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4-(1-Azi-2,2,2-trifluoroethyl)benzoic Acid, a Highly Photolabile Carbene Generating Label Readily Fixable to Biochemical Agents

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The title compound is synthesized starting from either 4-bromobenzyl *tert*-butyldimethylsilyl ether (**5b**) or 4-bromobenzyl *tert*-butyl ether (**5c**) or – most simply – from 4-bromotoluene (**5a**). In the first step Br was replaced by Li using *n*-butyllithium, then the organometallic compounds were converted into the respective trifluoroacetophenones **6a – c** with *N*-trifluoroacetylpiperidine. The azi moiety (diazirine) was prepared from the oximes **7a – c** *via* *O*-tosyloximes **8a – c** plus ammonia yielding the diaziridines **9a – c** and oxidation of the latter with Ag_2O. Oxidation by permanganate – of the ethers after acidic cleavage – yields the title compound **12**. On irradiation ($\lambda > 300$ nm) **12** by elimination of N_2 with a half-life period of 22 s generates the corresponding carbene. At the same time from **12** with ca. 20% the yellow isomeric 4-(1-diazo-2,2,2-trifluoroethyl)benzoic acid (**20**) is formed which is photolyzed generating the same carbene as **12**. The synthesis of **20** is described starting from 4-bromobenzaldehyde. – The diazirine **12** as its *N*-hydroxysuccinimide ester **13**, or using other methods of amide synthesis, can readily be coupled to amino functions of biochemically interesting agents thus forming photoaffinity labels.

4-(1-Azi-2,2,2-trifluorethyl)benzoesäure, eine hoch lichtempfindliche Carben-bildende, leicht an biochemische Wirkstoffe anknüpfbare Verbindung

Die Titelverbindung wird ausgehend von (4-Brombenzyl)(*tert*-butyldimethylsilyl)ether (**5b**) oder von (4-Brombenzyl)(*tert*-butyl)ether (**5c**) oder, am einfachsten, von 4-Bromtoluol (**5a**) synthetisiert. Hierzu wird Br mit Hilfe von *n*-Butyllithium durch Li ersetzt und durch Reaktion der metallorganischen Verbindung mit *N*-Trifluoracetylpiperidin das entsprechende Trifluoracetophenon erhalten. Die Herstellung der Azigruppe (Diazirin) erfolgt über die Oxime **7a – c**, deren *O*-Tosylverbindungen **8a – c**, die mit Ammoniak die Diaziridine **9a – c** bilden, welche dann mit Ag_2O zu den Diazirinen oxidiert werden. Oxidation mit Permanganat – bei den Etherverbindungen nach Etherspaltung mit Säure – ergibt die Titelverbindung **12**. Bei Bestrahlung mit Licht ($\lambda > 300$ nm) spaltet **12** mit einer Halbwertszeit von 22 s N_2 ab unter Carbenbildung. Gleichzeitig entsteht aus **12** zu etwa 20% die gelbe isomere 4-(1-Diazo-2,2,2-trifluorethyl)benzoesäure (**20**), die zum selben Carben wie **12** photolysiert wird. Die Synthese von **20** ausgehend von 4-Brombenzaldehyd wird beschrieben. Das Diazirin **12** kann als *N*-Hydroxysuccinimidester oder mit anderen Methoden der Amidsynthese sehr einfach an Aminogruppen biochemisch interessanter Substanzen geknüpft und zur Photoaffinitätsmarkierung eingesetzt werden.

For studying interactions between biologically active molecules the technique of photoaffinity labelling is increasingly utilized[1,2]. However, none of the photolabile compounds employed thus far has optimal properties. Aromatic azides[3] are photolyzable under conditions endurable for biological material, but on irradiation electro-

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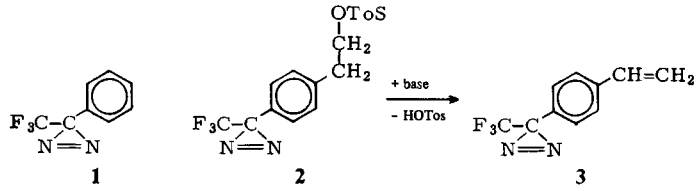
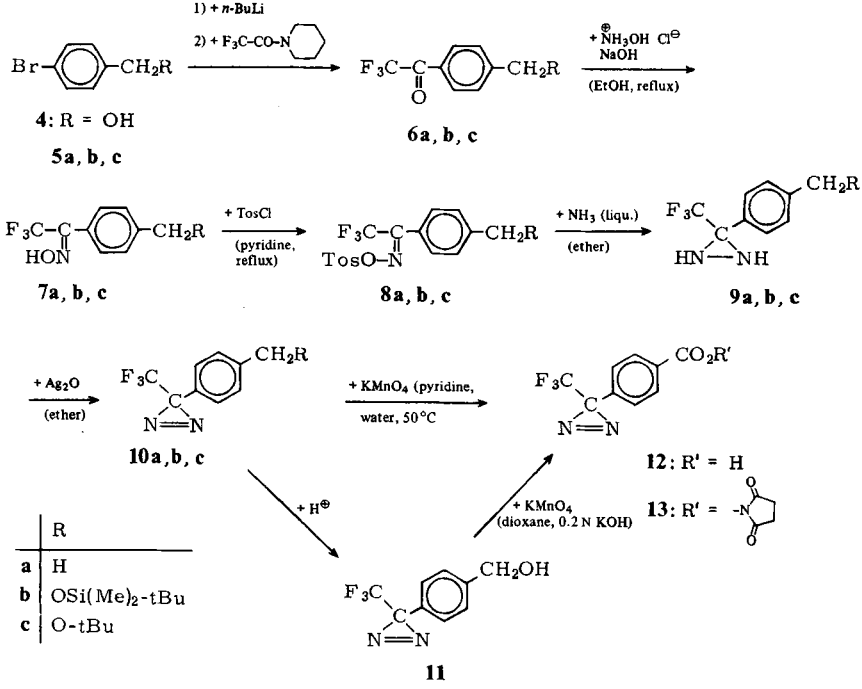
philic intermediates are formed having life times in the range of milliseconds[4] or even minutes[5a,b]! These products, probably no nitrenes, but azacycloheptatetraenes or benzazirines[4], are no longer capable to insert between C and H atoms. Carbene generating reagents on irradiation are forming highly reactive products attacking also non-nucleophilic groups[6], but the photolysis of diazo compounds studied so far required wave lengths shorter than 300 nm (noxious for biological macromolecules), or proceeded only within several hours[7,8]. Therefore, diazirines[9a,b,c] seem more promising as carbene forming reagents, since they are photolyzed at wave lengths around 350 nm within time intervals of minutes or even seconds.



1 2 3

Brunner et al.[10] described the synthesis of phenyl(trifluoromethyl)diazirine (**1**) and its 4-(2-tosyloxyethyl)phenyl derivative **2** which should be suitable for binding to effector molecules. While **2** readily reacts with ethyl xanthogenate[11], we unsuccessfully attempted to alkylate amino groups of amino acids or peptides, since **2**, in presence of bases underwent β-elimination of toluenesulfonic acid yielding the corresponding styrene derivative **3**.



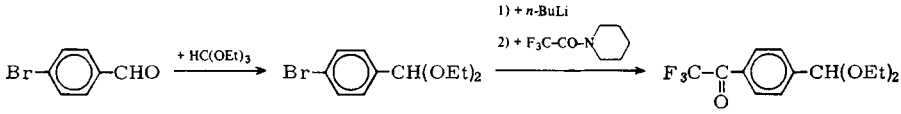
In order to obtain a diazirine with a more suitable anchoring group we synthesized 4-(1-azi-2,2,2-trifluorethyl)benzoic acid (**12**) starting from 4-bromobenzyl *tert*-butyldimethylsilyl ether (**5b**), or from 4-bromobenzyl *tert*-butyl ether (**5c**), or – most simply – from 4-bromotoluene (**5a**).

As a first step of the syntheses the aromatic bromine atom is replaced by lithium by use of *n*-butyllithium. The lithium compounds then are reacted with *N*-trifluoroacetylpiperidine[12] to yield the corresponding acetophenones **6a–c**. This procedure is superior to the Grignard reaction used in lit.[10]. The diazirine ring is formed according to lit.[10] *via* the oximes **7a–c**, *O*-tosyloximes **8a–c**, and diaziridines **9a–c** by oxidation with Ag_2O.

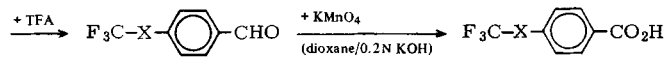
The formation of the carboxy function after removal of the protecting ether groups by acid was easily achieved by oxidation of the benzyl alcohol functions with $KMnO_4$ in dioxane-aqueous KOH. The methyl group in position 4 was oxidized either with tetrabutylammonium permanganate[13] in pyridine or – avoiding this self-inflammable reagent[14] – with $KMnO_4$ in pyridine-water mixtures at 50 °C.

The photolabile benzoic acid derivative **12** is converted with *N*-hydroxysuccinimide and *N,N'*-dicyclohexylcarbodiimide into the crystalline *N*-hydroxysuccinimide ester **13**, which serves as an acylating agent of amines[15,16]. Amide formation by the mixed-anhydride method is likewise feasible[17], as, most probably, are all methods of activation used in peptide chemistry.

Since on irradiation of the diazirine in the first phase an increase of the absorption around 280 nm was observed in parallel to a decrease of the absorption maximum at 348 nm, we assumed – as described for other diazirines[9a,10,18] – that a rearrangement to the isomeric diazo compound may occur. Hence, for comparison 4-(1-diazo-2,2,2-trifluorethyl)benzoic acid (**20**) was synthesized.

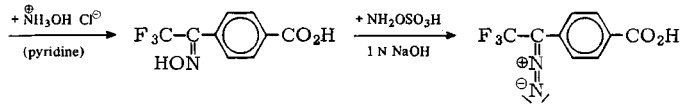


14 **15** **16**



17a: X = CO
17b: X = $C(OH)_2$

18a: X = CO
18b: X = $C(OH)_2$



19 **20**

The diethyl acetal **15** of 4-bromobenzaldehyde (**14**) is converted into the corresponding lithiated derivative by reaction with *n*-butyllithium, the lithium compound reacted as

above with *N*-trifluoroacetylpiperidine yielding the trifluoroacetophenone derivative **16**. The acetal group is smoothly cleaved by trifluoroacetic acid in dichloromethane thus avoiding the need of solvent mixtures at the use of aqueous hydrochloric acid. Surprisingly, the product crystallized as needles of m.p. 106 – 108 °C whereas 4-methylacetophenone has a m.p. of 33 – 34 °C[19]. Elemental analysis as well as mass spectrometry (*m/z* = 220, *i.e.* $M^{\oplus} + 18$) suggested the existence of **17** as a hydrate. In ^1H NMR at $\delta = 6.8$ a broad singulett is visible which disappears on addition of D_2O. On excessive drying *in vacuo* the crystals decompose to give an oil which does not show the signal at $\delta = 6.8$, while the signals of the aromatic protons and that of the aldehyde are shifted to lower field. The carboxylic acid **18a**[20] obtained from the aldehyde by oxidation with potassium permanganate crystallizes from chloroform-hexane with correct elemental analysis, from water crystals are obtained containing 1.5 moles of water. X-ray analysis[21] proves the structure of 4-(2,2,2-trifluoro-1,1-dihydroxy)benzoic acid (**18b**).

The oxime **19** is prepared in almost quantitative yield by boiling **18** with 3 equivalents of hydroxylamine hydrochloride in pyridine. On treatment of the oxime **19** with hydroxylamine *O*-sulfonate in aqueous NaOH the desired diazo compound **20** is obtained in yellow crystals, although in only 21% yield. Another approach to diazo compounds, elimination of *p*-toluenesulfonic acid from tosylhydrazones with bases, was unsuccessful as the formation of a tosylhydrazone from our oxo acid failed.

Photochemical properties of the diazirine derivative 12

The long-wave absorption maximum of **12** is at 348 nm (in ethanol, $\varepsilon = 390$, see Figure 1) and disappears on irradiation of a solution in ethanol in a pyrex tube (filter for wave lenghts < 300 nm) with a half-live period of 22 seconds (see Figures 2 and 3).

During the first 30 seconds the absorption around 280 nm quickly increases (see Figure 4) and likewise a new maximum arises at 450 nm visible by a faintly yellow color

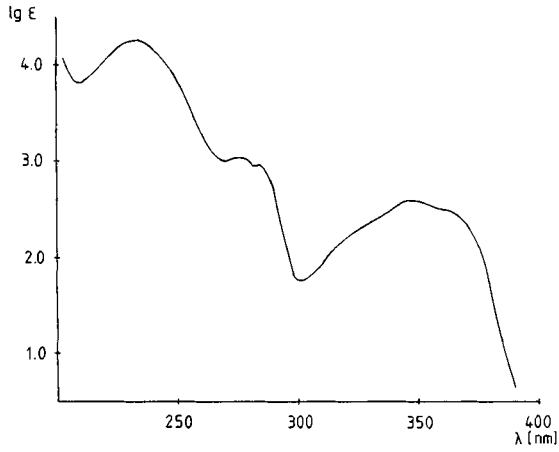


Figure 1. UV spectrum of 4-(1-azi-2,2,2-trifluoroethyl)benzoic acid (**12**) in ethanol

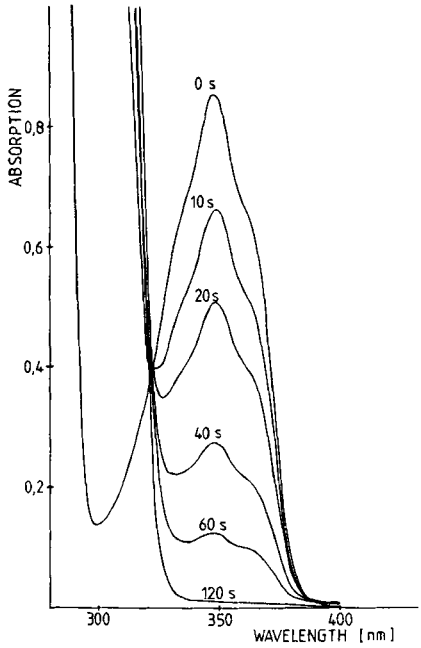


Figure 2. Long-wave UV maximum of **12** after different times of irradiation (Photolysis conditions as given in the experimental section; concentration: 2.19 mM in ethanol)

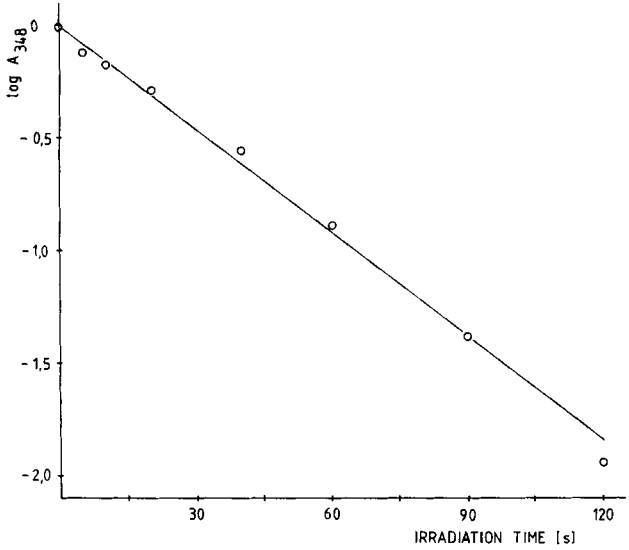


Figure 3. Logarithmic plot of the decrease of the absorption maximum at 348 nm of **12** on irradiation, indicating first-order kinetics for the photolysis (concentration: 2.19 mM in ethanol)

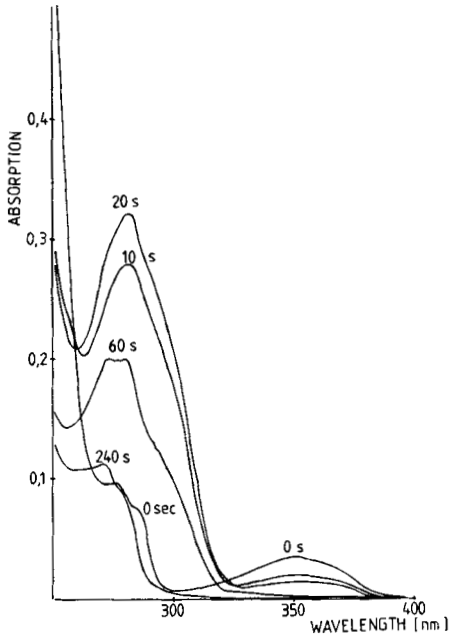


Figure 4. UV spectra of **12** after different times of irradiation showing the initial increase and subsequent decrease of the absorption around 280 nm (concentration: 0.0876 mM in ethanol)

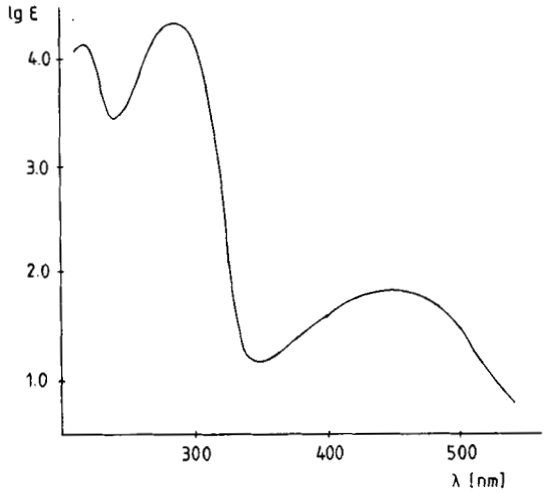
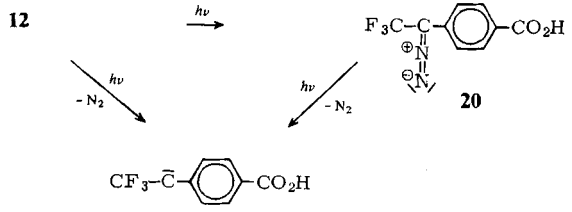


Figure 5. UV/VIS spectrum of 4-(1-diazo-2,2,2-trifluoroethyl)benzoic acid (**20**) in ethanol

of the solution. This spectroscopical observation along with TLC analysis proves that an isomerization of the diazirine **12** takes place yielding 4-(1-diazo-2,2,2-trifluoroethyl)benzoic acid (**20**) (λ_{max} = 284, ε = 22,000; λ_{max} = 450, ε = 68, see Figure 5).

From the extinctions observed it can be concluded that the concentration of the diazo product increases maximally to about 20% of the initial concentration of the diazirine.

20 decomposes photolytically yielding the same carbene as **12**, but with a velocity which depends on its concentration. The half-life period in 0.047 mM solution is 18 s, in 1.02 mM solution 2.66 min, and in 2.35 mM solution 4 min. These values differ markedly from those observed with the diazo isomers of compound **1** and its tosyl derivative **2** whose half-live periods are 22 min[10] and 24 min, respectively[22]. It is very improbable that the rapid decomposition of **20** is due to its acidic nature; diazo compounds with an adjacent trifluoromethyl group are almost stable against protonic influence. The high sensitivity of **20** towards light points to a strong influence of the *p*-standing carboxylic group in **20**. Since amides of **12** are equally light-sensitive as their parent compound one may presume that **12** yields as an acyl photolabel at an amino group of biologically active agonists the carbene species also *via* the diazo form rapidly enough as to warrant intactness of living cells which endure irradiation times of up to 10 minutes.



The new photolabel bound to an adrenergic drug has recently successfully been applied in the characterization of a β-receptor protein from turkey red cells[15]. It has also been coupled to amino-functionalized antamanide[17] as well as to an aminophallotoxin[16], two peptides whose incorporation into hepatocyte membranes is currently being investigated.

I thank Mrs. *T. Korte* for the mass spectrometric analyses, Mr. *G. Riethmüller* for the elemental analyses and the *Deutsche Forschungsgemeinschaft* for a grant. My special thanks are due to Prof. *Th. Wieland* for his lively interest in this investigation.

Experimental

Abbreviations: DCC = *N,N'*-dicyclohexylcarbodiimide, DMF = dimethylformamide, HOSu = *N*-hydroxysuccinimide, MeOH = methanol, NMM = *N*-methylmorpholine, TEA = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = tetramethylsilane; DMSO = dimethylsulfoxide.

General methods: ^{1}H NMR spectra were recorded on a Hitachi Perkin Elmer R600 spectrometer (60 MHz) with TMS as internal standard, UV/VIS spectra on a Pye Unicam SP 8 – 100 spectrophotometer. Mass spectra were obtained with a Dupont type 21 – 492 mass spectrometer. Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates, layer thickness 0.25 mm (Merck, Darmstadt) using the following solvent systems: (A) *n*-hexane-dichloromethane (1 : 1); (B) petroleum ether-dichloromethane (2 : 1); (C) *n*-hexane-dichloromethane-methanol (60 : 40 : 5); (D) dichloromethane-petroleum ether (3 : 1); (E) dichloromethane-*n*-hexane (2 : 1); (F) benzene-acetic acid (7 : 1); (G) trichloromethane-ethyl acetate (5 : 1); (H) trichloro-

methane-methanol-water (65:25:4); (I) trichloromethane-methanol-acetic acid (95:5:3). Spots were visualized by fluorescence quenching under a 254-nm UV light source, by iodine vapor, or with ninhydrin. Column chromatography was performed on silica gel 60, 70–200 mesh (Merck, Darmstadt) and Sephadex LH-20 (Pharmacia, Uppsala) with methanol as eluent. UV-absorbing substances were detected with an Uvicord II detector at 254 nm and collected with an Ultrorac 7000 fraction collector (LKB, Stockholm). Diazirines were handled under dim light. Photolyses were performed using a Philips HPK 125 W/L high-pressure mercury lamp (125 Watt). The lamp is fixed in a double-walled Pyrex-glass tube which, for cooling, is passed through with water (or a filter solution). The cooling jacket is mounted on an aluminum plate (15 × 15 cm, thickness 8 mm) containing 6 concentric boreholes in a distance of 7 cm from the center of the light source, which the screw cap Pyrex-glass tubes used as reaction vessels fit into.

2-[4-(1-Azi-2,2,2-trifluoroethyl)phenyl]ethyl tosylate (**2**): This compound is prepared according to lit.[10] except, that the introduction of the trifluoroacetyl group into [2-(4-bromophenyl)ethoxy]-(*tert*-butyl)(dimethyl)silane yielding 1-(4-[2-(*tert*-butyldimethylsiloxy)ethyl]phenyl)-2,2,2-trifluoro-1-ethanone is achieved with *n*-butyllithium and *N*-trifluoroacetylpiperidine as described for **6a**; yield after column chromatography on silica gel with solvent (A): 4.1 g from 5.7 g of the bromophenyl compound (68% based on the latter instead of 19% *via* the Grignard procedure described in lit.[10]).

3-(4-Ethenylphenyl)-3-trifluoromethyl-3H-diazirine (**3**): During treatment of the *O*-tosylate **2** with γ-aminobutyric acid, γ-aminobutyric acid methyl ester, and *O*-(γ-aminobutyrylaminoethyl)-Tyr^6-antamanide in the presence of 1 equivalent of NMM in acetonitrile-DMF or ethanol no reaction occured. Adding more NMM or K_2HPO_4 gave the same product in different yields, which could be obtained almost quantitatively by the following procedure: 110 mg (0.286 mmol) of **2** is dissolved in 3 ml of DMSO and stirred with 2 equivalents of potassium butoxide. After 30 min, the mixture is extracted 3 times with 10 ml of petroleum ether. The combined extracts are washed with water, dried with Na_2SO_4, and the solvent is removed under reduced pressure; yield 55 mg (91%), colorless oil. – MS: m/z = 212 ($M^{\oplus}$, shortly visible), 184 ($M^{\oplus} - N_2$, 10%), 43 (100%). – ^{1}H NMR ($CDCl_3$): δ = 5.34 (1H, R–CH=CH_2; J_{cis} = 11 Hz), 5.79 (1H, R–CH=CH_2; J_{trans} = 18 Hz), 6.74 (1H, R–CH=CH$_2$; J = 11 and 18 Hz), 7.19 and 7.46 (4H, AA'BB' system, aromatic H).

(4-Bromobenzyloxy)(tert-butyl)(dimethyl)silane (**5b**): The silyl-protected 4-bromobenzyl alcohol is prepared analogously to lit.[10] from 5.0 g (26.7 mmol) of the alcohol **4**, 4.48 g (29.7 mmol) of *tert*-butyl dimethyl silyl chloride and 4.70 g (69.0 mmol) of imidazole. After diluting the reaction mixture with water and extracting it 3 times with petroleum ether, the combined organic extracts are washed 5 times with water, dried with Na_2SO_4, and the solvent is removed *in vacuo*. The resulting colorless oil (pure on TLC) is used for the next reaction without further purification; yield 7.80 g (97%). – TLC: R_F(A) = 0.86. – MS: m/z = 300 + 2 ($M^{\oplus}$, 5%). – ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 6H), 0.91 (s, 9H), 4.70 (s, 2H), 7.20 and 7.49 (4H, AA'BB' system, aromatic H).

4-Bromobenzyl tert-butyl ether (**5c**): *tert*-butylation of **4** is achieved analogously to lit.[23] with isobutene in dichlormethane and conc. H_2SO_4 as catalyst. The reaction mixture is purified by column chromatography using $CHCl_3$ as eluent. During evaporation the product crystallizes spontaneously; m.p. 47–49 °C [(lit.[24] 48–50 °C); yield 10.5 g from 15.0 g of **4** (54%)]. – TLC: R_F($CHCl_3$) = 0.60 (**4**: 0.15). – MS: m/z = 242 + 2 ($M^{\oplus}$, 14%), 169 + 2 ($M^{\oplus}$ – OtBu, 100%). – ^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 9H), 4.41 (s, 2H), 7.22 and 7.50 (4H, AA'BB' system, aromatic H).

2,2,2-Trifluoro-1-(4-methylphenyl)-1-ethanone[25] (**6a**): To a stirred solution of 3.42 g (20 mmol) of 4-bromotoluene (**5a**) in 100 ml of absol. ether is dropwise added 1.1 equivalent of

n-butyllithium (15-% in hexane) at −30 °C under dry argon. The reaction mixture is allowed to warm up to 0 °C within 2h and cooled down again to −50 °C. Then 3.62 g (20 mmol) of *N*-trifluoroacetylpiperidine [synthesized by reacting 1.2 equivalents of piperidine in ether with 1 equivalent of trifluoroacetic anhydride in the presence of 1 equivalent of triethylamine, washing with 0.1 N aqueous HCl and distillation of the organic layer *in vacuo*; b.p. 75 °C/14 torr (lit.[18] b.p. 77 °C/15 torr)] is added (dissolved in 20 ml of absol. ether). After 3 h at this temperature, the cooling bath is removed and the mixture is hydrolyzed with saturated aqueous NH_4Cl. The organic phase is washed 5 times with aqueous NH_4Cl, 3 times with water, dried with Na_2SO_4, and the solvent is evaporated *in vacuo*. The crude oily residue can be converted directly into the oxime **7a** or purified by column chromatography on silica gel with solvent (B). Yield after chromatography: 2.7 g (72%), colorless oil. – TLC: $R_F(CHCl_3)$ = 0.86; R_F(B) = 0.76. – MS: *m/z* = 188 ($M^{\oplus}$, 18%), 119 (100%), 91 (64%). – ^{1}H NMR ($CDCl_3$): δ = 2.48 (s, 3H), 7.38 and 8.05 (4H, AA'BB' system, aromatic H).

1-⟨4-[(tert-Butyldimethylsiloxy)methyl]phenyl⟩-2,2,2-trifluoro-1-ethanone (**6b**): This compound is obtained analogously to **6a** and purified by column chromatography on silica gel with *n*-hexane-dichloromethane (2:1) as eluent; yield (from 7.33 g of **5b**): 6.08 g (85%), colorless oil. – TLC: R_F(A) = 0.64; R_F(F) = 0.85, R_F(C) = 0.72. – MS: *m/z* = 318 ($M^{\oplus}$, 15%), 303 (100%). – ^{1}H NMR ($CDCl_3$): δ = 0.09 (s, 6H), 0.94 (s, 9H), 4.84 (s, 2H), 7.61 and 8.07 (4H, AA'BB' system, aromatic H).

1-[(4-tert-Butoxymethyl)phenyl]-2,2,2-trifluoro-1-ethanone (**6c**): This compound is prepared in an analogous manner as **6a** and purified by column chromatography on silica gel with trichloromethane as solvent; yield (from 6.5 g of **5c**): 4.7 g (68%), colorless oil. – TLC: $R_F(CHCl_3)$ = 0.43, R_F(C) = 0.56. – MS: *m/z* = 260 ($M^{\oplus}$, 5%), 191 (5%), 187 (100%), 118 (15%). – ^{1}H NMR ($CDCl_3$): δ = 1.25 (s, 9H), 4.50 (s, 2H), 7.49 and 8.01 (4H, AA'BB' system, aromatic H).

2,2,2-Trifluoro-1-(4-methylphenyl)-1-ethanone oxime (**7a**): To a stirred mixture of 2.77 g (39.9 mmol) of hydroxylamine hydrochloride and 1.60 g (39.9 mmol) of NaOH in 150 ml of boiling absol. ethanol is added a solution of 2.5 g (13.29 mmol) of **6a** in 20 ml of ethanol. After refluxing for 16 h the solvent is evaporated *in vacuo*, and the residue is partitioned between ether and water. The organic layer is washed 3 times with 0.01 N aqueous HCl and 3 times with water, dried with Na_2SO_4, and the solvent is removed under reduced pressure. From *n*-hexane at −20 °C the oxime is obtained as colorless crystals melting between 63 and 86 °C (*syn*/anti oxime?); yield 2.4 g (89%). – TLC: $R_F(CHCl_3)$ = 0.28; R_F(B) = 0.16; R_F(trichloromethane-ethyl acetate, 9:1) = 0.73. – MS: *m/z* = 203 ($M^{\oplus}$, 100%). – ^{1}H NMR ($CDCl_3$): δ = 2.38 (s, 3H), 7.1 – 7.6 (m, 4H, aromatic H), 8.5 (s, broad, 1H).

$C_9H_8F_3NO$ (203.2) Calc. C 53.21 H 3.97 N 6.90 Found C 52.97 H 4.07 N 7.26

1-⟨4-[(tert-Butyldimethylsiloxy)methyl]phenyl⟩-2,2,2-trifluoro-1-ethanone oxime (**7b**): The oxime is prepared as described for **7a**. Minor amounts of unreacted **6b** and a compound with lower R_F value (without protective group) are removed by column chromatography on silica gel with solvent (C) as eluent; yield (from 6.5 g of **6b**): 6.3 g (93%), colorless oil. – TLC: R_F(C) = 0.35; R_F(hexane-dichloromethane, 5:2) = 0.10; R_F(F) = 0.66. – MS: *m/z* = 333 ($M^{\oplus}$, 10%), 318 (5%), 276 ($M^{\oplus}$ – OtBu, 95%), 75 (100%). – ^{1}H NMR ($CDCl_3$): δ = 0.10 (s, 6H), 0.96 (s, 9H), 2.83 (s, broad, 1H), 4.76 (s, 2H), 7.40 (m, 4H, aromatic H).

1-[(4-tert-Butoxymethyl)phenyl]-2,2,2-trifluoro-1-ethanone oxime (**7c**): This compound is prepared analogously to **7a** and purified by column chromatography on silica gel with solvent (C) and subsequent crystallization from methanol-ethanol-water (m.p. 97 – 98 °C); yield (from 4.5 g of **6c**): 2.7 g (57%), 1.5 g of unreacted **6c** is recovered by column chromatography. – TLC:

R_F(C) = 0.32. – MS: *m/z* = 275 ($M^{\oplus}$, 4%); 202 ($M^{\oplus}$ – OtBu, 100%). – ^{1}H NMR ($CDCl_3$): δ = 1.25 (s, 9H), 2.12 (s, broad, 1H), 7.38 (m, 4H, aromatic H).

$C_{13}H_{16}F_3NO_2$ (275.3) Calc. C 56.72 H 5.86 N 5.09 Found C 56.57 H 6.08 N 5.30

2,2,2-Trifluoro-1-(4-methylphenyl)-1-ethanone O-(p-tolylsulfonyl)oxime (**8a**): 1.8 g (8.86 mmol) of **7a**, dissolved in 30 ml of dry pyridine, is refluxed with 2.53 g (13.29 mmol) of *p*-toluenesulfonyl chloride. After 3 h the solvent is evaporated *in vacuo*, and the residue is subjected to column chromatography with solvent (D). The resulting, chromatographically pure product crystallizes from ether-*n*-hexane in colorless needles (m.p. 104 – 105 °C); yield 2.90 g (92%). – TLC: R_F(D) = 0.65 (**7a**: 0.24); R_F($CHCl_3$) = 0.84. – MS: *m/z* = 357 ($M^{\oplus}$, 16%), 91 (100%). – ^{1}H NMR ($CDCl_3$): δ = 2.36 (s, 3H), 2.42 (s, 3H), 7.26 (m, 4H, aromatic H), 7.33 and 7.87 (4H, AA'BB' system, aromatic H).

$C_{16}H_{14}F_3NO_3S$ (357.4) Calc. C 53.78 H 3.95 N 3.92 S 8.97
Found C 53.84 H 3.80 N 3.73 S 9.08

1-⟨4-[(tert-Butyldimethylsiloxy)methyl]phenyl⟩-2,2,2-trifluoro-1-ethanone O-(p-tolylsulfonyl)-oxime (**8b**): Preparation analogously to **8a**. The reaction mixture is purified by column chromatography on silica gel with solvent (E); yield (from 6.3 g of **7b**): 6.4 g (70%), colorless oil. – TLC: R_F(E) = 0.57; R_F(F) = 0.85; R_F(C) = 0.80. – ^{1}H NMR ($CDCl_3$): δ = 0.09 (s, 6H), 0.96 (s, 9H), 2.40 (s, 3H), 4.82 (s, 2H), 7.26 – 7.58 (m, 6H, aromatic H), 7.96 (2H, part of an AA'BB' system, aromatic H).

1-[(4-tert-Butoxymethyl)phenyl]-2,2,2-trifluoro-1-ethanone O-(p-tolylsulfonyl)oxime (**8c**): This compound is synthesized analogously to **8a** and purified by column chromatography with solvent (D) and crystallization from *n*-hexane: m.p. 83 – 84 °C; yield (from 2.0 g of **7c**): 2.7 g (87%). – TLC: R_F(D) = 0.65; R_F($CHCl_3$) = 0.57; R_F(C) = 0.58; R_F(G) = 0.97. – MS: *m/z* = 429 ($M^{\oplus}$, 1%), 356 ($M^{\oplus}$ – OtBu, 28%), 201 (100%), 155 (82%). – ^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 9H), 2.44 (s, 3H), 4.48 (s, 2H), 7.20 – 7.40 (m, 6H, aromatic H), 7.86 (2H, part of an AA'BB' system, aromatic H).

$C_{20}H_{22}F_3NO_4S$ (429.5) Calc. C 55.94 H 5.16 N 3.26 S 7.47
Found C 56.13 H 5.33 N 3.18 S 7.62

3-(4-Methylphenyl)-3-trifluoromethyldiaziridine (**9a**): 1.7 g (4.76 mmol) of **8a** in 10 ml of precooled ether is added to 2 ml of liquid ammonia in a thick-walled screw-cap glass tube. After stirring the mixture for about 12 h at room temperature in the closed tube, the solution is cooled down to –40 °C, poured into a beaker in order to evaporate the ammonia, and subsequently concentrated under reduced pressure. The residue is partitioned between ether and water, the organic layer is dried with Na_2SO_4, the solvent removed *in vacuo* and the residue purified by column chromatography on silica gel with trichloromethane-ethyl acetate (19:1) as eluent. Crystallization from *n*-hexane at –20 °C gives the diaziridine as colorless needles: m.p. 45 – 46 °C yield 0.88 g (91%). – TLC: R_F($CHCl_3$) = 0.20; R_F(trichloromethane-ethyl acetate, 19:1) = 0.58; red color with ninhydrin. – MS: *m/z* = 202 ($M^{\oplus}$, 30%), 201 (100%). – ^{1}H NMR ($CDCl_3$): δ = 2.16 and 2.75 (2H, AB system, J_{AB} = 7.8 Hz), 2.35 (s, 3H), 7.19 and 7.49 (4H, AA'BB' system, aromatic H).

$C_9H_9F_3N_2$ (202.2) Calc. C 53.47 H 4.49 N 13.86 Found C 53.24 H 4.32 N 13.70

3-⟨4-[(tert-Butyldimethylsiloxy)methyl]phenyl⟩-3-trifluoromethyldiaziridine (**9b**): Preparation analogously to **9a**. Compound **9b** is purified by column chromatography on silica gel with solvent (C) as eluent; yield (from 2.6 g of **8b**): 1.52 g (86%), colorless oil. – TLC: R_F(C) = 0.20; R_F($CHCl_3$) = 0.30; red color with ninhydrin. – MS: *m/z* = 332 ($M^{\oplus}$, 10%), 275 (100%), 245

(17%), 201 (12%). – ^{1}H NMR ($CDCl_3$): δ = 0.06 (s, 6H), 0.91 (s, 9H), 2.21 and 2.80 (2H, AB system, J_{AB} = 8.4 Hz), 4.78 (s, 2H), 7.40 and 7.66 (4H, AA'BB' system, aromatic H).

3-[(4-tert-Butoxymethyl)phenyl]-3-trifluoromethyldiaziridine (**9c**): This compound is prepared as described for **9a**. For purification, the reaction mixture is subjected to column chromatography on silical gel with solvent (G) as eluent; yield (from 2.7 g of **8c**): 1.38 g (80%), colorless oil. – TLC: R_F(G) = 0.60; red color with ninhydrin. – MS: *m/z* = 274 ($M^{\oplus}$, 28%), 273 (68%), 201 (100%). – ^{1}H NMR ($CDCl_3$): δ = 1.24 (s, 9H), 2.09 and 2.73 (2H, AB system, J_{AB} = 9.0 Hz), 4.42 (s, 2H), 7.35 and 7.55 (4H, AA'BB' system, aromatic H).

3-(4-Methylphenyl)-3-trifluoromethyl-3H-diazirine (**10a**): 600 mg (2.97 mmol) of **9a**, dissolved in 30 ml of absol. ether, is stirred with 1.4 g of freshly prepared Ag_2O[10]. The progress of the slightly exothermic reaction is followed by TLC ($CHCl_3$). After 1 h silver and silver oxide are filtered off, washed 3 times with ether, and the combined filtrates are concentrated *in vacuo*. The chromatographically pure diazirine **10a** crystallizes upon storage at −20°C, but melts while warming up to room temperature; yield 540 mg (91%). – TLC: R_F($CHCl_3$) = 0.84. – MS: *m/z* = 200 ($M^{\oplus}$, 1%), 172 ($M^{\oplus}$ – N_2, 100%), ^{1}H NMR ($CDCl_3$): δ = 2.23 (s, 3H), 7.10 (m, 4H, aromatic H).

3-(4-[(tert-Butyldimethylsiloxy)methyl]phenyl)-3-trifluoromethyl-3H-diazirine (**10b**): The diazirine is obtained by Ag_2O oxidation analogously to **10a**; yield (from 2.0 g of **9b**): 1.79 g (91%), colorless oil. – TLC: R_F(C) = 0.9; R_F(hexane-ether, 3:2) = 0.95. – ^{1}H NMR ($CDCl_3$): δ = 0.06 (s, 6H), 0.90 (s, 9H), 4.70 (s, 2H), 7.11 and 7.34 (4H, AA'BB' system, aromatic H).

3-[(4-tert-Butoxymethyl)phenyl]-3-trifluoromethyl-3H-diazirine (**10c**): The synthesis of **10c** is performed as described for **10a**; yield (from 1.1 g of **9c**): 1.0 g (92%), colorless oil. – TLC: R_F($CHCl_3$) = 0.63. – MS: *m/z* = 272 ($M^{\oplus}$, 13%), 244 ($M^{\oplus}$ – N_2, 22%), 199 ($M^{\oplus}$ – OtBu, 30%), 171 ($M^{\oplus}$ – OtBu – N_2, 100%), 57 (100%). – ^{1}H-NMR ($CDCl_3$): δ = 1.24 (s, 9H), 4.40 (s, 2H), 7.10 and 7.36 (4H, AA'BB' system, aromatic H).

4-(1-Azi-2,2,2-trifluoroethyl)benzyl alcohol (**11**). – A) *From* **10b**: The protective group of **10b** is cleaved by conc. hydrochloric acid in methanol as described in lit.[10] and the product is purified by column chromatography on silica gel with $CHCl_3$ as solvent; yield (from 2.0 g of **10b**): 1.20 g (92%), colorless oil. – TLC: R_F($CHCl_3$) = 0.20; R_F(E) = 0.14; R_F(H) = 0.95. – MS: *m/z* = 188 ($M^{\oplus}$ – N_2, 100%), 159 (55%). – ^{1}H-NMR ($CDCl_3$): δ = 2.45 (s, broad, 1H), 4.73 (s, 2H), 7.26 and 7.50 (4H, AA'BB' system, aromatic H).

B) *From* **10c**: 800 mg (2.94 mmol) of **10c** is dissolved in 10 ml of dichloromethane and stirred for 2 h at room temperature with 5 ml of TFA. The reaction mixture is diluted with 100 ml of ether and extracted with saturated aqueous $NaHCO_3$. The organic layer is washed 5 times with water, dried with Na_2SO_4, and the solvent is removed *in vacuo*; yield 550 mg (86%). The product, according to TLC, mass spectrum and ^{1}H NMR spectrum, is identical with the one obtained from **10b**.

4-(1-Azi-2,2,2-trifluoroethyl)benzoic acid (**12**): A) *From* **10a**: Oxidation of **10a** with theoretical amounts of $KMnO_4$ in acetone or benzene with equimolar amounts of dicyclohexyl[18]crown-6 went on unsatisfactory. Tetrabutylammonium permanganate[13] in pyridine showed no advantage compared to the following procedure: 1.0 g (4.99 mmol) of **10a** is dissolved in 20 ml of pyridine and such an amount of water is added, that the solution still remains homogeneous. Then 4 equivalents of powdered solid $KMnO_4$ is added and the solution is stirred at 50°C. After 20 h the reaction mixture is diluted with 150 ml of water, acidified with 1 N H_2SO_4 to pH = 2–3, and aqueous $NaHSO_3$ is added until the precipitated MnO_2 has dissolved. The colorless solution is extracted with ether (three 100-ml portions) and washed with water. With 0.1 N KOH the

carboxylic acid is extracted into the aqueous layer, washed with ether, and after acidification again extracted with ether. Final purification is achieved by gel permeation chromatography on Sephadex LH 20 with methanol. The product is crystallized from ether-hexane or methanol-water: m.p. 123–125 °C, decomp. with foaming (N_2); yield 660 mg (58%). – TLC: R_F(H) = 0.58. – MS: m/z = 230 ($M^{\oplus}$, 1%), 202 ($M^{\oplus} - N_2$, 100%), 185 (12%). – ^{1}H-NMR ($CDCl_3$): δ = 7.27 and 8.13 (4H, AA'BB' system, aromatic H). – UV/VIS: λ_{max} (ε) = 233 (17,000), 276 (1,100), 284 sh (900), 348 nm (390).

$C_9H_5F_3N_2O_2$ (230.2) Calc. C 46.97 H 2.19 N 12.17 Found C 47.06 H 2.05 N 12.15

B) *From* **11**: 860 mg (3.98 mmol) of **11** is dissolved in 3 ml of dioxane and 25 ml of 0.2 N aqueous KOH. Then 950 mg (5.97 mmol) of $KMnO_4$ is added in batches and the mixture is stirred at room temperature, following the progress of the reaction by TLC; solvent (H). After 2 h the precipitated MnO_2 is removed by filtration, washed several times with methanol, and the combined filtrates are concentrated under reduced pressure. The residual alkaline aqueous phase is extracted with ether, acidified with 1 N H_2SO_4 to pH = 2–3 and extracted again with ether. The organic layer is washed with water until neutral, dried with Na_2SO_4, and the solvent is removed *in vacuo*. The residual white solid foam is crystallized from ether-hexane; yield 660 mg (72%). According to TLC, mass spectrum, ^{1}H NMR spectrum, UV/VIS spectrum, and elemental analysis the product is identical with the one obtained from **10a**.

Succinimido 4-(1-azi-2,2,2-trifluoroethyl)benzoate (**13**): 230 mg (1 mmol) of **12** is mixed with 115 mg (1 mmol) of *N*-hydroxysuccinimid in 20 ml of dioxane-ethyl acetate (1 : 1), cooled down to –10 °C, and a solution of 206 mg (1 mmol) of DCC in 10 ml of dioxane is added. After stirring for 6 h at room temperature, the precipitated dicyclohexylurea is removed by filtration and, after concentrating the filtrate *in vacuo*, the product is crystallized from 2-propanol: m.p. 106 °C; yield 240 mg (73%). – TLC: R_F(H) = 0.95 (HOSu: 0.44). – MS: m/z = 327 ($M^{\oplus}$, 1%), 299 ($M^{\oplus} - N_2$, 26%); 213 ($M^{\oplus}$ – OSu, 100%), 185 ($M^{\oplus}$ – OSu – N_2, 80%), 157 (65%), 137 (14%). – ^{1}H NMR ($CDCl_3$): δ = 2.91 (s, broad, 4H), 7.36 and 8.20 (4H, AA'BB' system, aromatic H).

$C_{13}H_8F_3N_3O_4$ (327.2) Calc. C 47.72 H 2.46 N 12.84 Found C 47.82 H 2.25 N 12.84

4-Bromobenzaldehyde diethyl acetal (**15**): The acetal is prepared from 4.07 g (22 mmol) of 4-bromobenzaldehyde (**14**) and 3.26 g (22 mmol) of triethyl orthoformate in ethanol with *p*-toluenesulfonic acid as catalyst, and purified by distillation under reduced pressure: b.p. 135 °C/12 torr (lit.[26] b.p. 140 °C/16 torr); yield 5.25 g (92%). – ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 6H), 4.60 (q, 4H), 5.50 (s, 1H), 7.45 (m, 4H, aromatic H).

4-Trifluoroacetylbenzaldehyde diethyl acetal (**16**): Preparation analogously to **6a**. The acetal is purified by column chromatography on silica gel using $CHCl_3$ as eluent; yield (from 5.18 g of **15**): 5.0 g (90%). – TLC: R_F($CHCl_3$) = 0.66; R_F(trichloromethane-petroleum ether, 3 : 2) = 0.68. – ^{1}H NMR ($CDCl_3$): δ = 1.26 (t, 6H), 4.64 (q, 4H), 5.60 (s, 1H), 7.70 and 8.14 (4H, AA'BB' system, aromatic H).

4-Trifluoroacetylbenzaldehyde (**17a**) *and 4-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzaldehyde* (**17b**): 4.0 g (14.5 mmol) of **16** is stirred at room temperature with 5 ml of TFA and 5 ml of dichloromethane. After 2 h the reaction mixture is diluted with 50 ml of dichloromethane and washed with 5-% aqueous $KHCO_3$ and water. The organic layer is dried with Na_2SO_4 and the solvent removed *in vacuo*. Crystallization of the residue from ether-hexane gives the product as colorless needles: m.p. 106–107 °C. The same compound is obtained by cleavage of **16** with aqueous HCl/THF; yield: 2.95 g (92%). – TLC: R_F($CHCl_3$) = 0.43. – MS: m/z = 220 ($M^{\oplus}$ for **17b**, 7%), 202 ($M^{\oplus} - H_2O$ or $M^{\oplus}$ for **17a**, 40%), 180 (14%), 151 (24%), 133 (100%), 105

(36%), 77 (26%). – ^{1}H NMR ([D]$_6$acetone): δ = 6.81 (s, 2H, exchangable with D_2O), 7.98 (m, 4H, aromatic H), 9.86 (s, 1H).

17b: $C_9H_7F_3O_3$ (220.2) Calc. C 49.10 H 3.21 Found C 49.37 H 3.03

During drying at 60 °C over P_2O_5 *in vacuo* the crystals liquified to give a viscous oil (= **17a**). – ^{1}H NMR ($CDCl_3$): δ = 8.08 and 8.32 (4H, AA'BB' system, aromatic H), 10.17 (s, 1H).

4-Trifluoroacetylbenzoic acid (**18a**): *and 4-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzoic acid* (**18b**): 1.01 g (5 mmol) of **17a** is dissolved in 3 ml of dioxane and 30 ml of 0.2 N KOH and stirred for 2 h with 525 mg (3.33 mmol) of $KMnO_4$. The reaction mixture is diluted with 50 ml of ether, acidified with 1 N H_2SO_4 to pH = 2–3, and the precipitated MnO_2 is dissolved by adding the sufficient amount of aqueous $NaHSO_3$. The organic layer is separated, and the organic phase is washed 3 times with ether. The combined ether layers are extracted with 0.01 N KOH, the aqueous phase is acidified to pH = 2–3 and extracted 3 times with ether. After drying with Na_2SO_4 the combined extracts are concentrated *in vacuo*. The residue is crystallized from either trichloromethane-*n*-hexane (yielding **18a**, m.p. 176 °C; lit.[20]: 178–179 °C) or water (yielding **18b**, m.p. 176–177 °C); yield 800 mg (73%). – TLC: R_F(I) = 0.33; R_F(H) = 0.53, MS: *m/z* = 218 ($M^{\oplus}$, 32%), 201 (7%), 149 (100%), 121 (19%). Analytical data for the product from trichlormethane-hexane (**18a**):

$C_9H_5F_3O_3$ (218.1) Calc. C 49.56 H 2.31 Found C 49.62 H 2.11

Analytical data for the product from water (**18b**):

Calc. for $C_9H_7F_3O_4 \times 0.5\ H_2O$ (245.2) Calc. C 44.09 H 3.29 Found C 43.72 H 3.20

^{1}H NMR ([D]$_6$acetone): δ = 7.08 (s, broad, 3H), 7.87 and 8.12 (4H, AA'BB' system, aromatic H). After drying the crystals *in vacuo* over P_2O_5: δ = 5.97 (broad, 1H), 8.28 (narrow m, 4H, aromatic H). – X-ray analysis of the crystals proved the structure of **18b** as 4-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzoic acid[21].

4-(2,2,2-Trifluoro-1-hydroxyiminoethyl)benzoic acid (**19**): 500 mg (2.29 mmol) of **18a** is dissolved in 15 ml of pyridine and stirred with 475 mg (6.87 mmol) of hydroxylamine hydrochloride at 70 °C. After 16 h the reaction mixture is diluted with 50 ml of ethyl acetate and extracted 4 times with 0.1 N aqueous hydrochloric acid. The organic layer is washed 3 times with water, dried with Na_2SO_4 and concentrated *in vacuo*. The residue is taken up in ether-hexane and crystallizes during evaporation: m.p. 183–184 °C. – TLC: R_F(H) = 0.55, R_F(I) = 0.34; indistinguishable from **18**. – MS: *m/z* = 233 ($M^{\oplus}$, 100%), 216 (15%), 130 (28%), 121 (32%), 102 (20%), 78 (24%), 65 (44%). – ^{1}H NMR ([D]$_6$acetone): δ = 7.56 and 8.14 (4H, AA'BB' system, aromatic H). – The same product is obtained from **18b**.

$C_9H_6F_3NO_3$ (233.2) Calc. C 46.36 H 2.59 N 6.01 Found C 46.50 H 2.43 N 6.28

4-(1-Diazo-2,2,2-trifluoroethyl)benzoic acid (**20**): 200 mg (0.82 mmol) of **19** is dissolved in 10 ml of 1 N aqueous NaOH, and 196 mg (1.72 mmol) of hydroxylamine-*O*-sulfonic acid is added at 0 °C. During 15 h at this temperature the colorless solution turns orange-yellow. The reaction mixture is acidified with 1 N HCl to pH = 3, extracted with three 30-ml portions of ether, the combined extracts are washed with water, dried with Na_2SO_4 and concentrated *in vacuo*. Final purification is achieved by gel permeation chromatography on Sephadex LH 20 with methanol. The yellow diazo compound is eluted first. From ether-hexane orange-red crystals are obtained: m.p. 128–129 °C, dec. with foaming; yield 40 mg (21%). – TLC: R_F(I) = 0.66; R_F(H) = 0.76. – MS: *m/z* = 230 ($M^{\oplus}$, 46%), 202 ($M^{\oplus} - N_2$, 100%). – UV/VIS: λ_{max} (ε) = 284 (22,000), 450 nm (68).

$C_9H_5F_3N_2O_2$ (230.2) Calc. C 46.97 H 2.19 N 12.17 Found C 47.12 H 1.95 N 12.00

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