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About the "Physiological Size" of Fluorine Substituents : Comparison of Sensorially Active Compounds with Fluorine and Methyl Substituted Analogues

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Abstract : The taste of four fluoro substituted derivatives (**2a**, **2b**, **2c** and **2d**) is almost indistinguishable from that of the parent compound 4-(4-hydroxyphenyl)butan-2-one (**1**), the main flavor component of raspberries. The same holds for the comparison between the corresponding acetate, another raspberry ingredient, and its 1-fluoro analogue (**2e**). In contrast, methyl substituents (as present in compounds **3a**, **3b**, **3c**, **3d** and **3e**) profoundly alter the organoleptic properties. - The preparation of the fluorinated derivatives (**2**) involved the three principal options existing for the incorporation of fluorine into organic molecular skeletons : the use of "prefabricates" (*i.e.*, of fluoroaromatic building blocks), the formation of chlorofluorocarbene cycloadducts followed by their solvolytic ring opening and the addition of fluoride to olefinic double bonds.

The steric requirements of fluorine relative to other atoms or groups have always been and remain to be a controversial issue. Although most researchers tend to attribute to the lightest halogen a size similar to that of hydrogen [1], others prefer to assimilate it to hydroxy or even methyl groups [2].

Van der Waals radii are a popular measure of space requirements. On this basis, fluorine would be hardly 5% bigger than hydrogen if one compares the initially reported radii (r^{F}_{VdW} 1.35 Å [3] and r^{H}_{VdW} 1.29 Å [4]). More recently, the difference has quintupled (r^{F}_{VdW} 1.47 vs. r^{H}_{VdW} 1.20 Å) [5]. In this way, the smallest halogen approximates the values proposed for oxygen and nitrogen (see Table 1). There is, of course, some ambiguity when one compares mono-, di- and polyvalent elements. For example, the general accepted number of 1.70 Å for carbon is perfectly appropriate if one considers half of the thickness of an aromatic ring [6]. The hemisphere of a methyl group, however, is defined by the considerably larger radius of 2.00 - 2.05 Å [6, 7].

Table 1. Van der Waals radii of hydrogen and first-period elements [5]

X	r_{VdW} [Å]
H	1.20
F	1.47
O	1.52
N	1.55
C	1.70

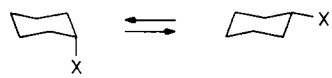
The steric parameter υ introduced by Charton [8] *a priori* reflects the Van der Waals radii, although attempts are made to link them to Taft's E_s^0 [9] values which rely on kinetic data, *i.e.* rates of ester hydrolysis. Both sets of numbers correlate remarkably well with each other (see Table 2). Fluorine lies half-way between hydrogen and methyl, although a bit closer to the former atom, while a trifluoromethyl moiety almost doubles in bulk a methyl and does not fall much behind that of a *tert*-butyl group (Table 2). Trifluoromethyl is often claimed to be "at least as large as isopropyl" [10]. Actually, if one refers to the E_s^0 scale, its diameter is approximately 40% bigger than that of the *sec*-alkyl group and only some 15% inferior to that of a the *tert*-butyl group (E_s^0 -2,78).

Table 2. Steric parameters E_s^0 [9] and υ [8] of selected substituents.

X	$-E_s^\circ$ (Taft)	υ (Charton)
H	0.00	0.00
F	0.46	0.27
CH_3	1.24	0.52
$CH(CH_3)_2$	1.71	0.76
CF_3	2.40	0.91

The empirical facts underlying Van der Waals volumes are the non-ideal behavior of gases and intermolecular distances in crystals. In such situation, the interaction between two nuclei resembles a "frontal collision" trajectory. Another extreme is the parallel alignment of bonds as adopted by 1,3-diaxial substituents in cyclohexanes. This "sliding tackle" orientation can easily attenuate repulsive forces by modest deformations and may thus be quite typical for the steric encounter of chemical entities. In other words, the energy required for the conformational promotion of an equatorial substituent to the axial position, should be a particularly meaningful criterion in the context outlined above. Judged by the strain (0.15 kcal/mol) [11] caused by an axial fluorine, the lowest halogen is a tiny element, much smaller than a methoxy or, in non polar environments, a hydroxy (0.65 kcal/mol) [12], not to speak of a methyl group (1.7 kcal/mol) [12, 13]. The bulk increases slightly from metnyl over isopropyl [12] to trifluoromethyl (2.1 kcal/mol by ir [14], 2.4 kcal/mol by nmr [15] spectroscopy; see Table 3). With an axial *tert*-butyl moiety, however, inevitably the energy shoots up (≥ 3.9 kcal/mol [16]).

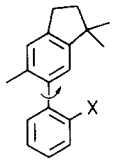
Table 3. Conformational energies $\Delta G^\circ_{ax/eq}$ [kcal/mol] of selected substituents [11 - 16].



X	$\Delta G^\circ_{ax/eq}$ [kcal/mol]
H	0.00
F	0.15
OCH_3	0.65
CH_3	1.7
$CH(CH_3)_2$	2.1
CF_3	2.4

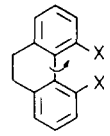
The interaction between an in-plane methyl group and the aromatic ring of *o,o'*-disubstituted cumenes (isopropylbenzenes; see Table 6) [17] is neither of the collinear nor parallel contact type but rather is defined by inclined angles. The same holds for the transition state geometries of the torsional processes around the biaryl axes of 6-aryl-1,1,5-trimethylindanes [18], 9,10-dihydrophenanthrene [19] and 2,2'-bis(diphenylphosphino)-biphenyls [20 - 23]. In the first three cases (Tables 4,5 and 6), fluorine pretends to be small : the fluoro compounds fall closer to the unsubstituted than the methyl bearing congeners as far as the barriers of rotation are concerned. However, 6,6'-difluoro-2,2'-bis(diphenylphosphino)biphenyl [21] does not follow this pattern since its barrier to racemization is at least twice that of the unsubstituted bisphosphine [20] (Table 7).

Table 4. *ortho*-Substituted 6-aryl-1,1,5-trimethylindanes : barriers to axial torsion [18].



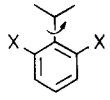
X	$\Delta G^{tors}_{(340)}$ [kcal/mol]
H	10.6
F	14.2
OH	16.1
CH_3	19.3
$CH(CH_3)_2$	22.2
CF_3	22.0

Table 5. 4,5-Disubstituted 9,10-dihydrophenanthrenes : barriers to axial torsion [19].



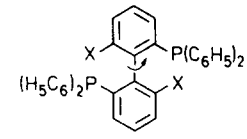
X	$\Delta G^{tors}_{(340)}$ [kcal/mol]
H	4.1
F	10.3
OCH_3	15.6
CH_3	23.4
CF_3	≥ 29

Table 6. *o,o'*-Disubstituted isopropylbenzenes : barriers to axial torsion [17].



X	$\Delta G^{tors}_{(155)}$ [kcal/mol]
H	2.0
F	6.9
CH_3	12.8

Table 7. 6,6'-Disubstituted 2,2'-bis(diphenylphosphino)biphenyls [20].

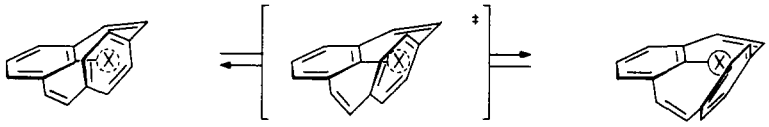


X	$\Delta G^{tors}_{(340)}$ [kcal/mol]
H	22
F	> 35
CH_3	> 30

Cyclophanes [24] have a tailor-made architecture that, when forced into coplanarity, gives rise to precisely defined steric interferences. Thus, they appear to be ideally suited for probing spatial requirements. However, even if they prove to be flexible enough to permit an investigation of their internal mobility by variable temperature nmr spectroscopy, the exact nature of the process establishing time averaged equivalence between diastereotopic hydrogens is not always obvious. Sometimes the *syn*, sometimes the *anti* isomer being thermodynamically favored [24], the conformational changes monitored generally appear to relate simply to an inversion of the horseshoe-like *syn* or the stairstep-like *anti* structure, always passing through the planar transition state, rather than to a *syn* ⇄ *anti* flip. All these ambiguities have to be kept in mind when one attempts

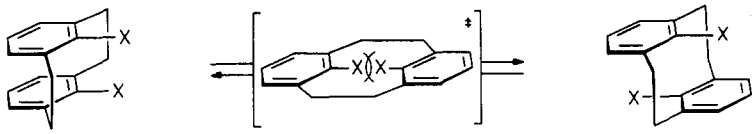
to rationalize the coalescence phenomena reported in the literature. Nevertheless, when reviewing the symmetrization barriers (ΔE^{symm}) calculated for 8-substituted [2.2]metaparacyclophane-1,9-dienes [25] (Table 8), 8,16-disubstituted [2.2]metacyclophanes [26] (Table 9) and 9,18-disubstituted 2,11-dithia[3.3]metacyclophanes [27, 28] (Table 10), one gains the impression of fluorine being incomparably larger than hydrogen, even larger than methyl.

Table 8. [2.2]Metaparacyclophane-1,9-dienes : symmetrization barriers [25].



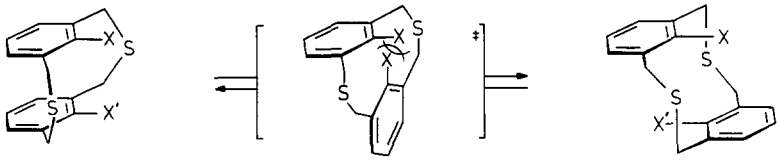
X	$\Delta E^{symm.}$ [kcal/mol]
H	~ 8
F	≥ 17

Table 9. [2.2]Metacyclophanes : symmetrization barriers [26].



X	$\Delta E^{symm.}$ [kcal/mol]
H	~ 20
F	≥ 40
CH_3	~ 35

Table 10. 2,11-Dithia[3.3]metacyclophanes : symmetrization barriers [27, 28].



X	X'	$\Delta E^{symm.}$ [kcal/mol]
H	H	≤ 8
H	H	12 [a]
H	F	23
F	F	22
F	CH_3	21

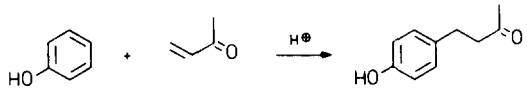
[a] Additional substituents in the aromatic rings [28]

All in all, the more results one sees, the more one feels frustrated. Whenever the question about the effective size of fluorine is asked again, a different answer is obtained. Obviously the interplay between attractive and repulsive forces depends in a most critical way on both the *distance* to neighboring elements and the mutual

orientation of the bonds involved, in other terms the anisotropy of electron densities. As a consequence, segments of the energy potential of a fluorine atom may closely match that of a hydrogen atom, if in the same chemical environment, while others may differ profoundly. Thus, fluorine may mimic hydrogen because of quasi-identical space requirements, may appear to be much bulkier or even, at least in molecular mechanics [29], considerably smaller than the latter element.

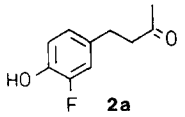
Fluorine is an attractive substituent since it often amplifies or modulates biological activities. In the years 1990 - 1993, 45 new pesticides were featured at the annual Brighton Crop Protection conference and 18 thereof, exactly 40%, contained one or several fluorine atoms [30]. Similar statistics may be assumed to apply to modern pharmaceuticals. Aware of this economically important background we may be inclined to rephrase our problem and ask : *"What is the biologically relevant size of fluorine ?"* Of course, many fluorinated drugs or agrochemicals are known to act as enzyme inhibitors. In general, these antagonistic effects are attributed to differences in the reactivity profiles rather than in the volumes of fluorine and hydrogen. However, often it is difficult to elucidate the precise role assumed by a fluorine substituent in a biogenetic sequence. In order to escape from all complications due to metabolism we suggest to study receptor-signal rather than enzyme-substrate interactions. The approach is unsophisticated and totally empirical. Characteristically smelling or tasting natural products are selected, artificial analogues carrying fluorine and methyl substituents synthesized and the organoleptic properties within such triplet series compared. The crucial issue would be whether the fluoro derivative resembles more closely the parent ("hydrogen") compound or its methyl bearing homologue.

Our first target was 4-(4-hydroxyphenyl)butan-2-one (**1**), the principal flavor substance of raspberries. It is an important industrial commodity, the worldwide production of which amounts to 100 tons a year [31]. The process of manufacturing consists of a single step, an acid catalyzed, *para* selective Michael addition of phenol onto methyl vinyl ketone [32].

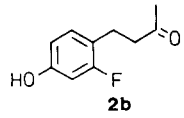


1

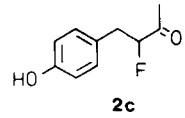
In the same way, it was possible to prepare a number of fluorine and methyl substituted analogues. Replacing phenol by *o*- and *m*-fluorophenol gave 4-(3-fluoro-4-hydroxyphenyl)butan-2-one (**2a**) and 4-(2-fluoro-4-hydroxyphenyl)butan-2-one (**2b**), by *o*- and *m*-cresol 4-(4-hydroxy-3-methylphenyl)butan-2-one (**3a**) and 4-(4-hydroxy-2-methylphenyl)butan-2-one (**3b**). Replacing methyl vinyl ketone by 3-fluorobut-3-en-2-one [33] and 3-methylbut-3-en-2-one afforded 3-fluoro-4-(4-hydroxyphenyl)butan-2-one (**2c**) and 4-(4-hydroxyphenyl)-3-methylbutan-2-one (**3c**).



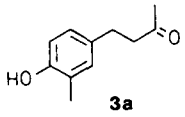
2a



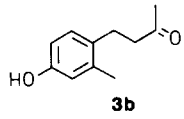
2b



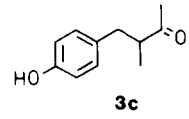
2c



3a

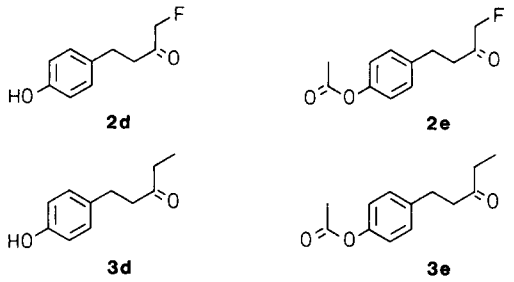


3b

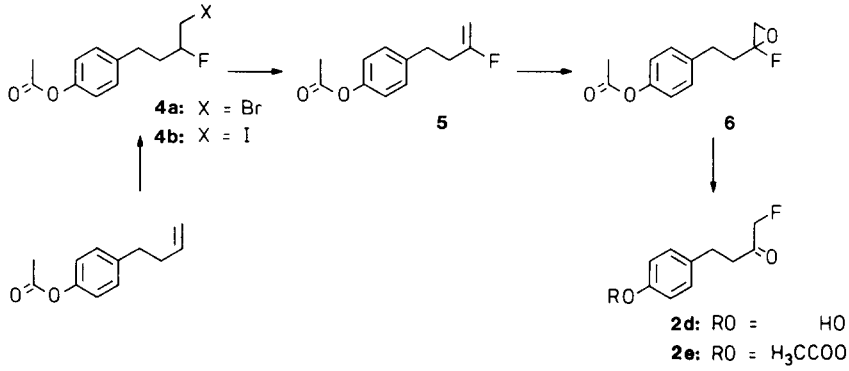


3c

The higher homologue 1-(4-hydroxyphenyl)butan-3-one (**3d**) could again be obtained by acid catalyzed reaction between phenol and ethyl vinyl ketone. The conversion into the corresponding acetate (**3e**) was quantitative. On the other hand, the access to the 1-fluorosubstituted butanones **2d** and **2e** necessitated the elaboration of a new route.



To this end, 4-(but-3-enyl)phenyl acetate was simultaneously treated with *N*-bromosuccinimide in the presence of triethylamine tri(hydrofluoride) and the resulting *vic*-bromofluoride **4** was submitted to *tert*-butoxide promoted dehydrobromination. The fluoroolefin **5** thus formed was converted with *m*-chloroperbenzoic acid into the corresponding fluorooxirane **6**. The isomerization [34] of the latter to the fluoroketone **2e** was accomplished with trace amount of triethylamine-tri(hydrofluoride) before the final hydrolysis to the free phenol **2d** was carried out.



In all the examples studied, both taste and smell of the raspberry ketone was little affected by fluorine substituents but profoundly altered upon the introduction of methyl groups. It would be premature to draw far-reaching conclusions on the basis of results achieved with a single target compound. However, as forthcoming publications will demonstrate, our present observations are corroborated by the comparative evaluation of a large number of other key structures. The biological properties of the fluorinated compound resemble much more those of the unsubstituted parent member of the family than those of the methyl bearing homologues. In other words, the biochemical and physiological size of hydrogen and fluorine appear to be very similar.

EXPERIMENTAL

1. Generalities

For standard laboratory praxis, techniques and abbreviations see related articles, *e.g.* ref. [35] and the accompanying publication. - ^{1}H-nmr : spectra were recorded of $CDCl_3$ solutions at 250 MHz (or 360 MHz, if indicated by an asterisk), ^{19}F-nmr spectra at 376 MHz. Chemical shifts refer to tetramethylsilane and, respectively, α,α,α-trifluorotoluene as internal standards (δ = 0).

2. Methyl Substituted or Chain Lengthened Analogues of Raspberry Ketone

4-(4-Hydroxyphenyl)-3-methylbutan-2-one (3c) [36] **and 1-(4-hydroxyphenyl)butan-3-one (3d)** [36] are known compounds. **4-(3-Oxobutyl)phenyl acetate (3e)** was prepared by treatment of phenol **3d** with equivalent amounts of acetyl chloride and pyridine in dichloromethane and was purified by elution from silica gel with a 1 : 2 (v/v) mixture of diethyl ether and pentane [76%; mp 42 - 43 °C. - ^{1}H-NMR : δ 7.19 (2 H, dt, *J* 8.5, 2.5), 6.99 (2 H, dt, *J* 8.5, 2.5), 2.80 (4 H, symm. m), 2.41 (2 H, q, *J* 7.4), 2.29 (3 H, s), 1.04 (3 H, t, *J* 7.4). - Analysis : calc. for $C_{13}H_{16}O_3$ (220.27) C 70.89, H 7.32; found C 71.31, H 7.19%)]. The acid catalyzed addition of phenols onto but-3-en-2-one (methyl vinyl ketone) applied to *ortho*- and *meta*-cresol afforded **4-(4-hydroxy-3-methylphenyl)butan-2-one** [**3a**; 44%; bp 180 - 183 °C/3 mmHg; n_D^{20} 1.5415. - ^{1}H-NMR : δ 6.9 (1 H, m), 6.87 (1 H, dd, *J* 8.0, 2.2), 6.68 (1 H, d, *J* 8.0), 5.1 (1 H, s, broad), 2.76 (4 H, symm. m), 2.22 (3 H, s), 2.14 (3 H, s). - Analysis : calc. for $C_{11}H_{14}O_2$ (178.23) C 74.13, H 7.92; found C 74.09, H 7.91%] and **4-(4-hydroxy-2-methylphenyl)butan-2-one** [**3b**; 41%; mp 71 - 72 °C; bp 181 - 183 °C/4 mmHg. - ^{1}H-NMR : δ 6.96 (1 H, d, *J* 8.1), 6.66 (1 H, d, *J* 2.5), 6.60 (1 H, dd, *J* 8.1, 2.5), 5.3 (1 H, m), 2.75 (4 H, symm. m), 2.25 (3 H, s), 2.17 (3 H, s). - Analysis : calc. for $C_{11}H_{14}O_2$ (178.23) C 74.13, H 7.92; found 74.27, H 8.05%].

3. Fluoro Analogues of Raspberry Ketone

4-(3-Fluoro-4-hydroxyphenyl)butan-2-one (2a) : But-3-en-2-one (8.1 mL, 7.0 g, 0.10 mol) in toluene (10 mL) was added dropwise, in the course of 1 h to a well stirred mixture of 2-fluorophenol (28 mL, 34 g, 0.30 mol) and conc. sulfuric acid (2.7 mL, 5.0 g, 51 mmol) in toluene (25 mL) cooled to 0 °C. The organic layer was thoroughly washed with water (3 × 50 mL) dried and concentrated by evaporation of the solvent. Upon distillation, first some unconsumed phenol and then the product (**2a**) was collected; 51%; white needles; mp 87 - 88 °C; bp 172 - 174 °C/6 mmHg. - ^{1}H-NMR : δ 6.9 (3 H, m), 5.3 (1 H, m), 2.77 (4 H, symm. m), 2.15 (3 H, s). - ^{19}F-NMR : -77.5 (t, *J* 10). Analysis : calc. for $C_{10}H_{11}FO_2$ (182.19) C 65.92, H 6.09; found C 66.11, H 6.13%.

4-(2-Fluoro-4-hydroxyphenyl)butan-2-one (2b) : Obtained in a strictly analogous manner as above using 3-fluorophenol (27 mL, 34 g, 0.30 mol) rather than the 2-isomer; 28%; white needles; mp 62 - 64 °C; bp 180 - 181 °C/7 mmHg. - ^{1}H-NMR : δ 7.02 (1 H, t, *J* 8.8), 6.5 (2 H, m), 5.1 (1 H, m), 2.79 (4 H, symm. m), 2.16 (3 H, s). - ^{19}F-NMR *: -53.6 (t, *J* 10). - Analysis : calc. for $C_{10}H_{11}FO_2$ (182.19) C 65.92, H 6.09; found C 66.08, H 6.14%.

3-Fluoro-4-(4-hydroxyphenyl)butan-2-one (2c) : Prepared, as described above for the isomer **2a**, but using phenol (18 g, 0.30 mol) and 3-fluorobut-3-en-2-one [33] (9.8 mL, 8.8 g, 0.10 mol) as the reaction components; 33%; mp 51 - 53 °C/0.5 mmHg. - ^{1}H-NMR *: δ 7.1 (2 H, dm, *J* 8.5), 6.79 (2 H, dt, *J* 8.5, 2.3), 5.12 (1 H, s), 4.91 (1 H, ddd, *J* 50.0, 7.5, 4.0), 3.14 (1 H, ddd, *J* 27.5, 15.0, 4.0), 3.01 (1 H, ddd, *J* 27.5, 15.0, 7.5), 2.15 (3 H, d, *J* 4.5). - ^{19}F-NMR : -125.7 (dtq, *J* 50, 28, 5). - Analysis : calc. for $C_{10}H_{11}FO_2$ (182.19) C 65.92, H 6.09; found C 65.98, H 6.12%.

1-Fluoro-4-(4-hydroxyphenyl)butan-2-one (2d) : 4-(4-Fluoro-3-oxobutyl)phenyl acetate (**2e**, see below; 1.0 g, 4.5 mmol) was dissolved in anhydrous diethyl ether that contained boron trifluoride (50 mmol). After 150 h at 25 °C, water (20 mL) was added, the organic layer was separated and the organic one extracted with more diethyl ether (3 × 20 mL). The product left behind after evaporation of the solvent was purified by chromatography on silica gel using a 1 : 2 (v/v) mixture of diethyl ether and pentane. The colorless liquid collected crystallized spontaneously; 59%; mp 98 - 100 °C. - ^{1}H-NMR : δ 7.06 (2 H, dt, *J* 8.5, 2.5), 6.76 (2 H, dt, *J* 8.5, 2.5), 4.9 (1 H, s, broad), 4.76 (2 H, d, *J* 47.6), 2.9 (4 H, m). - ^{19}F-NMR : -164.5 (tt, *J* 47, 3). - Analysis : calc. for $C_{10}H_{11}FO_2$ (182.19) C 65.92, H 6.09; found C 65.91, H 6.01%.

4-(4-Fluoro-3-oxobutyl)phenyl acetate (2e) : A mixture of crude 4-(1,2-epoxy-2-fluorobutyl)phenyl acetate (6, see below; 2.2 g, 10 mmol) and triethylamine-tris(hydrogen fluoride) (0.32 mL, 0.32 g, 2.0 mmol) was heated 5 min to 120 °C. The product was isolated by elution of the crude residue from silica gel using 1 : 10 (v/v) mixture of diethyl ether and pentane; 68%; mp 26 - 27 °C. - ^{1}H-NMR : δ 7.19 (2 H, dt, *J* 8.5, 2.5), 6.99 (2 H, dt, *J* 8.5, 2.5), 4.76 (2 H, d, *J* 47.5), 2.9 (4 H, m), 2.28 (3 H, s). - ^{19}F-NMR : -164.8 (tt, *J* 47, 3). - Analysis : calc. for $C_{12}H_{13}FO_3$ (224.23) C 64.28, H 5.84; found C 63.96, H 6.07%.

4. Precursors to the α-Fluoroketone **2e**

a) **4-(1,2-Epoxy-2-fluorobutyl)phenyl acetate (6)** : 4-(3-Fluorobut-3-enyl)phenyl acetate (**5**, see below; 4.2 g, 20 mmol) was dissolved in a solution of *m*-chloroperbenzoic acid obtained by extraction of the technical, approx. 55%, material (12 g, 38 mmol) with chloroform (100 mL). After 24 h at 25 °C potassium fluoride (5.8 g, 0.10 mol) was added and the suspension was vigorously stirred. Upon filtration and evaporation of the solvent, a colorless oil was left behind, that was found to undergo spontaneous decomposition in the course of several hours; 75%; n_D^{20} 1.5074. - ^{1}H-NMR : δ 7.22 (2 H, dm, *J* 8.5), 7.02 (2 H, dm, *J* 8.5), 3.1 (1 H, m), 2.85 (2 H, t, *J* 8.0), 2.61 (1 H, dd, *J* 4.0, 1.0), 2.29 (3 H, s), 2.2 (2 H, m). - ^{19}F-NMR : -72.4 (t, *J* 15).

b) **4-(3-Fluorobut-3-enyl)phenyl acetate (5)** : 4-(4-Bromo-3-fluorobutyl)phenyl (**4a**, see below; 2.9 g, 10 mmol) was added to a solution of sublimed potassium *tert*-butoxide (2.2 g, 20 mmol) in anhydrous tetrahydrofuran (50 mL). After 24 h at 0 °C, the reaction mixture was absorbed on alumina (5 g, actif grade) and product **5** was eluted from a column with 1 : 5 (v/v) diethyl ether/hexane and distilled; 63%, bp 130 - 133 ° C/5 mmHg; n_D^{20} 1.4991. - ^{1}H-NMR : δ 7.20 (2 H, dt, *J* 8.6, 2.4), 7.01 (2 H, dt, *J* 8.6, 2.4), 4.53 (1 H, dd, *J* 17.7, 2.9), 4.21 (1 H, ddt, *J* 50.4, 2.9, 1), 2.38 (2 H, t, *J* 8.0), 2.5 (2 H, m), 2.29 (3 H, s). - ^{19}F-NMR : -33.0 (dq, *J* 50, 17). Analysis : calc. for $C_{12}H_{13}FO_2$ (208.23) C 69.22, H 6.29; found C 69.58, H 6.08%. - The yield raised to 68% when iodide **4b** was used instead of bromide **4a** as the reaction substrate.

c) **4-(4-Bromo-3-fluorobutyl)phenyl acetate (4a)** : Triethylamine-tris(hydrofluoride) (6.6 mL, 6.5 g, 40 mmol) was added to a solution of 4-(but-3-enyl)phenyl acetate (5.7 g, 30 mmol; prepared from 4-but-3-enyl-phenol by treatment with acetyl chloride and pyridine and isolated by distillation; 75%, bp 115 - 117 °C/4 mmHg; n_D^{20} 1.5104) and *N*-bromosuccinimide (7.1 g, 40 mmol in dichloromethane (60 mL). The residue obtained after evaporation of the solvent was submitted to chromatography on silica gel using a 1 : 10 (v/v) mixture of diethyl ether and pentane as the eluent; 72%; mp -14 to -12 °C; n_D^{20} 1.5218. - ^{1}H-NMR : δ 7.20 (2 H, dt, *J* 8.5, 2.2), 7.01 (2 H, dt, *J* 8.5, 2.2), 4.63 (1 H, dm, *J* 48.0), 3.48 (2 H, dd, *J* 19.7, 5.1), 2.8 (2 H, m), 2.29 (3 H, s), 2.1 (2 H, m). - ^{19}F-NMR : -117.0 (ddtd, *J* 48, 32, 20, 15). - Analysis : calc. for $C_{12}H_{14}BrFO_2$ (289.14) C 49.84, H 4.88; found C 49.78, H 4.60%.

Replacing *N*-bromosuccinimide by *N*-iodosuccinimide (9.0 g, 40 mmol), gave under identical reaction and work-up conditions **4-(3-fluoro-4-iodobutyl)phenyl acetate (4b)**; 67%; n_D^{20} 1.5472. - ^{1}H-NMR : δ 7.20 (2 H, dt, *J* 8.5, 2.4), 7.01 (2 H, dt, *J* 8.5, 2.4), 4.44 (1 H, dm, *J* 48.0), 3.31 (1 H, dd, *J* 19.4, 5.0), 3.30 (1 H, dd, *J* 20.2, 5.7), 2.8 (2 H, m), 2.29 (3 H, s), 2.0 (2 H, m). - ^{19}F-NMR : -110.0 (symm. m). - Analysis : calc. for $C_{12}H_{14}FIO_2$ (336.14) C 42.88, H 4.20; found C 43.00, H 4.40%.

5. Organoleptic Properties

a) *Odor (of 10% solutions in propylene glycol) :*

1 : Fruity, sweet, raspberry.

2a : Slightly fruity, maltol-like, phenolic, cresolic, acetophenone.
2b : Fruity, raspberry-like, lactonic note.
2c : Less fruity than **1**, raspberry, woody, dusty, hay.
2d : Fruity, raspberry-like, but weaker than **1**, metallic, slightly green.
2e : Weakly fruity, aldehyde-like, powdery, heliotropic, acetophenone (head note).

3a : Very weak, slightly caramel-like at the beginning.
3b : Weak, medical, phenolic, cresolic, anisic, metallic.
3c : Solvent-like (head note), slightly fruity (only in the dry-out), earthy, mushrooms, burnt plastic.
3d : Similar like **1**, but 20 times weaker.
3e : Very weak, fruity, wine barrel.

b) *Taste (of 10 ppm in water)*

1 : Fresh, fruity, raspberry.

2a : Weaker, flat, medical, phenolic, powdery-dusty.
2b : Slightly fruity, weak, raspberry.
2d : Herbaceous, green, chemical, thiocyanate, radish.
2e : Relatively strong, acetophenone, phenolic, flowery.

3a : Flat, weak, metallic.
3b : Chemical, phenolic.
3d : Weak, slightly fruity, raspberry.
3e : Very weak, undefinable.

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