available [12], the latter method offers an option for stereoselective synthesis of such type of compounds [13]. We have preferred, however, to carry out a racemate resolution of 2-fluoro-2-(4-isobutylphenyl)propanoic acid ("α-fluoroibuprofen", **1c**) by enzymatic hydrolysis of its methyl ester **7c**. The lipase of *Candida cylindracea* (OF-360) was found to be uniquely suited for catalyzing the desired transformation. This enzyme enantioselectively cleaved the ester of the (*R*) enantiomer (*R*-**7c**) to give the levorotatory (*R*) acid (*R*-**1c**) in 40% yield and in 93.5% enantiomeric excess (e.e.). The methyl ester **7c**, recovered to the extent of 44%, proved to have an e.e. of 94.5%. On this basis, an enantiomeric ratio (E) [14] of 70 was calculated. The stereostructure of the acid **1c** was assigned by analogy to the parent compound of the series, 2-fluoro-2-phenyl-propanoic acid **1a** for the levorotatory antipode of which the (*R*) configuration has been unequivocally established. [6]



When tested in comparison with the halogen-free model ibuprofen, both enantiomers showed only little biological activity. On the other hand, the racemic mixture of 2-fluoro-2-(6-methoxynaphth-2-yl)propanoic acid ("α-fluoronaproxene", **1d**) was found to inhibit cyclooxygenase type 2 quite selectively (IC_{50} : COX-1 23 μM, COX-2 6.9 μM).

EXPERIMENTAL

1. Generalities

Starting materials have been purchased from Fluka AG (Buchs), Aldrich-Chemie (Steinheim), or Merck-Schuchardt (Hohenbrunn), unless literature references or details of the preparation are given. All commercial reagents were used without further purification.

Tetrahydrofuran was obtained anhydrous by distillation from sodium wire after the characteristic blue color of *in situ* generated sodium diphenyl ketyl [15] was found to persist. *Ethereal extracts* were dried with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids a spatula tip of *hydroquinone* or, respectively, *potassium carbonate* was added.

"Room temperature" (22 - 26 °C) is consistently indicated as 25 °C. *Melting ranges* (mp) are reproducible after resolidification, unless stated otherwise ("dec."), and are corrected using a calibration curve which was established with authentic standards. If no melting points are given, it means that all attempts to crystallize the liquid product have failed even at temperatures as low as -75 °C. If reduced pressure is not specified, *boiling ranges* were determined under ordinary atmospheric conditions (720 ± 25 mmHg).

Silica gel (Merck Kieselgel 60) of 70 - 230 mesh (0.06 - 0.20 mm) particle size was used for *column chromatography*. The solid support was suspended in hexane and, when all air bubbles had excaped, was sluiced into the column. When the level of the liquid was still some 3 - 5 cm above the silica layer, the dry powder obtained by absorption of the crude product mixture on 5 g silica gel and subsequent evaporation of the solvent was poured on top of the column.

^1H-NMR spectra were recorded at 250 MHz (if marked with an asterisk, at 400 MHz) in deuterochloroform solution and ^{19}F-NMR spectra in the same solvent at 376 MHz. Chemical shifts δ refer to the signal of tetramethylsilane in the case of ^1H spectra and to fluorotrichloromethane in the case of ^{19}F-NMR. Coupling constants (*J*) are measured in Hz. Abbreviations of coupling patterns : s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and td (triplet of doublets). High resolution nuclear magnetic resonance spectroscopy commonly produces signals showing fine structure due to long-range coupling. Except in very special cases, coupling constants smaller than 1 Hz have little informative value and hence are neglected.

Elementary analyses were made by the laboratory of I. Beetz, D-96'302 Kronach, Germany.

2. Ethyl 2-aryl-2-fluoropropionates (4)

The required ethyl 2-aryl-2-hydroxypropionates were prepared by addition of ethyl pyruvate (5.5 mL, 5.8 g, 20 mmol) to the arylmagnesium bromide (or iodide; 50 mmol) dissolved in tetrahydrofuran (10 mL). After 20 h at 0 °C, the mixture was hydrolyzed with a saturated aqueous solution (30 mL) of ammonium chloride and extracted with diethyl ether (3 × 20 mL). After evaporation of the organic solvents, the residue was purified by chromatography on silica gel affording the α-hydroxy ester in yields averaging 50% (**3a** : 56%; **3b** : 53%; **3c** : 49%; **3d** : 45%).

Ethyl 2-fluoro-2-phenylpropionate (4a) : Under nitrogen, diethylaminosulfur trifluoride ("DAST"; 4.9 mL, 6.4 g, 40 mmol) in dichloromethane (0.1 L) was added dropwise, in the course of 20 min, to an ice-cold solution of ethyl 2-hydroxy-2-phenylpropionate[16] (**3a**; 3.9 g, 20 mmol) in dichloromethane (0.2 L). After 30 min at 0 °C, the mixture was thoroughly washed with a saturated aqueous solution of sodium hydrogen carbonate (2 × 0.2 L) and brine (0.1 L) before being concentrated and absorbed on silica gel (10 g). Elution from more silica (0.10 kg) with a 1 : 1 (v/v) mixture of diethyl ether and hexane gave the α-fluoro ester **4a**[17]; mp -57 to -53 °C; bp 96 - 97 °C/4 mmHg; n_D^{20} 1.4806; 71%. - ^{1}H-NMR* : δ 7.5 (2 H, m), 7.3 (3 H, m), 4.21 (2 H, q, *J* 7.1), 1.93 (3 H, d, *J* 22.2), 1.25 (3 H, t, *J* 7.1). - ^{19}F-NMR : δ -152.5 (q, *J* 22.2).

Ethyl 2-(4-chlorophenyl)-2-fluoropropionate (4b) : Analogously from ethyl 2-(4-chlorophenyl)-2-hydroxypropionate[18] (**3b**); bp 91 - 94 °C/4 mmHg; n_D^{20} 1.5106; 91%. - ^{1}H-NMR : δ 7.45 (2 H, dt, *J* 8.5, 2.3), 7.31 (2 H, dm, *J* 8.5), 4.22 (2 H, q, *J* 7.2), 1.91 (3 H, d, *J* 22.4), 1.27 (3 H, t, *J* 7.2). - ^{19}F-NMR : δ -152.9 (q, *J* 21.8). - Analysis : calc. for $C_{11}H_{12}ClFO_2$ (230.66) C 57.28, H 5.24; found C 57.29, H 5.21%.

Ethyl 2-fluoro-2-(4-isobutylphenyl)propionate (4c) : From ethyl 2-hydroxy-2-(4-isobutylphenyl)-propionate[19] (**3c**); n_D^{20} 1.4798; 57%. - ^{1}H-NMR* : δ 7.39 (2 H, dt, *J* 8.3, 2.0), 7.11 (2 H, dm, *J* 8.3), 4.21 (2 H, q, *J* 7.1), 2.47 (2 H, d, *J* 7.1), 1.92 (3 H, d, *J* 22.4), 1.86 (1 H, sept, *J* 6.8), 1.26 (3 H, t, *J* 7.1), 0.90 (6 H, d, *J* 6.6). - ^{19}F-NMR : δ -151.2 (q, *J* 21.8). - Analysis : calc. for $C_{15}H_{21}FO_2$ (252.33) C 71.40, H 8.39; found C 71.72, H 8.05%.

Ethyl 2-fluoro-2-(6-methoxynaphth-2-yl)propionate (4d) : From ethyl 2-hydroxy-2-(6-methoxynaphth-2-yl)propionate[20] (**3d**); mp 68 - 70 °C; 82%. - ^{1}H-NMR* : δ 7.9 (1 H, m), 7.76 (1 H, d, *J* 9.0), 7.74 (1 H, d, *J* 8.5), 7.56 (1 H, dd, *J* 8.5, 1.7), 7.17 (1 H, dd, *J* 9.0, 2.5), 7.13 (1 H, d, *J* 2.5), 4.23 (2 H, symm. m), 3.92 (3 H, s), 2.01 (3 H, d, *J* 22.3), 1.25 (3 H, d, *J* 7.1). - ^{19}F-NMR : δ -150.9 (q, *J* 22.8). - Analysis : calc. for $C_{16}H_{17}FO_3$ (276.31) C 69.55, H 6.20; found C 69.69, H 5.92%.

3. 2-Aryl-2-fluoropropionic Acids (1)

2-Fluoro-2-phenylpropanoic acid (1a) : Potassium hydroxide (2.2 g, 40 mmol) and ethyl 2-fluoro-2-phenylpropionate (**4a**; 2.0 g, 10 mmol) were dissolved in methanol (0.10 L). After 15 h at 25 °C, the solvent was evaporated and water (0.20 L) was added. Extraction with diethyl ether (3 × 0.10 L) and crystallization from hexane afforded the acid **1a**[6]; mp 51 - 53 °C; 60%. - ^{1}H-NMR* : δ 7.9 (1 H, s, broad), 7.5 (2 H, m), 7.4 (3 H, m), 1.96 (3 H, d, *J* 22.4).

2-(4-Chlorophenyl)-2-fluoropropanoic acid (1b) : From ethyl 2-(4-chlorophenyl)-2-fluoropropionate (**4b**); mp 77 - 78 °C; 73%. - ^{1}H-NMR* : δ 7.47 (2 H, dm, *J* 8.5), 7.38 (2 H, dm, *J* 8.5), 1.94 (3 H, d, *J* 22.2). - ^{19}F-NMR : δ -152.9 (q, *J* 22.0). - Analysis : calc. for $C_9H_8ClFO_2$ (202.61) C 53.35, H 3.98; found C 53.33, H 4.11%.

2-Fluoro-2-(4-isobutylphenyl)propanoic acid (1c) : From ethyl 2-fluoro-2-(4-isobutylphenyl)propionate (**4c**); mp 70 - 71 °C; 70%. - ^{1}H-NMR* : δ 7.42 (2 H, d, *J* 8.2), 7.17 (2 H, d, *J* 8.2), 2.48 (2 H, d, *J* 7.1), 1.95 (3 H, d, *J* 22.4), 1.85 (1 H, sept, *J* 6.9), 0.89 (6 H, d, *J* 6.8). - ^{19}F-NMR : δ -151.2 (q, *J* 22.0). - Analysis : calc. for $C_{13}H_{17}FO_2$ (224.27) C 69.62, H 7.64; found C 69.53, H 7.62%.

2-Fluoro-2-(6-methoxynaphth-2-yl)propionic acid (1d) : From ethyl 2-fluoro-2-(6-methoxynaphth-2-yl)propionate (**4d**); mp 110 - 111 °C; 47%. - ^{1}H-NMR* : δ 7.9 (1 H, s, broad), 7.75 (2 H, d, *J* 8.7), 7.57 (1 H, dd, *J* 8.7, 1.6), 7.16 (1 H, dd, *J* 8.7, 2.4), 7.12 (1 H, d, *J* 2.4), 3.92 (3 H, s), 2.04 (3 H, d, *J* 22.3). - ^{19}F-NMR : δ -150.0 (q, *J* 21.8). - Analysis : calc. for $C_{14}H_{13}FO_3$ (248.25) C 67.74, H 5.28; found C 67.85, H 5.02%.

4. 2-Aryl-2-fluoropropiononitriles (6)

2-Aryl-2-fluoropropiononitriles (2-aryl-2-fluoropropanonitriles, 2-aryl-2-fluoropropanenitriles) slowly undergo decomposition by elimination of hydrogen fluoride. Therefore, no attempt has been made to obtain elementary analysis data.

2-Fluoro-2-phenylpropiononitrile (6a) : A solution of acetophenone (2.9 mL, 3.0 g, 25 mmol), trimethylsilyl cyanide (3.3 mL, 2.5 g, 25 mmol) and zinc iodide (1.0 g, 3.1 mmol) in dichloromethane (25 mL) was heated for 2 h to reflux. At 0 °C, diethylaminosulfur trifluoride ("DAST"; 3.3 mL, 4.0 g; 25 mmol) in dichloromethane (25 mL) was added dropwise, in the course of 15 min. The reaction mixture was kept 2 h in an ice-bath before being washed with water (3 × 10 mL) and brine (2 × 10 mL). Distillation gave the fluorinated product **6a** [10] as a colorless liquid; bp 53 - 55 °C/4 mmHg; n_D^{20} 1.4852; 75%. - ^{1}H-NMR : δ 7.5 (2 H, m), 7.4 (3 H, m), 2.07 (3 H, d, *J* 21.5). - ^{19}F-NMR : δ -139.0 (q, *J* 21.0).

2-(4-Chlorophenyl)-2-fluoropropiononitrile (6b) : Analogously from *p*-chloroacetophenone; bp 85 - 86 °C/4 mmHg; n_D^{20} 1.5062; 65%. - ^{1}H-NMR : δ 7.46 (4 H, symm. m), 2.06 (3 H, d, *J* 21.3). - ^{19}F-NMR : δ -149.7 (dq, *J* 21.8, 11.8).

2-Fluoro-2-(4-isobutylphenyl)propiononitrile (6c) : From *p*-isobutylacetophenone [21]; bp 135 - 136 °C/5 mmHg; n_D^{20} 1.4858; 60%. - ^{1}H-NMR* : δ 7.44 (2 H, d, *J* 8.1), 7.23 (2 H, d, *J* 8.1), 2.50 (2 H, d, *J* 7.1), 2.05 (3 H, d, *J* 21.2), 1.87 (1 H, sept, *J* 6.8), 0.91 (6 H, d, *J* 6.6). - ^{19}F-NMR : δ -136.5 (q, *J* 21.0).

Hydrolysis of the 2-aryl-2-fluoropropiononitriles : At 0 °C, a gentle stream of hydrogen chloride was introduced into the solution of 2-fluoro-2-phenylpropiononitrile (**6a**; 1.5 g, 10 mmol) in ethanol (10 mL) until saturation. The mixture was left 12 h in an ice-bath before being evaporated to dryness. A 1 M aqueous solution (50 mL) of sodium carbonate and diethyl ether (50 mL) were added. After 15 min of vigorous stirring, the organic layer was decanted and the aqueous phase extracted with more diethyl ether (2 × 25 mL). The organic solvent was evaporated and the residue taken up in methanol (0.10 mL) containing potassium hydroxide (2.2 g, 40 mmol). After 12 h at 25 °C, the methanol was evaporated and water (50 mL) was added. After acidification with concentrated hydrochloric acid to pH 2, the α-fluorocarboxylic acid **1a** is extracted with diethyl ether (3 × 25 mL) and crystallized from hexane; mp 51 - 53 °C; 60%. - In the same way, 2-fluoro-2-(4-isobutylphenyl)-propiononitrile (**6c**) was converted into 2-fluoro-2-(4-isobutylphenyl)propionic acid (**1c**); mp 70 - 71 °C; 68%.

5. Resolution of Racemic 2-Fluoro-2-(4-isobutylphenyl)propanoic acid

The racemic acid **1c** (0.11 g, 0.50 mmol) were treated with an ethereal solution of diazomethane until the yellow color persisted. The mixture was filtered and evaporated to give **methyl (±)-2-fluoro-2-(4-isobutylphenyl)propionate (7c)**; mp -74 to -71 °C; 100%. - ^{1}H-NMR : δ 7.40 (2 H, d, *J* 8.2), 7.16 (2 H, d, *J* 8.1), 3.77 (3 H, s), 2.47 (2 H, d, *J* 7.3), 1.93 (3 H, d, *J* 22.3), 1.86 (1 H, sept, *J* 6.8), 0.90 (6 H, d, *J* 6.6). - Analysis : calc. for $C_{14}H_{19}FO_2$ (238.30) C 70.56, H 8.04; found C 70.60, H 8.10%. - This material (80 mg, 0.34 mmol) was suspended in a 0.2 M aqueous buffer of sodium phosphate (2.0 mL, pH 7.0) and *Candida cylindracea* lipase (40 mg, OF-360, Meito Sango Ltd.) was added. After stirring for 30 h at 25 °C, the reaction mixture was acidified with 1 M hydrochloric acid (0.5 mL) to pH 2 and extracted with ethyl acetate (3 × 5 mL). The extract was absorbed on silica gel (12 mL). Ester **(+)-7c** (44%; $[\alpha]_D^{24}$ +4.6, c 1.2, ethanol) and acid **(–)-1c** (40%; $[\alpha]_D^{24}$ -22.6, c 1.2 ethanol) were consecutively eluted with a 1 : 5 (v/v) mixture of ethyl acetate and hexane, then with a 1 : 50 : 50 (v/v) mixture of acetic acid, ethyl acetate and hexane.

The enantiomeric purity of the ester **7c** was determined by integration of the nmr signal of the methylene group which was split into two doublets (at δ 2.75 and 2.72) upon addition of Eu(hfc)$_3$ ("tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium", tris[3-(2,2,3,3,4,4,4-heptafluoro-1'-oxobutyl)1,7,7-trimethylbicyclo[2.2.1]heptan-2-onato-*O,O'*]europium, 60 mg) to a solution of **1c** (10 mg) in deuteriochloroform (0.60 mL). To determine the enantiomeric excess of the acid **R-1c**, the latter was isolated by extraction and again converted into the methyl ester **7c** using diazomethane.

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