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Convenient Routes to 2-Aryl-2-fluoropropionic Acids: Synthesis of Monofluorinated Analogues of (±)-Ibuprofen, (±)-Naproxen and Related Compounds [1]

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Abstract: The synthesis of α-fluorinated arylpropionic acids **5** as analogues of the nonsteroidal anti-inflammatory agents (NSAIDs) flurbiprofen **1,** ibuprofen **3** and naproxen **4** is accomplished by the oxidation of the corresponding primary alcohols **9** The latter are accessible on two different pathways showing their general applicability by variation of the aromatic moiety. Furthermore the influence of the fluorine substituent towards the conformation of the acid moiety in the crystal lattice is shown by comparative X-ray studies of compound **5c**. Copyright © 1996 Elsevier Science Ltd

Introduction

The permanently growing interest in the preparation of selectively fluorinated compounds, indicated by the increasing number of publications and presentations,[2] reveals to the fact that the introduction of fluorine into organic molecules can cause profound and often unexpected effects on their activities. In particular the attractiveness of fluorinated compounds as useful tools in medical diagnostics and fundamental studies of biochemical and metabolism processes[3] and the utility of fluorine in the design of drugs results from the almost extraordinary properties of this substituent. Its very high electronegativity frequently leads to strong electronic effects within a molecule and affects the overall reactivity and stability of compounds in changing the dipole moment and the acidity and basicity of the neighbouring groups.[4]

The combination of these properties and the ability of fluorine to mimic hydroxy functionalities and to act as hydrogen bond acceptor as well, often causes remarkable conformative changes and exerts profound pharmacological effects in improving the activity and selectivity of bioactive compounds and drugs.[5] Furthermore, the presence of fluorine in particular perfluoro substituents, sometimes leads to an increased lipophilicity of the molecules, thereby enhancing rates of absorption and transport *in vivo*.[6] What started as a trickle with the preparation of 9α-fluoro-hydrocortisone acetate by *Fried* and *Sabo*[7] as the first example of a

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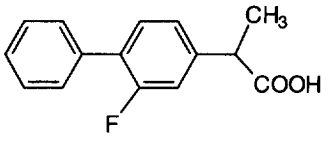
selective fluorination with the purpose of increasing the biological activity marked both the beginning of an intensive use of selectively fluorinated compounds as pharmaceuticals in general and the application of fluorosteroids as powerful anti-inflammatory drugs in particular.[8]

During the last three decades the development of non-steroidal anti-inflammatory drugs (NSAIDs) has shown to be one of the major advances in chemotherapeutical research. One of the important groups of anti-inflammatory agents is the class of 2-arylpropionic acids („profen" family)[9] which, by inhibition of the cyclo-oxygenase system,[10] are able to reduce inflammation and pain.[11] A broad variety of such compounds has been synthesized using manyfold synthetic methodologies.[12,13] Among them fluorinated surrogates such as flurbi-profen **1** and flunoxaprofen **2** are known to be very effective agents. Compound **1** acts as a prostaglandin synthesis inhibitor and **2** is an effective inhibitor of lipoxygenase producing reportedly less severe gastric disturbances.[14]



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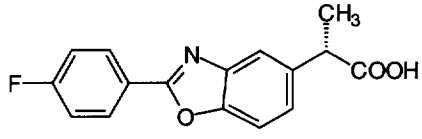

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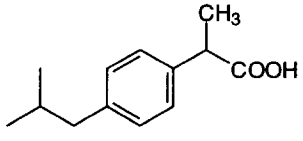

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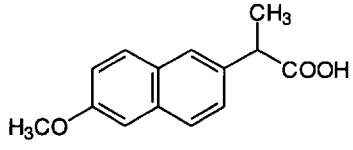

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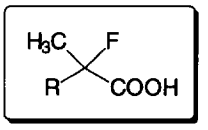
In 2-arylpropionic acid NSAIDs usually the (*S*)-enantiomer is the biologically active one.[15] However, there is good evidence that the (*R*)-enantiomer *in vivo* is isomerized.[16] Substitution at the stereogenic center of hydrogen by fluorine should prevent the possibility of racemization, and can consequently give rise to the study of the biological properties of both enantiomers separately, based upon the understanding, that the fluorinated analogues exhibit biological activity which is related to that of the parent compounds. However, nothing was known about arylpropionic acids bearing a fluorine substituent in the α-position to the carboxylic group directly linked to the stereogenic center.[17] We wish to report our results on syntheses of several 2-aryl-2-fluoro-propanoic acids.

Results and Discussion

The anticipated change in their mode of action and our interest in getting more information about the metabolism prompted us to synthesize α-fluorinated acid **5a** as a regioisomer of flurbiprofen **1** and **5b** or **5c** as analogues of ibuprofen **3** and naproxen **4**, respectively, which are both known as very effective drugs with anti-inflammatory, analgesic and antipyretic activity.[15,16]



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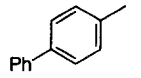
a R^1 =



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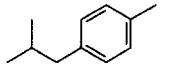
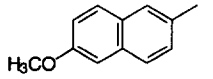
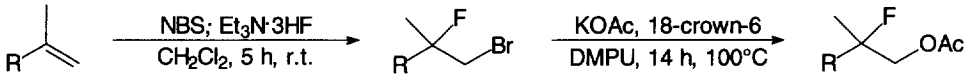


c R^3 =



As an extension of our previous work we choose a synthetic strategy which was recently published by us for the synthesis of other 2-fluoro-2-phenylalkanoic acids.[18] The variation of the aromatic moiety could prove the general applicability of these new methods and also be a convenient route to obtain the desired target compounds **5a-5c**.

Following our first route the bromo-fluoro compounds **7a** and **7b** are accessible in very high yields by bromofluorination[19] of the *para*-substituted α-methyl styrene derivatives **6a** and **6b** which were synthesized by *Wittig* olefination[20] of the corresponding acetophenones.



6a-c **7a-c** **8a-c**

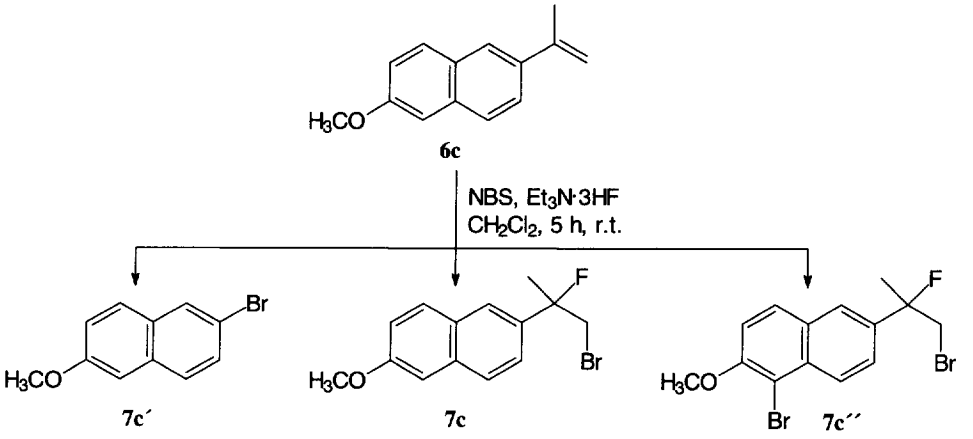
9a-c **5a-c**

On treatment with potassium acetate and 18-crown-6 in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) the bromofluorides are converted to the β-fluoro acetates **8a** and **8b** with 29% and 62% yield, respectively. In comparison to our former results[18] we observed a remarkable influence of the *para*-substitution towards the formation of the acetates **8a** and **8b**. Whereas in the cases of the acetates the yield of compound **8b** shows an enhancement compared to the monosubstituted one[18] lower yield was found for the biphenyl derivative **8a**. These compounds are smoothly hydrolyzed to their corresponding alcohols **9a** and **9b** and *Jones* oxidation leads to the acids **5a** and **5b**, however, in low yields of 13% and 33%, respectively.[21]

Regarding compound **5a** the main reason for this result is probably due to the special structure of the molecule bearing the biphenyl moiety as a nonpolar part on one side and the very polar α-fluoro propionic acid functionality on the other side. This imparts a tenside-like behaviour to the compound and makes the usually appropiate extraxtive work-up procedure here to be less successful. Using chromium trioxide in acetic acid and changing the work-up procedure increased the yield (36%) for **5a**.

The synthesis of 2-fluoro-2-(6-methoxy-2-naphthyl)propionic acid (**5c**) as the monofluorinated analogue of naproxen **4** is the second example of our investigations. Using 2-isopropenyl-6-methoxy naphthalene (**6c**) as the starting material opens both the opportunity to prove our synthetic pathways in the presence of an electron rich aromatic compound and gives, in addition, the access to the corresponding fluoroalcohol **9c** as a fluorinated analogue of "naproxol". The (-)-isomer of **9c** is also known to possess anti-inflammatory activity.[15]

Whereas the olefins **6a** and **6b** yield the bromofluorides in very good yields we established a profound difference in the bromofluorination of **6c**. Instead of the pure bromo fluoro adduct **7c**, we obtained a mixture of brominated compounds with the desired product as a minor component (29%). The major product is the bromofluorinated compound **7c''**(67%) bearing an additional bromine substituent in 5-position of the naphthalene ring. The presence of a small amount of 2-bromo-6-methoxynaphtalene **7c'**(4%) was also determind by GLC.



To our opinion the main reason for this reaction course is the concerted acting of an activated aromatic compound within an acidic medium which facilitates the aromatic substitution in the presence of an electrophile. Thus more basic conditions and enhancement of the nucleophilicity of the fluoride ion [22] by addition of 1.5 equivalents of triethylamine to the reaction mixture disfavoured the formation of **7c''** and the adduct **7c** was formed in high yield. However, this compound is very unstable so that in this case the crude product is directly converted into the fluoroacetate **8c** with an overall yield of 42% after column chromatography. The hydrolysis gave the alcohol **9c** in 80% yield but its oxidation under the usual *Jones* conditions failed all together. After extensive studies we finally succeeded in oxidizing **9c** using pyridinium dichromate in dimethylformamide according to a method of *Brown* et al. [23] and we obtained the acid **5c** in 16% yield as colorless crystals.

The second synthetic approach to the β-fluoro alcohols **9a-9c** is accomplished by the ring opening of the oxiranes **11a-11c** using our new procedure.[18] In consideration to an effective synthesis of the epoxides **11a-11c** this reaction pathway seems to be the more convenient one. As shown below the styrenes **6a-6c** are bromohydroxylated in excellent yields and the epoxides **11a-11c** are obtained effectively by subsequent dehydrobromination. Finally, treatment of **11a-11c** with the BF_3-modified $Et_3N{\cdot}3HF$ reagent[18] gives the fluorohydrins **9a-9c** in reasonable yields.

The packing diagram of **5c** along the *b* axis is shown in Fig. 2. What is worth noting is that hydrogen/fluorine exchange alters the crystal lattice from acentric monoclinic ($P2_1$ for naproxen)[24] to centrosymmetric orthorhombic lattice (*Pbca* for compound **5c**). It is also surprising that fluorine does not participate in hydrogen bonding, but molecules form dimers with their enantiomers through intermolecular hydrogen bonding of carboxylic acid groups. The hydrogen bonding distances and angles in these dimers are: O2···H2 0.95 Å, H2···O1'(1–x, 1–y, –z) 1.73 Å, O2···O1' 2.68(1) Å, O2-H2···O1' 173°. Dimerization via carboxylic acids is quite typical behaviour for phenylpropionic acids (see crystal structures of indoprofen,[25] ketoprofen,[26] flurbiprofen[27] and benoxaprofen[28]). However, naproxen[24] does not form dimers, but shows a continuous-chain type of hydrogen bonding between carboxylic groups.

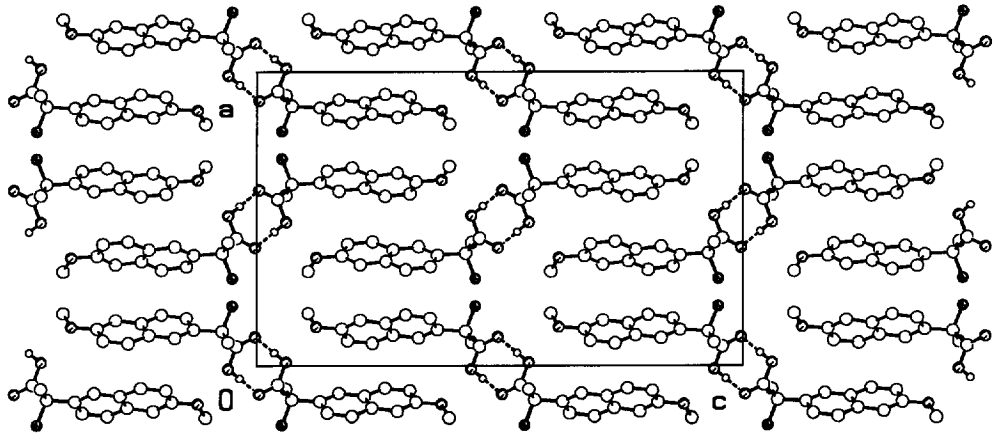


Fig. 2. Packing diagram of **5c** [molecule A, 79(2)%] along the *b* axis. The intermolecular hydrogen bonds between carboxyl groups across a center of symmetry are illustrated by dashed lines.

Conclusion

The syntheses of the acids **5a-5c** on two different pathways have shown that the variation of the aromatic moiety in some cases leads to pronounced differences concerning the yield of a reaction or the distribution of products so that some modifications of the used procedures[18] were necessary. In comparison to the nonfluorinated compound it should be noted that the formal fluorine/hydrogen exchange effects some profound conformative changes within the molecule and also causes a modification of the crystal lattice changing from a monoclinic system[24] to an orthorhombic one for compound **5c**. The first results of the biological assays give the indication that the substitution in α-position is essential for the anti-inflammatory activity which is decreased very dramatically by the incorporation of fluorine at this key position.

EXPERIMENTAL

Melting/boiling points are uncorrected. Refraction indices were obtained on an Abbé refractometer (Carl Zeiss, Jena). ^{1}H NMR (300 MHz), ^{13}C NMR (75.5 MHz), and ^{19}F NMR (282.3 MHz) were recorded on a Bruker WM 300. Chemical shifts for ^{1}H and ^{13}C NMR are reported as δ values in ppm relative to TMS as an internal standard in $CDCl_3$, and for ^{19}F NMR relative to α,α,α-trifluorotoluene (δ = –63.0 ppm from $CFCl_3$) as an internal standard in $CDCl_3$. Mass spectra (electron-impact ionization, 70 eV) (GLC/MS coupling) were registrered on a Varian GC 3400/Varian Saturn IT (ion trapping) using the data system NIST. For gas liquid chromatography (GLC) a Hewlett-Packard 5890 II gas chromatograph, quartz capillary column 0.33 mm x 25 m, 0.52 µm HP-1 (Hewlett-Packard) and quartz capillary column 0.2 mm x 25 m, 0.11 µm HP-5 (Hewlett-Packard), was used with nitrogen as carrier gas and FID-detection. Silica gel (Merck 60, 70-230 mesh) was used for column chromatography. Elemental analyses were carried out by the Mikroanalytisches Laboratorium, OC, University of Münster.
The olefins **6a-6c** have been synthesized by *Wittig* olefination according to a general procedure.[29] Physical and spectroscopic data are in agreement with such given in the literature.[30] Triethylamine tris-hydrofluoride ($Et_3N{\cdot}3HF$) was a gift from *Hoechst AG/Frankfurt*. All other starting materials and applied reagents were obtained from Fluka or Janssen chemicals; all solvents were purified by distillation and dried by storage over molecular sieves 0.4 nm.

Synthesis of vicinal bromo fluoro compounds. A mixture of the olefin **6** (10 mmol) and triethylamine-trishydrofluoride ($Et_3N{\cdot}3HF$) (7.5 mL, 25 mmol) in 10 mL of dichloromethane was treated in portions with N-bromosuccinimide (NBS) (1.96 g, 11 mmol) at 0°C. The solution was stirred for a period of 14 h at room temperature. After the reaction mixture was poured into ice water (250 mL), neutralized with 25% aq. ammonia and extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with 0.1 N hydrochloric acid (2 x 50 mL) and subsequently with 5% aq. $NaHCO_3$ (2 x 50 mL), and dried over magnesium sulfate. After evaporation of the solvent under reduced pressure the products were purified by column chromatography.

1-Bromo-2-fluoro-2-(4-isobutylphenyl)propane (7a). According to the general procedure **7a** (1.96 g, 80%) was obtained: ^{1}H NMR δ 1.14 (d, 6 H, $^3J_{H,H}$ = 6.4 Hz, $CH(C\underline{H}_3)_2$), 2.05 (d, 3 H, $^3J_{H,F}$ = 24.5 Hz, CH_3CF), 2.09 (m, 1 H, $C\underline{H}(CH_3)_2$), 2.72 (d, 2 H, $^3J_{H,H}$ = 7.2 Hz, $C\underline{H}_2CH(CH_3)_2$), 3.85-3.95 (m, 2 H, CH_2Br), 7.40 (d, 2 H, $^3J_{H,H}$ = 8.3 Hz, arom. H), 7.51 (d, 2 H, $^3J_{H,H}$ = 8.3 Hz, arom. H); ^{13}C NMR δ 22.6 (2q, $CH(\underline{C}H_3)_2$), 25.5 (dq, $^2J_{C,F}$ = 24.2 Hz, CH_3CF), 30.4 (d, $\underline{C}H(CH_3)_2$), 40.7 (dt, $^2J_{C,F}$ = 29.3 Hz, CH_2Br), 45.3 (t, $C_6H_5\underline{C}H_2$), 95.0 (ds, $^1J_{C,F}$ = 178.0 Hz, $C_6H_5\underline{C}F$), 125.9 (2dd, $^3J_{C,F}$ = 8.9 Hz, C-2, C-6), 129.5 (2d, C-3, C-5), 139.1 (ds, $^2J_{C,F}$ = 21.6 Hz, C-1), 142.1 (s, C-4); ^{19}F NMR δ -146.8 (ddq, $^3J_{F,H}$ = 15.8 Hz, $^3J_{F,H}$ = 22.2 Hz); GC/MS *m/z* (%) 272 (18) [M^+], 252 (5) [M^+-HF], 229 (23) [M^+-C_3H_7], 209 (11) [229 - HF], 179 (100) [M^+ - CH_2Br], 136 (52) [179 - C_3H_7], 115 (21) [$C_9H_7^+$], 91 (18) [$C_7H_7^+$], 57 (9) [$C_4H_9^+$], 43 (18) [$C_3H_7^+$]; Anal. calcd. for $C_{13}H_{18}BrF$ (273.2), C 57.11, H 6.64, found C 57.69, H 6.75%

1-Bromo-2-(4-biphenylyl)-2-fluoropropane (7b). According to the general procedure **7b** (2.63 g, 90%) was obtained as a white solid: mp 52 °C; ^{1}H NMR δ 1.92 (d, 3 H, $^3J_{H,F}$ = 22.0 Hz, CH_3CF), 3.74 (m, 2 H, $BrCH_2CF$), 7.38-7.44 (m, 1 H, arom. H), 7.47-7.52 (m, 4 H, arom. H), 7.64-7.68 (m, 4 H, arom. H); ^{13}C NMR δ 25.3 (dq, $^2J_{C,F}$ = 22.0 Hz, CH_3), 40.2 (dt, $^2J_{C,F}$ = 28.0 Hz, CH_2), 94.8 (ds, $^1J_{C,F}$ = 178.0 Hz, CF), 124.9 (2dd, $^3J_{C,F}$ = 10.2 Hz, C-2, C-6), 127.0, 127.1, 128.8 (5d, C-3, C-5, C-8, C-9, C-11, C-12), 127.5 (d, C-10), 140.3, 141.1 (2s, C-4, C-7), 140.5 (ds, $^2J_{C,F}$ = 22.9 Hz, C-1); ^{19}F NMR δ -144.0 (ddq, $^3J_{F,H}$ = 16.7 Hz, $^3J_{F,H}$ = 21.8 Hz, 20.3 Hz); GC/MS *m/z* (%) 292/294 (13) [M^+], 272/274 (11) [M^+ - HF], 199 (100) [M^+ - CH_2Br], 152/154 (14) [M^+ - C_6H_5 - C_6H_3], 115 (5) [$C_9H_7^+$], 76 (7) [$C_6H_4^+$], 51 (4) [$C_4H_3^+$], 39 (3) [$C_3H_3^+$]; Anal. calcd. for $C_{15}H_{14}BrF$ (293.2), C 61.45, H 4.81, found C 61.25, H 4.58%.

Bromofluorination of 2-isopropenyl-6-methoxynaphthalene (6c). According to the general procedure from **6c** (1.40 g, 7 mmol), $Et_3N{\cdot}3HF$ (3.5 mL, 17.5 mmol) and NBS (1.40 g 7.7 mmol) in 7 mL of dichloromethane a mixture of **7c'** (4%), **7c** (29%) and **7c''** (67%) was obtained which was separated by column chromatography. The desired compound **7c** could be obtained in 80% isolated yield by addition of three more equivalents of triethylamine to the reaction mixture.

2-Bromo-6-methoxynaphthalene (7c'). GC/MS m/z (%) 236/238 (81) [M^+], 221/223 (25) [M^+ - CH_3], 193/195 (100) [221/223 - CO], 126 (22), 114 (86) [195 - Br], 88 (24), 74 (18), 51 (10) [$C_4H_3^+$].

1-Bromo-2-fluoro-2-(6-methoxynaphth-2-yl)propane (7c). ^{1}H NMR δ 1.80 (d, 3 H, $^3J_{H,F}$ = 21.9 Hz, CH_3), 3.55-3.68 (m, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 7.03-7.13 (m, 2 H, arom. H), 7.28-7.31 (m, 1 H, arom. H), 7.62-7.71 (m, 3 H, arom. H); ^{13}C NMR δ 25.6 (dq, $^2J_{C,F}$ = 25.3 Hz, CH_3), 40.6 (dt, $^2J_{C,F}$ = 29.4 Hz, CH_2), 55.6 (q, OCH_3), 95.3 (ds, $^1J_{C,F}$ = 178.9 Hz, CF), 105.9 (d, C-5), 119.8 (d, C-7), 123.0 (dd, $^3J_{C,F}$ = 7.6 Hz, C-1 or C-3), 123.8 (dd, $^3J_{C,F}$ = 10.1 Hz, C-1 or C-3), 127.4 (d, C-4), 128.7 (s, C-10), 130.0 (d, C-8), 134.4 (s, C-9), 136.6 (ds, $^2J_{C,F}$ = 20.3 Hz, C-2), 158.5 (s, C-6); ^{19}F NMR δ -146.6 (ddq, $^3J_{F,H}$ = 16.8 Hz, $^3J_{F,H}$ = 22.1 Hz); GC/MS *m/z* (%): 296/298 (12) [M^+], 276/278 (11) [M^+ - HF], 203 (100) [M^+ - CH_2Br], 198 (21), 183 (18) [198 - CH_3], 155 (18) [183 - CO], 153 (16), 139 (12), 115 (8) [$C_9H_7^+$], 63 (8). (no satisfied elemental analysis could be obtained because of the unstability of the compound).

1-Bromo-2-fluoro-2-(5-bromo-6-methoxynaphth-2-yl)]propane (7c''). ^{1}H NMR δ 1.82 (d, $^3J_{H,F}$ = 22.2 Hz, 3H, CH_3), 3.63- 3.70 (m, 2 H, CH_2), 3.93 (s, 3 H, OCH_3), 7.20 (d, $^3J_{H,H}$ = 9 Hz, 1 H, arom. H), 7.44 (dd, 1 H, $^3J_{H,H}$ = 9.0 Hz, $^4J_{H,H}$ = 1.9 Hz, arom. H), 7.73 (d, 1 H, $^4J_{H,H}$ = 1.9 Hz, arom. H), 7.74 (d, 1 H, $^3J_{H,H}$ = 9.0 Hz, arom. H), 8.14 (d, 1 H, $^3J_{H,H}$ = 9.0 Hz, arom. H); ^{13}C NMR δ 25.7 (dq, $^2J_{C,F}$ = 22.9 Hz, CH_3), 40.3 (dt, $^2J_{C,F}$ = 30.5 Hz, CH_2), 57.3 (q, OCH_3), 96.4 (ds, $^1J_{C,F}$ = 180.7 Hz, CF), 108.8 (s, C-5), 114.5 (d, C-7), 124.1, 124.3 (2dd, $^3J_{C,F}$ = 10.2 Hz, C-1, C-3), 127.0 (d, C-4), 129.6 (d, C-8), 133.0 (s, C-10), 137.5 (s, C-9), 137.7 (ds, $^2J_{C,F}$ = 22.9 Hz, C-2), 154.5 (s, C-6); GC/MS *m/z* 373/375/377 (>0) [M^+], 353/355/357 (50/100/50) [M^+ - HF], 338/340/342 (11/22/11) [353/355/357 - CH_3], 310/312/314 (25/50/25) [338/340/342 - CO], 217/219 (10) [310/312/314 - CH_2Br], 196 (15), 181 (16), 165 (17) [198 - CH_3], 152 (67), 138 (12) [217/219 - Br], 126 (8), 98 (18), 76 (26) [$C_6H_4^+$], 63 (18).

Synthesis of bromohydrins. To a solution of the olefins **7** (10 mmol) in 20 mL of 1,4-dioxane, 10 mL of water and a catalytic amount of of concentrated sulfuric acid N-bromosuccinimide (NBS) (1.78 g, 10 mmol) was added in portions at 10-20 °C. The reaction mixture was stirred for 1 h at room temperature and subsequently poured into 1 L of water. The aqueous phase was extracted with *n*-hexane and the combined extracts were washed with 5 % aq. $NaHCO_3$ and water. After drying over magnesium sulfate the solvent was evaporated and about 500 mg of the residue was purified for analysis by column chromatography (silica gel, cyclohexane/ethyl acetate 10:1). The main portion was used without purification for preparation of the epoxides.

1-Bromo-2-(4-biphenylyl)propan-2-ol (10a). According to the general procedure from **6a** (2.91 g, 15 mmol) **10a** was isolated as a crystalline solid after recrystallization (4.27 g, 98%): mp 61-62 °C; ^{1}H NMR δ 1.95 (s, 3 H, CH_3), 2.85 (br. s, 1 H, OH), 3.96 (d, 1 H, $^2J_{AB}$ = 9.5 Hz, CH_2Br), 4.02 (d, 1 H, $^2J_{AB}$ = 10.3 Hz, CH_2Br), 7.59 (m, 1 H, arom. H), 7.67 (m, 2 H, arom. H), 7.75 - 7.85 (m, 6 H, arom. H); ^{13}C NMR δ 28.0 (q, CH_3), 46.1 (t, CH_2Br), 73.0 (s, COH), 125.3 (2d, C-2, C-6), 127.0 (4d, C-3, C-5, C-8, C-12), 127.3 (d, C-10), 128.7 (2d, C-9, C-11), 140.4, 140.5 (2s, C- 4, C-7), 143.1 (s, C-1); MS *m/z* 290/292 (6) [M^+], 277/279 (3) [M^+ - CH_3], 272/274 (5) [M^+ - H_2O], 210 (27) [M^+ - HBr], 197 (100) [M^+ - CH_2Br], 194 (46), 181 (32) [210 - CHO], 167 (68) [210 - C_2H_3O], 165 (31), 152 (32) [M^+ - C_3H_5BrOH], 115 (10) [$C_9H_7^+$], 76 (10) [$C_6H_4^+$], 43 (45) [$C_2H_3O^+$]. Anal. calcd. for $C_{15}H_{15}BrO$ (291.2) C 61.87, H 5.19; found C 61.84, H 5.42 %.

1-Bromo-2-(4-isobutylphenyl)propan-2-ol (10b). According to the general procedure **10b** (2.43 g, 90%) was isolated as a yellowish oil: n_D^{20} 1.5335; ^{1}H NMR δ 0.76 (d, 6 H, $^3J_{H,H}$ = 6.4 Hz, CH(C<u>H</u>$_3$)$_2$), 1.52 (s, 3 H, CH_3CO), 1.72 (sept, 1 H, $^3J_{H,H}$ = 6.8 Hz, C<u>H</u>(CH$_3$)$_2$), 2.32 (d, 2 H, $^3J_{H,H}$ = 7.2 Hz, C<u>H</u>$_2$CH(CH$_3$)$_2$), 2.41 (br. s, 1 H, OH), 3.53 (d, 1 H, $^2J_{AB}$ = 19.2 Hz, CH_2Br), 3.57 (d, 1 H, $^2J_{AB}$ = 18.8 Hz, CH_2Br), 7.00 (d, 2 H, $^3J_{H,H}$ = 8.3 Hz, arom. H), 7.21 (d, 2 H, $^3J_{H,H}$ = 8.3 Hz, arom. H); ^{13}C NMR δ 22.7 (2q, CH(<u>C</u>H$_3$)$_2$), 28.2 (q, <u>C</u>H$_3$CO), 30.4 (d, <u>C</u>H(CH$_3$)$_2$), 45.2 (t, <u>C</u>H$_2$CH(CH$_3$)$_2$), 46.7 (t, CH_2Br), 73.3 (s, CH$_3$<u>C</u>OH), 124.9 (d, arom. CH), 129.4 (d, arom. CH), 141.3, 141.7 (2s, C-1, C-4); GC/MS m/z (%): 270 (1) [M$^+$], 255 (2) [M$^+$ - CH_3], 161 (100) [M$^+$ - CHO], 177 (100) [M$^+$ - CH_2Br], 161 (4) [$C_{12}H_{17}^+$], 147 (5) [$C_{11}H_{15}^+$], 134 (7) [$C_{10}H_{14}^+$], 105 (6) [$C_8H_9^+$], 91 (10) [$C_7H_7^+$], 77 (3) [$C_6H_5^+$], 57 (2) [$C_4H_9^+$], 43 (29) [$C_3H_7^+$]; Anal. calcd. for $C_{13}H_{19}BrO$ (271.1), C 57.56, H 7.07, found C 57.76, H 7.23 %.

1-Bromo-2-(6-methoxynaphth-2-yl)propan-2-ol (10c). According to the general procedure from **6c** (0.30 g, 1.5 mmol) **10c** was isolated as a crystalline solid after recrystallization (0.36 g, 81%): mp 58 - 59 °C; ^{1}H NMR δ 1.76 (s, 3 H, CH_3), 3.77 (d, 1 H, $^2J_{AB}$ = 10.4 Hz, CH_2Br), 3.83 (d, 1 H, $^2J_{AB}$ = 10.4 Hz, CH_2Br), 3.91 (s, 3 H, OCH_3), 7.13 - 7.19 (m, 2 H, arom. H), 7.49 (dd, 1 H, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 1.9 Hz, arom. H), 7.74 (d, 2 H, $^3J_{H,H}$ = 8.6 Hz, arom. H), 7.88 (d, 1 H, $^4J_{H,H}$ = 2.0 Hz, arom. H); ^{13}C NMR δ 28.4 (q, <u>C</u>H$_3$COH), 46.6 (t, <u>C</u>H$_2$Br), 55.8 (q, O<u>C</u>H$_3$), 73.7 (s, CH$_3$<u>C</u>OH), 106.0 (d, C- 5), 119.6 (d, C-7), 124.0, 124.2 (2d, C-1, C-3), 127.5 (d, C-4), 129.0 (s, C-10), 130.1 (d, C-8), 134.2 (s, C-9), 139.7 (s, C-2), 158.4 (s, C-6); MS *m/z* 294 (6) [M$^+$], 276 (4) [M$^+$ - H_2O], 214 (28) [M$^+$ - HBr], 198 (40), 185 (28) [M$^+$ - CHO], 171 (100) [M$^+$ - C_3H_6BrO], 155 (22), 139 (10), 128 (34) [171 - C_2H_3O], 115 (13) [$C_9H_7^+$], 43 (56) [$C_2H_3O^+$]; Anal. calcd. for $C_{14}H_{15}BrO_2$ (295.2), C 56.97, H 5.12, found C 57.14, H 5.42 %.

Synthesis of epoxides. A mixture of 20 mmol of the respective bromohydrin **10** and KOH (2.24 g, 40 mmol) in methanol (50 mL) were refluxed over a period of 30 min. The mixture was poured into water (250 mL) and extracted with *n*-hexane (1 x 100 mL, 2 x 50 mL). The combined extracts were washed twice with water (100 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue was isolated by chromatography (silica gel, cyclohexane/ ethyl acetate 10:1).

2-(4-Isobutylphenyl)-2-methyloxirane (11b). According to the general procedure from **10b** (2.23 g, 8 mmol) **11b** was isolated as a colorless liquid (1.43 g, 94%, 92% purity, GC): n_D^{20} 1.4791; ^{1}H NMR δ 0.71 (d, 6 H, ^{3}J$_{H,H}$ = 6.8 Hz, CH(C<u>H</u>$_3$)$_2$), 1.51 (s, 3 H, CH_3CO), 1.66 (sept, 1 H, $^3J_{H,H}$ = 6.8 Hz, C<u>H</u>(CH$_3$)$_2$), 2.27 (d, 2 H, $^3J_{H,H}$ = 7.2 Hz, C<u>H</u>$_2$CH(CH$_3$)$_2$), 2.60 (d, $^3J_{H}$1 H,$_{,H}$ = 5.3 Hz, CH_2O), 2.75 (d, 1 H, $^2J_{H,H}$ = 5.6 Hz, CH_2O), 6.91 (d, 2 H, $^3J_{H,H}$ = 7.9 Hz, arom. H), 7.08 (d, 2 H, $^3J_{H,H}$ = 8.3 Hz, arom. H); ^{13}C NMR δ 22.1 (2q, CH(<u>C</u>H$_3$)$_2$), 22.6 (q, <u>C</u>H$_3$CO), 30.5 (d, <u>C</u>H(CH$_3$)$_2$), 45.3 (t, <u>C</u>H$_2$CH), 57.2 (t, CH_2O), 81.2 (s, CH$_3$<u>C</u>), 125.4 (2d, C-2, C-6), 129.9 (2d, C-3, C-5), 138.7 (s, C-4), 141.2 (s, C-1); MS *m/z* 190 (24) [M$^+$], 161 (100) [M$^+$ - CHO], 119 (71) [161 - C_3H_6, (McLafferty)], 105 (24) [$C_8H_9^+$], 91 (32) [$C_7H_7^+$], 77 (8) [$C_6H_5^+$], 65 (5) [$C_5H_5^+$], 57 (20) [$C_4H_9^+$], 43 (13) [$C_3H_7^+$], 41 (17), 39 (7) [$C_3H_3^+$].

2-(4-Biphenylyl)-2-methyloxirane (11c). According to the general procedure from **10c** (3.71 g, 12.74 mmol) **11c** was isolated as amorphous solid by column chromatography (1.74 g, 65%): mp 82 °C [ref.[19]: 82 °C]; ^{1}H NMR δ 1.65 (s, 3 H, CH_3), 2.73 (d, 1 H, $^2J_{AB}$ = 5.2 Hz, CH_2O), 2.89 (d, $^2J_{AB}$ = 5.2 Hz, 1 H, CH_2O), 7.26 (m, 1 H, arom. H), 7.33-7.38 (m, 4 H, arom. H), 7.48-7.52 (m, 4 H, arom. H); ^{13}C NMR δ 21.7 (q, CH_3), 56.5 (q, CH_3O), 57.0 (t, CH_2O), 125.8 (2d, C-2, C-6), 127.0 (4d, C-3, C-5, C-8, C-12), 127.3 (d, C-10), 128.7 (2d, C-9, C-11), 140.2, 140.4, 140.7 (C-1, C-4, C-7); MS *m/z* 210 (66) [M$^+$], 181 (100) [M$^+$ - CHO], 166 (89) [181 - CH_3], 153 (19) [M$^+$ - C_3H_5O], 152 (34), 133 (16), 115 (13) [$C_9H_7^+$], 77 (18) [$C_6H_5^+$], 76 (19) [$C_6H_4^+$], 51 (8) [$C_4H_3^+$].

2-(6-Methoxynaphth-2-yl)-2-methyloxirane (11c). According to the general procedure from **10c** (180 mg, 1.6 mmol) **11c** was isolated (0.1 g, 77%). Starting with 6-methoxyacetophenone **11c** was obtained in 73% yield using a one-step procedure.[31] Mp 110 °C (*n*-Hexan/Essigester 3:1) [ref.[31]: 107-109 °C]; ^{1}H NMR δ 1.80 (s, 3 H, CH_3), 2.88 (d, 1 H, $^2J_{AB}$ = 5.5 Hz, CH_2O), 3.02 (d, 1 H, $^2J_{AB}$ = 5.2 Hz, CH_2O), 3.89 (s, 3 H, OCH_3), 7.11-7.17 (m, 2 H, arom. H), 7.39-7.42 (m, 1 H, arom. H), 7.68-7.77 (m, 3 H, arom. H); ^{13}C NMR δ 21.8 (q, CH_3), 55.2 (q, OCH_3), 57.0 (t, CH_2O), 105.5 (d, C-5), 118.9 (d, C-7), 123.6, 124.2 (2d, C-1, C-3), 126.8 (d, C-4), 128.5 (s, $CH_2\underline{C}O$), 129.3 (d, C-8), 133.8, 136.2 (2s, C-9, C-10), 143.3 (s, C-2), 158.5 (s, C-6); MS *m/z* 214 (22) [M^+], 185 (100) [M^+ - CHO], 170 (21) [185 - CH_3], 153 (14), 142 (10) [179 - CO], 141 (21), 115 (15) [$C_9H_7^+$].

Synthesis of fluoroacetates. A mixture of the respective bromofluoro compound **3** (5 mmol), potassium acetate (0.98 g, 10 mmol), and [18]-crown-6 (2.64 g, 10 mmol) in DMPU (10 mL) are heated to 100 °C for 14 h. After cooling a 1:1 mixture of cyclohexane/ ethyl acetate (40 mL) was added and the precipitated solid was filtered off. After concentration of the filtrate pure fluoro acetates **8** were isolated by column chromatography (silica gel, cyclohexane/ethyl acetate 10:1).

2-(4-Biphenylyl)-2-fluoropropyl acetate (8a). According to the general procedure **7a** (2.13 g, 7.3 mmol) **8a** was isolated as a light yellow amorphous solid (0.58 g, 29%): mp 46 °C; ^{1}H NMR δ 1.73 (d, $^3J_{H,F}$ = 22.3 Hz, 3 H, CH_3CF), 2.05 (s, 3 H, CH_3CO_2), 4.30-4.42 (m, 2 H, $CH_3CO_2C\underline{H}_2CF$), 7.33-7.47 (m, 5 H, arom. H), 7.56-7.62 (m, 4 H, arom. H); ^{13}C-NMR δ 20.6 (q, $\underline{C}H_3CO_2$), 23.4 (dq, $^2J_{C,F}$ = 25.4 Hz, $\underline{C}H_3CF$), 69.0 (ds, $^2J_{C,F}$ = 24.7 Hz, $CH_3CO_2\underline{C}H_2CF$), 95.4 (ds, $^1J_{C,F}$ = 176.2 Hz, $CH_3CO_2CH_2\underline{C}F$), 124.2 (2dd, $^3J_{C,F}$ = 8.8 Hz, C-2, C-6), 127.0, 127.1 (4d, C-3, C-5, C-8, C-12), 127.4 (d, C-10), 128.1, 128.7 (2d, C-9, C-11 oder C-3, C-5), 139.9 (ds, $^2J_{C,F}$ = 21.8 Hz, C-1), 140.3, 140.8 (2s, C-4, C-7)), 170.4 (s, $CH_3\underline{C}O_2$); ^{19}F-NMR δ -150.1 (ddq, $^3J_{F,H}$ = 22.2 Hz, $CH_3\underline{C}FCH_2O_2CCH_3$); MS *m/z* 272 (20) [$M^+$], 252 (36) [$M^+$ - HF], 210 (92) [252 - C_2H_3O], 199 (100) [M^+-$CH_3CO_2CH_2$], 179 (44) [199 - HF], 152 (22) [C_6H_5-$C_6H_3^+$], 115 (10) [$C_9H_7^+$], 76 (12) [$C_6H_4^+$], 51 (9) [$C_4H_3^+$], 43 (86) [CH_3CO^+]. Anal. calcd. for $C_{17}H_{17}FO_2$ (272.3), C 74.98, H 6.29, found C 75.00, H 6.31%.

2-Fluoro-2-(4-isobutylphenyl)propyl acetate (8b). According to the general procedure **7b** (2.03 g, 7.5 mmol) **8b** was isolated as a colorless oil (0.93 g, 62%, 94% purity, GC): n_D^{20} 1.4791; ^{1}H NMR δ 1.15 (d, 6 H, $^3J_{H,H}$ = 6.8 Hz, $CH(C\underline{H}_3)_2$), 1.95 (d, 3 H, $^3J_{H,F}$ = 22.2 Hz, CH_3CF), 2.12 (sept, 1 H, $^3J_{H,H}$ = 6.8 Hz, $C\underline{H}(CH_3)_2$), 2.31 (s, 3 H, CH_3COO), 2.73 (d, 2 H, $^3J_{H,H}$ = 7.5 Hz, $C\underline{H}_2CH(CH_3)_2$), 4.46-4.60 (m, 2 H, $COOCH_2$), 7.40 (d, 2 H, $^3J_{H,H}$ = 7.9 Hz, arom. H), 7.52 (d, 2 H, $^3J_{H,H}$ = 8.3 Hz, arom. H); ^{13}C NMR δ 20.9 (2q, $CH(\underline{C}H_3)_2$), 22.6 (q, $\underline{C}H_3COO$), 23.6 (dq, $^2J_{C,F}$ = 25.4 Hz, $\underline{C}H_3CF$), 30.4 (d, $\underline{C}H(CH_3)_2$), 45.2 (t, $\underline{C}H_2CH(CH_3)_2$), 69.5 (dt, $^2J_{C,F}$ = 25.4 Hz, $CH_3COO\underline{C}H_2CF$), 95.8 (ds, $^1J_{C,F}$ = 175.5 Hz, CH_3CF), 124.5 (2dd, $^3J_{C,F}$ = 10.2 Hz, C-2, C-6), 129.3 (2d, C-3, C-5), 138.6 (ds, $^2J_{C,F}$ = 20.3 Hz, $\underline{C}CF$), 141.8 (s, $\underline{C}CH_2CH(CH_3)_2$), 170.8 (s, $CH_3\underline{C}OO$); ^{19}F NMR δ -152.9 (ddq, $^3J_{F,H}$ = 19.8 Hz, $^3J_{F,H}$ = 22.2 Hz); MS *m/z* (%) 252 (2) [M^+], 232 (16) [M^+ - HF], 190 (76) [M^+ - C_3H_6, (McLafferty)],179 (22) [M^+-CH_3COOCH_2], 147 (63) [190 - C_3H_7], 117 (22), 115 (28), 105 (7) [$C_8H_9^+$], 91 (20) [$C_7H_7^+$], 77 (8) [$C_6H_5^+$], 57 (16) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$]; Anal. calcd. for $C_{15}H_{21}FO$ (252.2), C 71.38, H 8.39, found C 71.37, H 8.39 %.

2-Fluoro-2-(6-methoxynaphth-2-yl)propyl acetate (8c). From the olefin **6c** (1g, 5 mmol) without isolation of the bromo fluoro compound **7c** the acetate **7c** was synthesized (0.58 g, 42%, two steps) as a colorless solid: mp 85 °C; ^{1}H NMR δ 2.04 (d, 3 H, $^3J_{H,F}$ = 22.4 Hz, CH_3CF), 2.31 (s, 3 H, CH_3CO_2), 4.15 (s, 3 H, OCH_3), 4.64 (dd, 1 H, $^2J_{AB}$ = 12.4 Hz, $^3J_{H,F}$ = 23.1 Hz, $CH_3CO_2C\underline{H}_2CF$), 4.68 (dd, 1 H, $^2J_{AB}$ = 12.4 Hz, $^3J_{H,F}$ = 20.2 Hz, $CH_3CO_2C\underline{H}_2CF$), 7.37-7.44 (m, 2 H, arom. H), 7.66 (m, 1 H, arom. H), 7.97-8.04 (m, 3 H, arom. H); ^{13}C NMR δ 21.1 (q, CH_3CO_2), 24.0 (dq, $^2J_{C,F}$ = 25.4 Hz, $\underline{C}H_3CF$), 55.7 (q, CH_3O), 69.6 (dt, $^2J_{C,F}$ = 22.9 Hz, $CH_3CO_2\underline{C}H_2CF$), 96.1 (ds, $^1J_{C,F}$ = 175.5 Hz, $CH_3CO_2CH_2\underline{C}F$), 106.0 (d, C-5), 119.7 (d, C-7), 123.4

(dd, $^3J_{C,F}$ = 7.6 Hz, C-1 or C-3), 123.9 (dd, $^3J_{C,F}$ = 10.1 Hz, C-3 or C-1), 127.5 (d, C-4), 128.9 (s, C-10), 130.1 (d, C-8), 134.5 (s, C-9), 136.6 (ds, $^2J_{C,F}$ = 20.3 Hz, C-2), 158.5 (s, C-6), 171.0 (s, $CH_3\underline{C}O_2$); ^{19}F NMR δ -151.8 (ddq, $^3J_{F,H}$ = 22.4 Hz); MS *m/z* 276 (12) [M^+], 256 (53) [M^+ - HF], 214 (59), 203 (100) [M^+ - $CH_3CO_2CH_2$], 198 (21), 185 (58) [214 - CHO], 183 (39) [203 - HF], 170 (36), 153 (25), 139 (18), 115 (15) [$C_9H_7^+$], 43 (52) [CH_3CO^+]; Anal. calcd. for $C_{16}H_{17}FO_3$ (276.3), C 69.55, H 6.20, found C 69.62, H 6.30 %.

Synthesis of fluorohydrins

a) by ring opening of oxiranes with $Et_3N{\cdot}3HF/BF_3{\cdot}OEt_2$

A mixture of the respective epoxide **11** (5 mmol) was treated with triethylamine-trishydrofluoride (5 mL, 5 mmol) and $BF_3{\cdot}OEt_2$ (0.12 mL, 1 mmol) in dichloromethane (10 mL). This mixture was stirred at room temperature for 7 hours. After the solution was poured into ice water (75 mL), neutralized with aq. ammonia and extracted two times with dichloromethane (each 30 mL). The organic layer was washed with 0.1 N hydrochloric acid (2 x 30 mL) and subsequently with 5% aq. $NaHCO_3$ solution (2 x 30 mL), and dried with magnesium sulfate. The solvent was evaporated in vacuum and the product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 5:1).

b) by base catalyzed hydrolysis of 2-fluoro-2-phenylalkyl acetates **8**.

A solution of the fluoro acetate **8** (1.2 mmol) and powdered KOH (214 mg, 3.8 mmol) in dry methanol (12.5 mL) were stirred over a period of 2.5 h at room temperature. Then the reaction mixture was poured into water (20 mL) and extracted four times with dichloromethane (each 20 mL). The organic phases were washed two times with water (each 30 mL) and dried over magnesium sulfate. The solvent was evaporated in vacuum and the product was isolated by column chromatography in the same manner as described above.

2-(4-Biphenylyl)-2-fluoropropanol (9a). According to the general procedure a) from **11a** (1.24 g, 5.9 mmol) **9a** was isolated as a colorless solid (1.0 g, 74%); according to b) from **8a** (0.29 g, 1.1 mmol) **9a** was isolated (0.24 g, 90%): mp 94 °C; ^{1}H NMR δ 1.95 (d, 3 H, $^3J_{H,F}$ = 22.7 Hz, CH_3CF), 2.26 (br. s, 1 H, OH), 4.00 (dd, 1 H, $^2J_{AB}$ = 12.2 Hz, $^3J_{H,F}$ = 22.4 Hz, $C\underline{H}_2OH$), 4.10 (dd, 1 H, $^2J_{AB}$ = 12.2 Hz, $^3J_{H,F}$ = 19.4 Hz, CH_2OH), 7.55-7.60 (m, 1 H, arom. H), 7.64-7.68 (m, 4 H, arom. H), 7.79-7.84 (m, 3 H, arom. H); ^{13}C NMR δ 23.2 (dq, $^2J_{C,F}$ = 25.4 Hz, $\underline{C}H_3CF$), 69.5 (dt, $^2J_{C,F}$ = 25.4 Hz, $HO\underline{C}H_2CF$), 97.8 (ds, $^1J_{C,F}$ = 172.9 Hz, $CH_3\underline{C}FCH_2OH$), 125.0 (2dd, $^3J_{C,F}$ = 7.6 Hz, C-2, C-6), 127.1, 127.2 (4d, C-3, C-5, C-8, C-12), 127.5 (d, C-10), 128.8 (2d, C-9, C-11), 140.5, 140.8 (2s, C-4, C-7), 140.6 (ds, $^2J_{C,F}$ = 22.4 Hz, C-2), 162.3 (s, C-6); ^{19}F-NMR δ -156.1 (ddq, $^3J_{F,H}$ = 20.1 Hz); MS *m/z* (%) 230 (8) [M^+], 210 (38) [M^+ - HF], 199 (60) [M^+ - CH_2OH], 181(100) [210 - CHO], 165 (52), 152 (27) [C_6H_5-$C_6H_3^+$], 115 (72) [$C_9H_7^+$], 89 (20), 77 (31) [$C_6H_5^+$], 76 (18) [$C_6H_4^+$], 63 (15), 51(22) [$C_4H_3^+$], 39 (11) [$C_3H_3^+$]; Anal. calcd. for $C_{15}H_{15}FO$ (230.3), C 78.24, H 6.57, found C 78.13, H 6.71 %.

2-Fluoro-2-(4-isobutylphenyl)propanol (9b). According to the general procedure a) from **11b** (0.90 g, 4.7 mmol) **9b** was isolated as a white crystalline solid (0.57 g, 57%); according to procedure b) from fluoro acetate **8b** (0.1 g, 0.4 mmol) **9b** (0.06 g, 71%) was isolated: mp 32-34 °C; ^{1}H NMR δ 0.75 (d, 6 H, $^3J_{H,H}$ = 6.8 Hz, $CH(C\underline{H}_3)_2$), 1.52 (d, 3 H, $^3J_{H,F}$ = 22.4 Hz, CH_3CF), 1.71 (sept, 1 H, $^3J_{H,H}$ = 6.8 Hz, $C\underline{H}(CH_3)_2$), 2.30 (br. s, 1 H, OH), 2.32 (d, 2 H, $^3J_{H,H}$ = 7.2 Hz, $C\underline{H}_2CH(CH_3)_2$), 3.58 (m, 2 H, $C\underline{H}_2OH$), 6.99 (d, 2 H, $^3J_{H,H}$ = 7.9 Hz, arom. H), 7.11 (d, 2 H, $^3J_{H,H}$ = 6.4 Hz, arom. H); ^{13}C NMR δ 22.6 (2t, $CH(\underline{C}H_3)_2$), 23.3 (dq, $^2J_{C,F}$ = 25.4 Hz, $\underline{C}H_3CF$), 30.4 (d, $\underline{C}H(CH_3)_2$), 45.3 (t, $\underline{C}H_2CH(CH_3)_2$), 69.8 (ds, $^2J_{C,F}$ = 25.4 Hz, $HOCH_2CF$), 98.2 (ds, $^1J_{C,F}$ = 172.9 Hz, CH_3CF), 124.6 (2dd, $^3J_{C,F}$ = 10.2 Hz, C-2, C-6), 129.4 (2d, C-3, C-5), 139.2 (ds, $^2J_{C,F}$ = 20.3 Hz, $\underline{C}CF$), 141.6 (s, $\underline{C}CH_2CH(CH_3)_2$); ^{19}F NMR δ -156.3 (ddq, $^3J_{F,H}$ = 19.3 Hz, $^3J_{F,H}$ = 22.8 Hz); MS *m/z* (%) 210 (7) [M^+], 190 (11) [M^+ - HF], 179 (100) [M^+ - CH_2OH], 161 (85) [190-CHO], 147 (17), 137 (30), 119 (31) [161-C_3H_6, (McLafferty)], 105 (12) [$C_8H_9^+$], 91 (23) [$C_7H_7^+$], 77 (6) [$C_6H_5^+$], 65 (5) [$C_5H_5^+$], 57 (10) [$C_4H_9^+$], 51 (4) [$C_4H_3^+$], 41 (13), 39 (7) [$C_3H_3^+$]; Anal. calcd. for $C_{13}H_{19}FO$ (210.2), C 74.23, H 9.11, found C 74.35, H 9.10 %.

2-Fluoro-2-(6-methoxynaphth-2-yl)propanol (9c). According to the general procedure a) from **11c** (1.50 g, 7.5 mmol) **9c** was isolated as a colorless solid (0.74 g, 45%); according to b) from acetate **8c** (1.0 g, 3.6 mmol) **9c** was isolated (0.68 g, 80%): mp 129 °C; ^{1}H NMR (CD_3OD) δ 1.70 (d, 3 H, $^3J_{H,F}$ = 22.4 Hz, CH_3CF), 3.68-3.86 (m, 2 H, $C\underline{H}_2OH$), 3.85 (s, 3 H, OCH_3), 4.78 (br. s, 1 H, OH), 7.08 (m, 2 H, arom. H), 7.42 (m. 1 H, arom. H), 7.69-7.77 (m, 3 H, arom. H); ^{13}C NMR (CD_3OD) δ 23.8 (dq, $^2J_{C,F}$ = 25.4 Hz, $\underline{C}H_3CF$), 56.0 (q, CH_3O), 70.2 (dt, 2 H, $^2J_{C,F}$ = 25.4 Hz, $HO\underline{C}H_2CF$), 99.1 (ds, $^1J_{C,F}$ = 172.9 Hz, $CH_3\underline{C}FCH_2OH$), 109.5 (d, C-5), 123.0 (d, C-7), 124.6, 124.7 (2dd, $^3J_{C,F}$ = 7.6 Hz, C-1, C-3), 130.9 (d, C-4), 132.9 (s, C-10), 133.6 (d, C-8), 138.4 (s, C-9), 141.8 (ds, $^2J_{C,F}$ = 22.9 Hz, C-2), 162.3 (s, C-6); ^{19}F-NMR (CD_3OD) δ -154.0 (ddq, $^3J_{F,H}$ = 22.8 Hz); MS *m/z* (%) 234 (30) [M^+], 214 (11) [M^+ - HF], 203 (100) [M^+ - CH_2OH], 185 (82) [214 - CHO], 183 (38) [203 - HF], 170 (36), 153 (30), 133 (24) [153 - HF], 115 (72) [$C_9H_7^+$], 76 (51) [$C_6H_4^+$], 63 (37), 51 (20) [$C_4H_3^+$]; Anal. calcd. for $C_{14}H_{15}FO_2$ (234.3), C 71.78, H 6.45, found C 71.77, H 6.39 %.

Synthesis of 2-Aryl-2-fluoroalkanoic acids. A solution of the fluoro alcohol **9** (5 mmol) in acetone (4 mL) was treated dropwise with *Jones* reagent (3 mL) (solution of 26 g of Cr(VI)oxide, 23 mL of concentrated sulfuric acid and 77 mL of water) at 0°C and stirred at this temperature for 20 h. Then the mixture was diluted with water (15 mL) and extracted with chloroform (5 x 15 mL). The organic phase was extracted with saturated $NaHCO_3$ solution (5 x 15 mL). The combined aquaous extracts were acidified to a pH of 1-2 with diluted sulfuric acid and extracted with chloroform (5 x 15 mL). After drying with magnesium sulfate the solvent was evaporated in vacuum and the residue was crystallized from *n*-hexane.

2-(4-Biphenylyl)-2-fluoropropanoic acid (5a). According to the general procedure from **9a** (0.5 g, 2.2 mmol) **5a** was isolated as a colorless crystalline solid (0.07 g, 13%): mp 129 °C; ^{1}H NMR δ 2.02 (d, 3 H, $^3J_{H,F}$ = 22.2 Hz, CH_3CF), 7.36 (m, 1 H, arom. H), 7.44-7.47 (m, 2 H, arom. H), 7.54-7.68 (m, 6 H, arom. H). ^{13}C NMR δ 23.5 (dq, $^2J_{C,F}$ = 22.9 Hz, CH_3), 94.3 (ds, $^1J_{C,F}$ = 190.7 Hz, $CH_3\underline{C}F$), 124.2 (2dd, $^3J_{C,F}$ = 10.2 Hz, C-2, C-6), 126.1, 126.3 (4d, C-3, C-5, C-8, C-12), 126.6 (d, C-10), 127.8 (2d, C-9, C-11), 139.3, 140.9 (2d, C-4, C-7), 174.4 (ds, $^2J_{C,F}$ = 28.0 Hz, $CF\underline{C}O_2$); ^{19}F NMR δ - 150.7 (q, $^3J_{F,H}$ = 22.0 Hz); GC/MS (of the $Si(CH_3)_3$ ester) *m/z* (%) 316 (2) [M^+], 296 (9) [M^+ - HF], 281 (13) [296 - CH_3], 199 (100) [M^+ - $CO_2Si(CH_3)_3$], 180 (32) [199 - F], 152 (10) [C_6H_5-C_6H_3], 77 (22) [$C_6H_5^+$],73 (100) [$Si(CH_3)_3^+$]; IR (KBr): $\tilde{\nu}$ [cm^{-1}]: 3440, 3118, 2657, 2524, 1757, 1717, 1488, 1136, 1109, 838; Anal. calcd. for $C_{15}H_{13}FO_2$ (244.3), C 73.76, H 5.37, found C 73.55, H 5.54 %.

2-Fluor-2-(4-isobutylphenyl)propanoic acid (5b). According to the general procedure from **9b** (0.8 g, 3.8 mmol) **5b** was isolated as a colorless crystalline solid (0.28 g, 33%): mp 72 °C (*n*-hexane) [ref. [17] : mp 70-71°C]; ^{1}H NMR δ 0.82 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, $CH(C\underline{H}_3)_2$), 1.76 (sept, $^3J_{H,H}$ = 6.7, 1 H, $C\underline{H}(CH_3)_2$), 1.86 (d, $^3J_{H,F}$ = 22.4 Hz, 3 H, CH_3CF), 2.39 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, $C\underline{H}_2CH(CH_3)_2$), 7.08 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, arom. H), 7.34 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, arom. H), 10.60 (br. s, 1 H, COOH); ^{13}C NMR δ 22.6 (2q, $CH(\underline{C}H_3)_2$), 24.5 (ds, $^2J_{C,F}$ = 22.9 Hz, $CH_3\underline{C}F$), 25.4 (t, $\underline{C}H_2CH_2CH_3$), 30.4 (d, $\underline{C}H(CH_3)_2$), 45.3 (t, $\underline{C}H_2CH(CH_3)_2$), 94.4 (ds, $^1J_{C,F}$ = 185.7 Hz, $CH_3\underline{C}F$), 124.8 (2dd, $^3J_{C,F}$ = 7.6 Hz, C-2, C-6), 129.6 (2d, C-3, C-5), 135.9 (d, $^2J_{C,F}$ = 22.9 Hz, $\underline{C}CF$), 177.2 (d, $^2J_{C,F}$ = 30.5 Hz, $CF\underline{C}OOH$); ^{19}F NMR δ -151.0 (q, $^3J_{F,H}$ = 22.0 Hz, $CH_3C\underline{F}$); GC/MS (of the $Si(CH_3)_3$ ester) *m/z* (%) 296 (0) [M^+], 281 (3) [M^+ - CH_3], 276 (5) [M^+ - HF], 261 (7) [276 - CH_3], 253 (8) [M^+ - C_3H_7], 233 (6) [253 - HF], 179 (18) [M^+ - $CO_2Si(CH_3)_3$],160 (27) [179 - F], 117 (100) [$CO_2Si(CH_3)_3^+$], 77 (14) [$C_6H_5^+$], 73 (94) [$Si(CH_3)_3^+$], 43 (8) [$C_3H_7^+$]; IR (KBr): $\tilde{\nu}$ [cm^{-1}]: 3039, 3025, 2959, 2931, 2871, 2644, 2526, 1716, 1267, 1147; Anal. calcd. for $C_{12}H_{15}FO_2$ (224.3), C 69.62, H 7.64, found C 69.47; H 7.57%.

2-Fluoro-2-(6-methoxynaphth-2-yl)propanoic acid (5c). The fluoro alcohol **9c** (0.6 g, 2.7 mmol) dissolved in DMF (3 mL) was dropped to a stirred solution of pyridinium dichromate (PDC) (5.5 g, 14.7 mmol) in DMF (11 mL) and stirred at room temperature for 17 h. Then the mixture was poured into water (150 mL),

stirred for 2 h and extracted with diethyl ether (3 x 40 mL). The combined organic extracts were extracted with saturated $NaHCO_3$ solution (3 x 25 mL) and acidified with conc. HCl. After extraction with diethyl ether (3 x 20 mL) and drying over $MgSO_4$ the solvent was evaporated and the residue was recrystallized from *n*-hexane/ethyl acetate (3:1v/v) to obtain **5c** (0.09 g, 16%) as colorless crystals: mp 132 °C; ^{1}H NMR (CD_3OD) δ 1.96 (d, 3 H, $^3J_{H,F}$ = 21.9 Hz, CH_3), 3.87 (s, 3 H, OCH_3), 7.07 -7.20 (m, 2 H, arom. H), 7.53-7.76 (m, 3 H, arom. H), 7.86-7.93 (m, 1 H, arom. H). ^{13}C NMR (CD_3OD) δ 24.3 (dq, $^2J_{C,F}$ = 25.5 Hz, $\underline{C}H_3CF$), 55.5 (q, $O\underline{U}H_3$), 95.7 (ds, $^1J_{C,F}$ = 183.1 Hz, $CH_3\underline{C}F$), 106.6 (d, C-5), 120.3 (d, C-7), 124.1(dd, $^3J_{C,F}$ = 5.1 Hz, C-1 or C-3), 124.8 (dd, $^3J_{C,F}$ = 7.6 Hz, C-3 or C-1), 128.2 (d, C-4), 131.2 (d, C-8), 135.8, 136.0 (C-9, C-10), 159.6 (s, C-6), 174.5 (ds, $^2J_{C,F}$ = 28.0 Hz, C-2); ^{19}F NMR (CD_3OD) δ -144.2 (q, $^3J_{F,H}$ = 22.0 Hz); GC/MS (of the $Si(CH_3)_3$-ester) *m/z* 320 (24) [M^+], 300 (28) [M^+-HF], 285 (12) [300-CH_3], 261 (38), 203 (100) [M^+-$CO_2Si(CH_3)_3$], 183 (30) [203 - HF], 73 (60) [$Si(CH_3)_3^+$]; IR (KBr) $\tilde{\nu}$ [cm^{-1}] 3439, 3063, 3003, 2963, 2923, 2850, 2664, 2524, 1738, 1609,1391, 1273, 1205, 895, 857, 825; Anal. calcd. for $C_{14}H_{13}FO_2$ (248.3), C 67.73, H 5.28, found C 67.80, H 5.51%.

X-Ray Analysis. Crystallographic data for **5c**: formula $C_{14}H_{13}FO_3$, formula weight 248.24, colorless plates (0.40 x 0.15 x 0.06 mm^3), orthorhombic, space group *Pbca* (No. 61), a = 15.421(3), b = 6.079(1), c = 25.474(7) Å, V = 2388.0(9) Å^3, Z = 8, F(000) = 1040, T = − 50 °C, $\rho_{calc.}$ = 1.381 g cm^{-3}, μ(CuKα) = 9.0 cm^{-1}, Enraf-Nonius-CAD4 diffractometer, λ(CuKα$_1$) = 1.54178 Å, ω-2θ scans, 1207 independent reflections (*-h*, *-k*, *+l*, $2\theta_{max}$ = 50°), 446 observed reflections [$I \geq 2\sigma(I)$], 188 refined parameters, R = 0.066, wR^2 = 0.147, goodness-of-fit on F^2 1.024, the residual electron density 0.31 / -0.29 eÅ^{-3} (max/min). The structure was solved by direct methods (SHELXS-86)[32] and refined against F^2 (SHELXL-93),[33] hydrogens were introduced to their calculated positions and refined isotropically as riding atoms, the hydrogen atom in the hydroxy group was located form the difference Fourier map. Too small thermal parameter was observed for C13 indicating occupational disorder for the methyl and fluorine groups. The disorder was refined using geometrical and thermal restraints. Molecule A is the dominant form with an occupancy of 0.79(2) and molecule B is the enantiomer with an occupancy of 0.21(2) (see Fig. 1). The figures were drawn with the SCHAKAL program.[34] Atomic coordinates, bond lenghts and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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1 Authorcollective, *Organikum,* 18th ed., Deutscher Verlag der Wissenschaften, Berlin, 1990, p 465.
2 I. Rivera, J. C. Colberg, J. A. Sonderquist, *Tetrahedron Lett.* **1992**, *33*, 6919-6922; R. A. Johnson, C. M. Hall, W. C. Krueger, H. C. Murray, *Bioorg. Chem.* **1973**, *99*, 100-104; Z.-J. Ni, N. W. Wai, X. Shi, Y.-L. Tang, M. C. Wang, T. Y. Luh, *J. Org. Chem.* **1991**, *56*, 4035-4042; G. Fraenkel, J. M. Geckle, *J. Am. Chem. Soc.* **1980**, *56*, 2869-2880; C. Fouquey, J. Jacques, G. Azadian-Boulanger, *Eur. J. Med. Chem., Chim. Ther.* **1978**, *13*, 303-308; K. Shishido, A. Yamashita, K. Hiroya, *J. Chem. Soc., Perkin Trans. I,* **1990**, 469-475.
3 T. Kutsuma, I. Nagayama, T. Okazaki, T. Sakamoto, S. Akaboshi, *Heterocycles* **1977**, *8*, 397-401.
4 G. M. Sheldrick, in: G. M. Sheldrick, C. Krüger, R. Goddard, Eds., *Crystallographic Computing 3,* Oxford University Press, Oxford, 1985, pp 175-189.
5 G. M. Sheldrick, SHELXL-93, *a program for crystal structure determination,* University of Göttingen, 1993.
6 E. Keller, SCHAKAL-92, *a* FORTRAN *program for the graphic representation of molecular and crystallographic models,* University of Freiburg, 1992.

7 J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1954**, *76*, 1455-1456.
8 A. Wettstein in *Carbon-Fluorine Compounds, Chemistry, Biochemistry & Biological Activities,* Associated Scientific Publishers, Ed., Ciba Fondation Symposium, Amsterdam, London, New York, 1972, p 281.
9 P. A. Insel, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed., A. Goodman Gilman, T. W. Rall, A. S. Nies, P. Taylor (Eds.), Pergamon Press, New York, 1990.
10 P. M. Brooks, R. O. Day, *New Engl. J. Med.* **1991**, *324*, 1716-1725; J. R. Vane, R. M. Botting, *Inflamm. Res.* **1995**, *44*, 1-10.
11 K. M. Williams, R. O. Day, S. N. Breit, *Adv. Drug. Res.* **1993**, *24*, 121-198.
12 J. P. Rieu, A. Boucherle, H. Cousse, G. Mouzin, *Tetrahedron* **1986**, *42*, 4095-4131; H. R. Sonawane, N. S. Bellur, J. R. Ahuja, D. G. Kulkarni, *Tetrahedron: Asymm.* **1992**, *3*, 163-192.
13 for some recent papers, cf.: J. D. Brown, *Tetrahedron: Asymm.* **1992**, *3*, 1551-1552; M. Garcia, C. del Campo, E. F. Llama, K. M. Sánchez-Montero, J. V. Sinisterra, *Tetrahedron*, **1993**, *49*, 8433-8440; T. Manimaran, T.-C. Wu, W. D. Klobucar, C. H. Kolich, G. P. Stahly, F. R. Fronczek, S. E. Watkins, *Organometallics* **1993**, *12*, 1467-1470; H. R. Sonawane, N. S. Bellur, D. G. Kulkarni, N.R. Ayyangar, *Tetrahedron* **1994**, *50*, 1243-1260; Calmes, J. Daunis, R. Jacquier, F. Natt, *Tetrahedron* **1994**, *50*, 6875-6880; P. S. Manchand, D. L. Coffen, P. S. Belica, F. Wong, H. S. Wong, L. Berger, *Heterocycles* **1994**, *39*, 833-845; R. Morrone, G. Nicolosi, A. Patti, M. Piattelli, *Tetrahedron: Asymm.* **1995**, *6*, 1773-1778; D. P. G. Hamon, R. A. Massy-Westropp, J. L. Newton, *Tetrahedron* **1995**, *51*, 12645-12660.
14 G. Quaglia, M. Periti, L. Dimarzio, A. Salvaggio, *Curr. Ther. Res.* **1986**, *39*, 66.
15 T. Y. Shen, *Angew. Chem.* **1972**, *84*, 512-526; *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 460-473.
16 S. C. Stinson, *Chem. Eng. News* **1992**, Sep 28, 46-79.
17 During final processing of this publication a paper appeared describing synthesis of „α-fluoro analogues of inflammation inhibiting α-arylpropionic acids" on an alternative pathway. M. Schlosser, D. Michel, Z.-W. Guo, C. J. Sih, *Tetrahedron* **1996**, *52*, 8257-8262.
18 O. Goj, G. Haufe, *Liebigs Ann.***1996**, 1289-1294.
19 G. Alvernhe, A. Laurent, G. Haufe, *Synthesis* **1987**, 562-564.
20 S. Pine, S. G. Shen, H. Hoang, *Synthesis* **1991**, 165-167.
21 P. Yates, J. Wong, S. Mc Lean, *Tetrahedron* **1981**, *37*, 3357-3363.
22 M. B. Giudicelli, D. Picq, B. Veyron, *Tetrahedron Lett.* **1990**, *31*, 6527-6530
23 H. C. Brown, S. V. Kulkarni, V. V. Khanna, V. D. Patil, U. S. Racherla, *J. Org. Chem.* **1992**, *56*, 6173-6177.
24 K. Ravikumar, S. S. Rajan, V. Pattabhi, E. J. Gabe, *Acta Cryst.* **1985**, *C41*, 280-282.
25 K. Ravikumar, *Acta Cryst.* **1994**, *C50*, 589-592.
26 P. P. Briard, J. C. Rossi, *Acta Cryst.* **1990**, *C46*, 1036-1038.
27 J. L. Flippen, R. D. Gilardi, *Acta Cryst.* **1975**, *B31*, 926-928.
28 M. G. B. Drew, P. G. Leslie, *Acta Cryst.* **1986**, *C42*, 174-177.
29 Authorcollective, *Organikum,* 18th ed., Deutscher Verlag der Wissenschaften, Berlin, 1990, p 465.
30 I. Rivera, J. C. Colberg, J. A. Sonderquist, *Tetrahedron Lett.* **1992**, *33*, 6919-6922; R. A. Johnson, C. M. Hall, W. C. Krueger, H. C. Murray, *Bioorg. Chem.* **1973**, *99*, 100-104; Z.-J. Ni, N. W. Wai, X. Shi, Y.-L. Tang, M. C. Wang, T. Y. Luh, *J. Org. Chem.* **1991**, *56*, 4035-4042; G. Fraenkel, J. M. Geckle, *J. Am. Chem. Soc.* **1980**, *56*, 2869-2880; C. Fouquey, J. Jacques, G. Azadian-Boulanger, *Eur. J. Med. Chem., Chim. Ther.* **1978**, *13*, 303-308; K. Shishido, A. Yamashita, K. Hiroya, *J. Chem. Soc., Perkin Trans. I,* **1990**, 469-475.
31 T. Kutsuma, I. Nagayama, T. Okazaki, T. Sakamoto, S. Akaboshi, *Heterocycles* **1977**, *8*, 397-401.
32 G. M. Sheldrick, in: G. M. Sheldrick, C. Krüger, R. Goddard, Eds., *Crystallographic Computing 3,* Oxford University Press, Oxford, 1985, pp 175-189.
33 G. M. Sheldrick, SHELXL-93, *a program for crystal structure determination,* University of Göttingen, 1993.
34 E. Keller, SCHAKAL-92, *a* FORTRAN *program for the graphic representation of molecular and crystallographic models,* University of Freiburg, 1992.

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