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para-Functionalized Aryl-di-*tert*-butylfluorosilanes as Potential Labeling Synthons for ^{18}F Radiopharmaceuticals

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Dedicated to Professor Dietmar Seyferth on the occasion of his 80th birthday

Abstract: The syntheses of the functionalized triorganofluorosilanes tBu$_2$-(p-XC$_6$H$_4$)SiF (**3a**, X = SH; **4a**, X = NCS; **4b**, X = NCO; **5**, X = NC$_4$H$_2$O$_2$; **7**, X = COOH; **8a**, X = COONC$_4$H$_4$O$_2$; **8b**, X = COOC$_6$F$_5$) are reported. These compounds display potential as silicon-based fluoride acceptors (SiFAs). The molecular structures of compounds **5**, **7**, and **8a** have been determined by single-crystal X-ray diffraction studies. With the exception of compounds **8a** and **8b**, all of the compounds could be ^{18}F-labeled by isotopic exchange in good to high radiochemical yields (RCY) with good to excellent specific activities. As proof of applicability, the maleimido-functionalized SiFA derivative **5**, which is specific for thiol groups, has been used for the labeling of rat serum albumin (RSA) that had been derivatized with 2-iminothiolane. The incorporation of [^{18}F]**5** into the derivatized RSA reached a maximum yield after 30 min at ambient temperature. After purification, the [^{18}F]RSA was evaluated in a healthy rat by means of μPET and displayed an expedient in vivo stability over 180 min.

Keywords: fluorine · isotopic labeling · positron emission tomography · radiopharmaceuticals · silicon · X-ray diffraction

Introduction

[^{18}F]Fluorine is among the most commonly used radionuclides for positron emission tomography (PET).[1a,b] This non-invasive imaging modality provides information about the in vivo distribution of radiolabeled biomolecules. It has become an important and powerful diagnostic imaging tool in clinical cardiology, neurology, and oncology. Conventional methods for the syntheses of ^{18}F-labeled peptides have hitherto been based on multi-step procedures involving prosthetic groups suitable for bioconjugation.[2a–c] However, given the short half-life of ^{18}F (110 min), this multi-step chemistry is a major drawback. Even novel methods such as solid-phase ^{18}F-fluoropropionylation[3] and the most recently introduced "click-chemistry" approach[4,5] require purification of the ^{18}F synthon by HPLC or distillation prior to final peptide coupling. Time-consuming work-up often reduces the final preparative yield and the specific activity of the product.[6] Consequently, the development of ^{18}F-acceptors bearing functionalities that allow facile conjugation to biomolecules under mild conditions is highly desirable. Recently, Perrin and co-workers published the carrier-added ^{18}F labeling of trialkoxysilanes as potential labeling precursors for PET,[2d] whereas Ametamey et al. described a similar labeling approach using silicon-containing building blocks for the ^{18}F-labeling of peptides in a single step.[2e] In previous publications,[6,7] we have demonstrated that di-*tert*-butylphenylfluorosilane, tBu$_2$PhSiF, displays ideal ^{19}F–^{18}F exchange with an ^{18}F source, and that the resulting [^{18}F]-labeled tBu$_2$PhSiF is inert towards hydrolysis under physiological conditions.[7]

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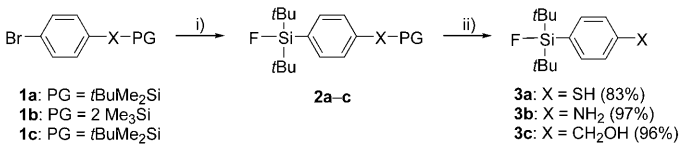
Consequently, the functionalized derivative $t\mathrm{Bu}_2[p\text{-}C(O)HC_6H_4]SiF$ was prepared as a silicon-based fluorine acceptor (SiFA) and linked, via the aldehyde function, to biomolecules. The latter could then be successfully applied for in vivo screenings. In continuation of these studies, we report here the syntheses and structures of aryl-di-*tert*-butylfluorosilanes bearing a variety of functional groups at the aryl substituent, and demonstrate that these compounds are particularly suitable as ^{18}F-labeling precursors for biomolecules. As a proof of principle, we have employed, in a convenient procedure, a maleimido-derivatized SiFA compound for the $[^{18}F^-]$-labeling of the protein rat serum albumin (hereafter referred to as RSA).

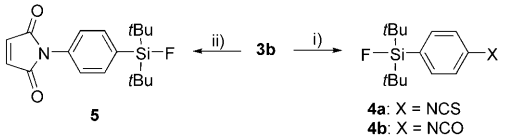
Results and Discussion

Reaction of silyl-protected functionalized *p*-bromobenzenes (**1a–c**) with *tert*-butyllithium and di-*tert*-butyldifluorosilane at −78 °C provided the triorganofluorosilanes (**2a–c**). Deprotection under acidic conditions gave the SiFA synthons **3a–c** in good to excellent yields (Scheme 1).



Scheme 1. Synthesis of the functionalized triorganofluorosilanes. i) *t*BuLi, $t\mathrm{Bu}_2\mathrm{SiF}_2$; ii) deprotection. X = functional group, PG = protecting group.

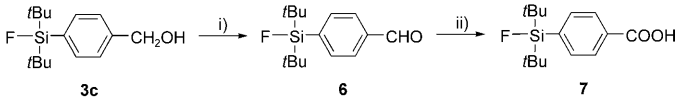
Treatment of the amine **3b** with thiophosgene in toluene provided the corresponding isothiocyanato derivative (**4a**), and analogous treatment with phosgene yielded the isocyanato derivative (**4b**). By reaction with maleic anhydride in diethyl ether followed by cyclization with acetic anhydride and sodium acetate, the *para*-substituted aniline derivative **3b** was quantitatively converted into 1-[4-(di-*tert*-butylfluorosilanyl)phenyl]pyrrole-2,5-dione (**5**) (Scheme 2).



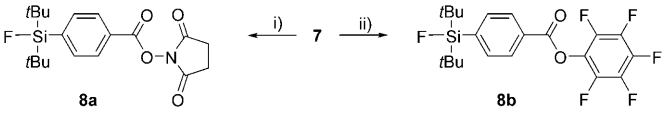
Scheme 2. Derivatization of the amine **3b**. i) Phosgene/thiophosgene, $PhCH_3$; ii) maleic anhydride, Et_2O, acetic anhydride, sodium acetate.

Single crystals of **5** suitable for X-ray diffraction analysis were obtained by recrystallization from *n*-hexane.

The alcohol **3c** was converted into the corresponding aldehyde **6** by reaction with pyridinium chlorochromate. Subsequent oxidation with $KMnO_4$ gave the carboxylic acid **7** (Scheme 3), from which the activated esters **8a** and **8b** were prepared (Scheme 4).



Scheme 3. Oxidation of the alcohol **3c**. i) pyridinium chlorochromate in CH_2Cl_2; ii) $KMnO_4$, CH_2Cl_2/*tert*-butanol/pH 3–4.



Scheme 4. Synthesis of the activated esters **8a** and **8b**. i) EDCI, HO-Su, DMF; ii) DCC, pentafluorophenol, dioxane.

The molecular structures of **5**, **7**, and **8a** are shown in Figures 1–3, respectively, and selected geometric parameters are collected in Table 1.

Table 1. Selected bond lengths [Å] and angles [°] for **5**, **7**, and **8a**.

	5	**7**	**8a**
Si–F	1.6110(14)	1.6130(14)	1.6115(12)
Si–C(1)	1.865(2)	1.898(2)	1.878(2)
Si–C(11)	1.877(2)	1.767(3)	1.880(2)
Si–C(15)	1.879(2)	1.801(3)	1.885(2)
F-Si-C(1)	105.42(8)	102.73(10)	103.82(8)
F-Si-C(11)	104.12(9)	103.78(11)	104.39(8)
F-Si-C(15)	105.15(9)	107.87(10)	105.87(8)
C(1)-Si-C(11)	111.33(9)	114.52(12)	112.71(9)
C(1)-Si-C(15)	110.89(10)	111.90(11)	109.49(9)
C(11)-Si-C(15)	118.63(10)	114.72(13)	119.05(9)

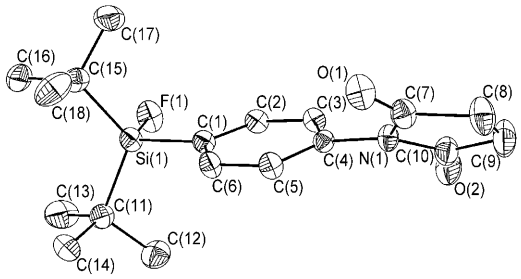


Figure 1. Molecular structure of **5**. Atomic displacement parameters are drawn at a 30% probability level.

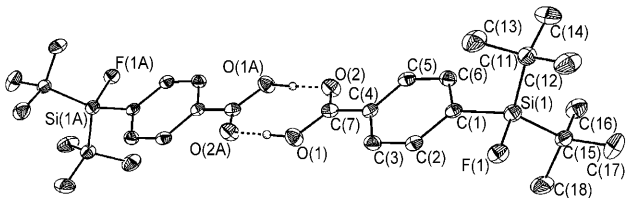


Figure 2. Molecular structure of **7**. Atomic displacement parameters are drawn at a 30% probability level.

All of the compounds crystallized monoclinically, with eight (**5**, **7**) or four (**8a**) molecules in the unit cell. The sili-

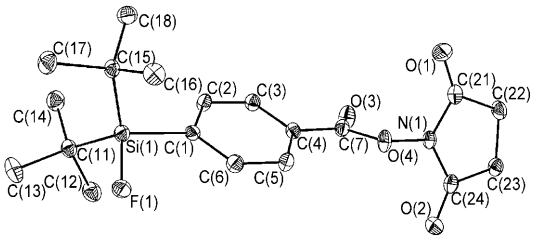


Figure 3. Molecular structure of **8a**. Atomic displacement parameters are drawn at a 30% probability level.

con atoms in these compounds are four-coordinate and show distorted tetrahedral configurations with average angles of 109.25° (**5**, **7**) and 109.22° (**8a**). The largest deviations from the tetrahedral angle are found for C(11)-Si-C(15) (119.05(9)°, **8a**) and F-Si-C(1) (102.73(10)°, **7**).

The Si–F distances are rather similar, ranging from 1.6110(14) (**5**) to 1.6130(14) Å (**7**). They are slightly longer than that in tBuPh$_2$SiF (1.6004(10) Å).[8] A noteworthy feature is the non-symmetric intramolecular O(1)-H(1)···O(2A) hydrogen bridge (O(1)-H(1) 1.06(3) Å, H(1)···O(2A) 1.59(3) Å, O(1)···O(2A) 2.651(2) Å; ∢O(1)-H(1)-O(2A) 176(2)°) that links two molecules of **7** to give a dimer. Such hydrogen bridges are common in the solid-state structures of *p*-silylarylcarboxylic acids.[9]

Radiolabeling: All of the functionalized SiFA compounds reported here are potentially useful for the further labeling of biomolecules such as peptides and proteins. Thus, the *p*-thiophenol-substituted compound **3a** could react with maleimido-derivatized molecules, while the aminobenzene derivative **3b** could react with epoxide-modified biomolecules. The benzylic alcohol **3c**, on the other hand, could be transformed into di-*tert*-butyl[4-(chloromethyl)phenyl]fluorosilane, which could undergo subsequent reactions with amino-, thiol-, or hydroxyl-substituted biomolecules. The isothiocyanato- and isocyanato-substituted derivatives **4a** and **4b** could be employed for the direct labeling of amines, providing stable thioureas and ureas, respectively. The *p*-maleimidophenyl-substituted fluorosilane **5** has the potential to selectively bind thiol functions in biomolecules, while the aldehyde **6** has already been shown to be suitable for labeling the peptide Tyr^3-octreotate through oxime formation.[6,7] Finally, the benzoic acid derivative **7**, in its ^{18}F-labeled form, could be transformed into an active ester, which, in turn, could be employed for direct protein coupling. Alternatively, the active esters **8a** and **8b** could be directly used for the same purpose, provided that the functionality is sufficiently stable under the radiolabeling conditions.

We therefore thoroughly investigated the isotopic ^{19}F-^{18}F exchange reactions of the abovementioned SiFA compounds using 5–50 nmol of each compound and non-aqueous $^{18}F^-$ in acetonitrile and/or DMSO. The radiolabeling was achieved by using either anhydrous $^{18}F^-$/Kryptofix 2.2.2./K^+ or an azeotropically dried mixture of [nBu$_4$N]HCO$_3$ and aqueous $^{18}F^-$ in acetonitrile or DMSO at room temperature. The method employed for the drying of $^{18}F^-$ had no influence on the RCYs of the labeled SiFA compounds. The isotopic exchange reactions of compounds **3a**–**8b** were terminated after 10–30 min at room temperature, yielding the ^{18}F-labeled SiFA derivatives in RCYs of 18–95% (Table 2). The

Table 2. Labeling of different SiFA compounds by isotopic ^{19}F–^{18}F exchange.[a]

Compound	Concentration [nmol mL^{-1}]	t [min]	$^{18}F^-$ [MBq] used in the reaction	RCY [%]
3a	30–50	10	1000–1500	40–60
3b	15–50	10–30	1000–1500	70–92
3c	50	10–30	1000–1500	0
4a	10–15	10	1000–2000	80–95
4b	50	10–30	1000–1500	18–25
5	20–50	10–30	1000–3000	40–42
6	8–10	10	1000–2500	80–95
7	30–50	10–30	1000–2000	64–70
8a	50	10–30	1000–1500	0
8b	50	10–30	1000–1500	0

[a] Labeling experiments were carried out at room temperature by using either $^{18}F^-$/Kryptofix 2.2.2./K^+ or [nBu$_4$N]/$^{18}F^-$ solution in acetonitrile or DMSO. The specific activities were in the range between 9 GBq per μmol (compound **4**) and 680 GBq/μmol (compound **6**).

RCYs were determined by means of radio-HPLC (see the Experimental Section). As has been reported previously,[6] the ^{18}F-labeling of compound **6** proceeds rather efficiently and just 3.75 nmol of **6** was needed to bind up to 3 GBq of $^{18}F^-$. However, such extremely efficient isotopic exchange could only be verified for two of the newly synthesized SiFA derivatives, namely compounds **3b** and **4a**. In these particular cases, 15–50 nmol of **3b** and 10–15 nmol of **4a**, respectively, were sufficient to react with up to 2.0 GBq of $^{18}F^-$ within 5–10 min at room temperature, yielding [^{18}F]**3b** and [^{18}F]**4a** in RCYs in the ranges 70–92% and 80–95%, respectively. The other derivatives bearing -SH, -NCO, -COOH, or maleimido functions gave significantly lower RCYs, even at higher concentrations. Interestingly, the reactions of the respective active esters **8a** and **8b** with basic $^{18}F^-$/Kryptofix 2.2.2./K^+ carbonate solution or with [nBu$_4$N]/$^{18}F^-$/[nBu$_4$N]HCO$_3$ in acetonitrile or DMSO did not give the ^{18}F-labeled products at all. Instead, quantitative cleavage of the Si–C$_{phenyl}$ bond was observed under the experimental conditions employed. After a reaction time of just 10 min, the ^{18}F-labeled carboxylic acid *p*-[^{18}F]FC$_6$H$_4$COOH was detected by HPLC in RCYs of 7 and 18% respectively, in addition to free $^{18}F^-$. Apparently, the modified ester functions in both **8a** and **8b** facilitate the nucleophilic attack of fluoride at silicon followed by Si–C bond cleavage. Thus, in a control NMR experiment, compound **8a** was treated with Bu$_4$NF·3H$_2$O, and the ^{19}F NMR

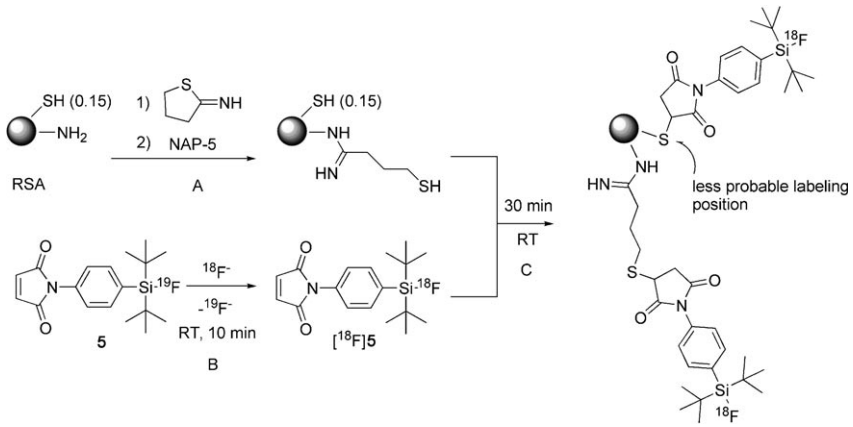
spectrum recorded after 24 h showed a singlet resonance at $\delta = -160$ ppm, corresponding to tBu$_2$SiF$_2$.

Notably, neither isotopic ^{18}F–^{19}F exchange nor Si–C bond cleavage was observed in the labeling experiment on the benzylic alcohol derivative **3c**. In contrast, the benzoic acid derivative **7** could be labeled in good RCYs of 64–70%. The labeling experiments are summarized in Table 2.

The ultimate aim of these syntheses of functionalized SiFA compounds is their use as labeling agents in PET radiochemistry. In particular, the field of protein labeling with ^{18}F has attracted the attention of many research groups and has been thoroughly reviewed.[10a–k] The [^{18}F]maleimido SiFA compound **5** is well suited for the labeling of larger molecules such as proteins with ^{18}F, taking advantage of the highly efficient and irreversible reaction between a maleimide and a thiol moiety to form a thiopyrrolidine-2,5-dione. This type of labeling reaction has itself proven valuable in many cases.[11] Therefore, we selected ^{18}F-labeled compound **5** for application to the synthesis of ^{18}F-labeled RSA (Scheme 5).

The RSA molecule contains insufficient thiol moieties for an adequate introduction of **5**. Consequently, in order to introduce additional thiol groups, which, in turn, should enhance the labeling efficiency, RSA (5 mg) was derivatized at its amino functions by reaction with 2-iminothiolane (10 equiv). Ellman's assay revealed two thiol moieties per modified RSA molecule. After derivatization, the RSA was purified using a size-exclusion gel cartridge (illustra NAP-5). In order to label the modified RSA dissolved in 50 mM phosphate buffer (pH 6.5), a solution of **5** (20–50 μg, 60–150 nmol) in acetonitrile (500 μL) was reacted with up to 1 GBq of azeotropically dried ^{18}F$^-$. The [^{18}F]**5** thus formed could be easily purified by simple solid-phase extraction (10 mg HLB cartridge) and subsequent elution with ethanol (250 μL), providing a labeling solution of high purity (<5% ^{18}F$^-$). The solution of [^{18}F]**5** was added to the modified RSA and the mixture was allowed to react at room temperature for 30 min. The crude reaction mixture was then purified by size-exclusion gel chromatography, yielding 20–40 MBq of pure [^{18}F]**5**-labeled RSA (5% RCY). The relatively low RCY may be attributed to the inefficient reaction between the maleimide and the thio-modified RSA as well as the instability of [^{18}F]**5** in the buffer solution. However, the overall reaction time was just 40 min, which is favorably brief in comparison to previously reported methods.[2c] Another advantage was that the synthesis of the labeling synthon [^{18}F]**5** did not require any HPLC purification. A rat biodistribution experiment with purified [^{18}F]RSA showed only a slight decrease of blood pool radioactivity between 10 min and 180 min after injection (Figure 4).

[^{18}F]Albumin was mainly excreted into the intestine, while kidney uptake was relatively low. Only a slight increase of radioactivity accumulation in the bone was observed over 180 min, which demonstrates a high in vivo stability of the



Scheme 5. Synthesis of [^{18}F]**5**-labeled RSA. A) Derivatization of RSA (10 mg, 150 nmol) with 2-iminothiolane (10 equiv) and subsequent purification by size-exclusion chromatography (NAP-5). B) Synthesis of [^{18}F]**5** by reacting **5** (20–50 μg, 60–150 nmol) for 10 min at room temperature with azeotropically dried ^{18}F$^-$ (1 GBq). C) Reaction of [^{18}F]**5** with 5 mg of the derivatized RSA (75 nmol) yielding ^{18}F$^-$-labeled RSA.

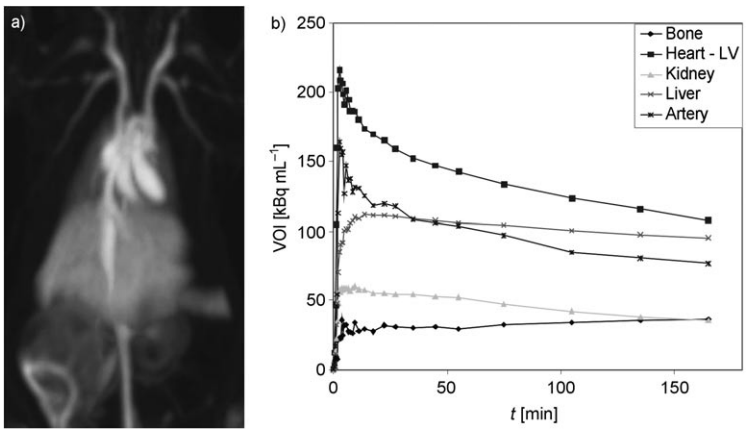


Figure 4. a) MIP image (maximum intensity projection) of an [^{18}F]albumin scan of a healthy rat acquired over 180 min, showing radiotracer accumulation in the large arteries, the liver, the heart, and the intestine. b) Time–activity curves of a CD rat after application of [^{18}F]albumin, derived from the image data. Radioactivity was measured over 180 min in the liver, the kidney, the arteries, the bone, and the left ventricle (LV), using a volume of interest (VOI) technique.

tracer. As an organ with a large blood volume, the liver showed high uptake similar to that of the blood pool.

Conclusion

Motivated by our breakthrough findings[6] that *p*-(*t*Bu_2FSi)C_6H_4CHO undergoes ^{18}F for ^{19}F exchange, that the resulting ^{18}F-labeled compound is sufficiently stable under physiological conditions, and that it can be easily coupled to biomolecules, we have synthesized a number of *para*-functionalized aryl-di-*tert*-butylfluorosilanes, *p*-(*t*Bu_2FSi)C_6H_4X (X = functional group). These compounds broaden the spectrum of silicon-based ^{18}F-acceptors (SiFAs) for potential PET applications. Exemplarily, we have demonstrated that the [^{18}F]maleimido derivative **5** can be employed for the synthesis of [^{18}F]**5**-labeled rat serum albumin (RSA), the applicability of which for PET has been verified by in vivo experiments. However, it has also become apparent that the efficiency of ^{18}F for ^{19}F exchange in *p*-(*t*Bu_2FSi)C_6H_4X depends on the identity of the functional group X.

Experimental Section

General methods: All solvents used for the syntheses of **3a**–**8b** were purified by distillation from appropriate drying agents under argon atmosphere. Solvents and chemicals used in the labeling experiments were purchased in the highest available grade and were used without further purification. The NMR experiments were carried out with Bruker DRX 400, Bruker DRX 300, and Varian Mercury 200 spectrometers. Chemical shifts (δ) are given in ppm and are referenced to the solvent peaks, with the usual values calibrated against tetramethylsilane (^{1}H, ^{13}C, ^{29}Si) and $CFCl_3$ (^{19}F). High-resolution mass spectra were obtained with an LTQ Orbitrap mass spectrometer (Thermo Electron) using acetonitrile as the mobile phase. Solutions in acetonitrile were injected by means of a TriPlus Autosampler onto a DFS system (perfluorokerosene as reference), connected to a Trace GC Ultra 2000 system; column: DB-5MS (25 m, 0.25 mm ID, film 0.1 μm). FT infrared spectra were recorded using a Bruker IFS 28 spectrometer. Elemental analyses were performed on a LECO CHNS-932 analyzer.

Crystallography: Crystals of compounds **5** and **8b** suitable for single-crystal X-ray diffraction analyses were grown by recrystallization from *n*-hexane. Compound **7** was recrystallized from *n*-hexane/Et_2O solution at −18 °C. Crystallographic data are summarized in Table 3. Intensity data were collected with a Nonius KappaCCD diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation. The data collections covered almost the whole sphere of the reciprocal space with three (**5**) or four (**7** and **8b**) sets at different κ angles and 227 (**5**), 339 (**7**), or 494 (**8b**) frames by ω rotation ($\Delta/\omega = 1°$) at 2 × 160 s (**5**), 80 s (**7**), or 60 s (**8b**) per frame. Crystal decay was monitored by repeating the initial frames at the end of the data collection. Analysis of the duplicate reflections revealed no indication of any decay. The structures were solved by direct methods (SHELXS-97[23]) and refined by full-matrix least-squares methods (SHELXL-97[24]). All H atoms were located in the difference Fourier map and their positions were isotropically refined with U_{iso} constrained at 1.2 times U_{eq} of the carrier C atom for non-methyl groups and 1.5 times U_{eq} of the carrier C atom for methyl groups. Atomic scattering factors for neutral atoms and real and imaginary dispersion terms were taken from the International Tables for X-ray Crystallography.[25] The figures were created with SHELXTL.[26] CCDC 704771, 704583, and 704772 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Table 3. Crystallographic data for **5**, **7**, and **8a**.

	5	**7**	**8a**
empirical formula	$C_{18}H_{24}FNO_2Si$	$C_{15}H_{23}FO_2Si$	$C_{19}H_{26}FNO_4Si$
formula mass [g mol^{-1}]	333.47	282.42	379.50
crystal system	monoclinic	monoclinic	monoclinic
crystal size	0.34 × 0.20 × 0.12	0.20 × 0.10 × 0.10	0.28 × 0.14 × 0.12
space group	*C*2/*c*	*C*2/*c*	*P*21/*n*
a [Å]	35.752(4)	26.625(3)	14.384(3)
b [Å]	6.9474(10)	6.4985(8)	6.4800(13)
c [Å]	14.9184(13)	21.560(3)	21.935(4)
β [°]	91.663(8)	126.35(3)	101.68(3)
V [Å^3]	3703.9(7)	3004.3(7)	2002.2(7)
Z	8	8	4
ρ_{calcd} [mg m^{-3}]	1.196	1.249	1.259
μ [mm^{-1}]	0.144	0.163	0.149
F(000)	1424	1216	808
θ range [°]	2.93–25.35	3.06–25.00	2.89–25.33
Index ranges	$-42 \le h \le 42$ $-8 \le k \le 8$ $-17 \le l \le 17$	$-31 \le h \le 31$ $-7 \le k \le 7$ $-19 \le l \le 25$	$-17 \le h \le 17$ $-7 \le k \le 7$ $-26 \le l \le 26$
no. of reflections collected	12415	15990	25569
completeness of θ_{max} [%]	99.6	99.7	99.4
no. of independent reflections/R_{int}	3377/0.029	2641/0.035	3640/0.047
no. of reflections observed with [$I > 2\sigma(I)$]	1822	1192	1827
no. of refined parameters	214	181	241
GooF (F^2)	0.875	0.870	0.861
$R_1(F)$ [$I > 2\sigma(I)$]	0.0405	0.0377	0.0370
wR_2 (F^2) (all data)	0.0996	0.0633	0.0705
$(\Delta/\sigma)_{max}$	0.001	0.000	0.000
largest difference peak/hole [e Å^{-3}]	0.135/−0.200	0.126/−0.248	0.180/−0.264

1-(*tert*-Butyldimethylsilanylsulfanyl)-4-(di-*tert*-butylfluorosilanyl)benzene (2a): At −78 °C under magnetic stirring, a solution of *t*BuLi in pentane was added to a solution of (4-bromophenylsulfanyl)-*tert*-butyldimethylsilane[11] (2.61 g, 8.60 mmol) in diethyl ether (30 mL). After the reaction mixture had been stirred for 30 min at −78 °C, the resulting suspension was added dropwise over a period of 20 min to a cooled (−78 °C) solution of di-*tert*-butyldifluorosilane[11] (1.86 g, 10.32 mmol) in diethyl ether (30 mL). The reaction mixture was allowed to warm to room temperature over a period of 12 h and then hydrolyzed with saturated aqueous NaCl solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over magnesium sulfate. After the magnesium sulfate had been filtered off, the filtrate was concentrated in vacuo to give a residue that contained 16 % di-*tert*-butylfluorophenylsulfanylsilane and 84 % 1-(*tert*-butyldimethylsilanylsulfanyl)-4-(di-*tert*-butylfluorosilanyl)benzene. The latter was separated by distillation (b.p. 188–190 °C at 5×10^{-3} Torr) to provide **2a** as a yellow oil (2.74 g, 7.13 mmol, 83 %). ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.44$ (m, 4H; H_{arom}), 1.03 (d, $^4J(^1H,^{19}F) = 1.1$ Hz, 18H; CH_3), 0.95 (s, 9H; CH_3), 0.17 ppm (s, 6H; CH_3); ^{13}C{^{1}H} NMR (100.63 MHz, $CDCl_3$): $\delta = 134.5$ (s; C_i), 134.0 (d, $^3J(^{13}C,^{19}F) = 4$ Hz; C_m), 133.6 (s, C_o), 131.7 (d, $^2J(^{13}C,^{19}F) = 14$ Hz; C_p), 27.2 (s; CH_3), 26.3 (s; *C*CH_3), 20.1 (d, $^2J(^{13}C,^{19}F) = 12$ Hz; *C*CH_3), 18.9 (s; CH_3), −6.8 ppm (s; $SiCH_3$); ^{19}F NMR (282.38 MHz, $CDCl_3$): $\delta = -191.5$ ppm (s, $^1J(^{19}F,^{29}Si) = 298$ Hz); ^{29}Si{^{1}H} NMR (59.63 MHz, $CDCl_3$): $\delta = 14.4$ ppm (d, $^1J(^{29}Si,^{19}F) = 298$ Hz); HR-MS: *m/z*: calcd for

$C_{20}H_{37}F^{32}S^{28}Si_2$: 384.2133; found 384.2146; elemental analysis calcd (%) for $C_{20}H_{37}FSSi_2$ (384.74): C 62.4, H 9.7; found C 62.3, H 9.4.

4-(Di-*tert*-butylfluorosilanyl)benzenethiol (3a): A solution of **2a** (2.6 g, 6.75 mmol) in a mixture of dichloromethane (10 mL) and trifluoroacetic acid (7.7 g, 5.2 mL, 67.5 mmol) was stirred for 24 h.[11] The volatiles were then evaporated in vacuo (at 10^{-3} Torr) to afford **3a** as a yellowish oil in quantitative yield. ^1H NMR (300.13 MHz, C_6D_6): $\delta = 7.47$ (d, $^3J(^1H,^1H) = 8$ Hz, 2H; H_{arom}), 7.07 (d, $^3J(^1H,^1H) = 8$ Hz, 2H; H_{arom}), 3.12 (s, 1H; SH), 1.09 ppm (d, $^4J(^1H,^{19}F) = 1$ Hz, 18H; CH_3); $^{13}C\{^1H\}$ NMR (75.48 MHz, C_6D_6): $\delta = 134.5$ (d, $^3J(^{13}C,^{19}F) = 4$ Hz; C_m), 133.9 (s; C_i), 129.9 (d, $^2J(^{13}C,^{19}F) = 14$ Hz; C_p), 128.2 (s; C_o), 27.2 (s; CH_3), 20.2 ppm (d, $^2J(^{13}C,^{19}F) = 12$ Hz; CCH_3); ^{19}F NMR (282.38 MHz, $CDCl_3$): $\delta = -190.7$ ppm (s, $^1J(^{19}F,^{29}Si) = 298$ Hz); $^{29}Si\{^1H\}$ NMR (59.63 MHz, $CDCl_3$): $\delta = 14.2$ ppm (d, $^1J(^{29}Si,^{19}F) = 298$ Hz); IR (KBr): $\tilde{\nu} = 2571$ cm^{-1} (SH); HR-MS: *m/z*: calcd for $C_{14}H_{23}F^{32}S^{29}Si$: 270.1268; found 270.1269; elemental analysis calcd (%) for $C_{14}H_{23}FSSi$ (270.48): C 62.2, H 8.6; found C 62.0, H 8.7.

2-[4-(Di-*tert*-butylfluorosilanyl)phenyl]-1,1,1,3,3,3-hexamethyldisilazane (2b): At −78 °C under magnetic stirring, a solution of *t*BuLi in pentane (24 mL, 1.5 mol L^{-1}) was added to a solution of 2-(4-bromophenyl)-1,1,1,3,3,3-hexamethyldisilazane[12] (5.50 g, 17 mmol) in diethyl ether (60 mL). After the reaction mixture had been stirred for 30 min at −78 °C, the suspension obtained was added dropwise over a period of 30 min to a cooled (−78 °C) solution of di-*tert*-butyldifluorosilane (3.67 g, 20.4 mmol) in diethyl ether (50 mL). The reaction mixture was allowed to warm to room temperature over a period of 12 h and then hydrolyzed with saturated aqueous NaCl solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate. After the latter had been filtered off, the filtrate was concentrated in vacuo to give **2b** (6.55 g, 16.5 mmol, 97%) as a colorless oil that solidified (m.p. 38 °C). ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.66$ (d, $^3J(H,H) = 8.1$ Hz, 2H; H_m), 7.01 (d, $^3J(H,H) = 8.1$ Hz, 2H; H_o) 1.19 (d, $^4J(^1H,^{19}F) = 1.0$ Hz, 18H; CH_3), 0.18 ppm (s, 18H; CH_3); $^{13}C\{^1H\}$ NMR (100.63 MHz, $CDCl_3$): $\delta = 149.5$ (s; C_i), 134.1 (d, $^3J(^{13}C\text{-}^{19}F) = 4$ Hz; C_m), 129.3 (s; C_o), 127.6 (d, $^2J(^{13}C,^{19}F) = 14$ Hz; C_p), 27.3 (s; CH_3), 20.3 (d, $^2J(^{13}C,^{19}F) = 12$ Hz; CCH_3), 1.9 ppm (s; $SiCH_3$); ^{19}F NMR (282.38 MHz, $CDCl_3$): $\delta = -191.5$ ppm (s, $^1J(^{19}F,^{29}Si) = 298$ Hz); $^{29}Si\{^1H\}$ NMR (59.63 MHz, $CDCl_3$): $\delta = 14.5$ (d, $^1J(^{29}Si,^{19}F) = 298$ Hz; $(tBu)_2FSi$), 4.8 ppm (s, 2Si; $(CH_3)_3Si$); HR-MS: *m/z*: calcd for $C_{20}H_{40}FN^{28}Si_3$ 397.2447; found 397.2450; elemental analysis calcd (%) for $C_{20}H_{40}FNSi_3$: (397.79): C 60.4, H 10.1, N 3.5; found C 60.2, H 9.8, N 3.4.

***p*-Aminophenyl-di-*tert*-butylfluorosilane (3b)**: Gaseous HCl (10 molar equiv, freshly generated from NaCl and H_2SO_4) was slowly passed through a solution of **2b** (2.45 g, 6.16 mmol) in chloroform (50 mL) that was maintained under reflux. After completion of the reaction, the volatiles were evaporated under reduced pressure to leave a residue that was dried in vacuo (1×10^{-3} Torr) to afford 4-(di-*tert*-butylfluorosilanyl)-phenylamine hydrochloride as a white powder in quantitative yield (1.78 g). This white powder was dissolved in diethyl ether and the resulting solution was washed with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$ and filtered. Concentration of the filtrate in vacuo afforded **3b** (1.56 g) as an orange oil in quantitative yield. ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.57$ (d, $^3J(^1H,^1H) = 8$ Hz, 2H; H_m), 6.42 (d, $^3J(^1H,^1H) = 8$ Hz, 2H; H_o), 2.97 (br, 2H; NH_2), 1.19 ppm (d, $^4J(^1H,^{19}F) = 1$ Hz, 18H; CH_3); $^{13}C\{^1H\}$ NMR (75.48 MHz, C_6D_6): $\delta = 148.2$ (s; C_i), 135.2 (d, $^3J(^{13}C\text{-}^{19}F) = 4$ Hz; C_m), 120.3 (d, $^2J(^{13}C,^{19}F) = 14$ Hz; C_p), 114.4 (s; C_o), 27.4 (s; CH_3), 20.3 ppm (d, $^2J(^{13}C,^{19}F) = 12$ Hz; CCH_3); ^{19}F NMR (282.38 MHz, $CDCl_3$): $\delta = -190.7$ ppm (s, $^1J(^{19}F,^{29}Si) = 296$ Hz); $^{29}Si\{^1H\}$ NMR (59.63 MHz, $CDCl_3$): $\delta = 14.2$ ppm (d, $^1J(^{29}Si,^{19}F) = 296$ Hz); IR (KBr): $\tilde{\nu} = 3388$ (ν_s NH_2), 3475 cm^{-1} (ν_s NH_2); HR-MS: *m/z*: calcd for $C_{14}H_{24}FN^{28}Si$: 253.1657; found 253.1659; elemental analysis calcd (%) for $C_{14}H_{24}FNSi$ (253.43): C 66.4, H 9.6, N 5.5; found C 66.5, H 9.6, N 5.4.

Di-*tert*-butylfluoro(4-isothiocyanatophenyl)silane (4a): A solution of 4-(di-*tert*-butylfluorosilanyl)phenylamine (0.91 g, 3.6 mmol) in toluene (20 mL) was added dropwise to a solution of thiophosgene (14.4 mmol, 1.14 mL) in toluene (30 mL) at 0 °C.[13] The reaction mixture was then heated at reflux for 4 h. After the solution had been cooled to room temperature, the volatiles were removed in vacuo to afford **4a** as a dark-brown oil in quantitative yield (1.05 g). ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.59$ (d, $^3J(^1H,^1H) = 8$ Hz, 2H; H_m), 7.23 (d, $^3J(^1H,^1H) = 8$ Hz, 2H; H_o), 1.04 ppm (s, 18H; CH_3); $^{13}C\{^1H\}$ NMR (75.48 MHz, $CDCl_3$): $\delta = 136.1$ (s; NCS), 135.1 (d, $^3J(^{13}C,^{19}F) = 4$ Hz; C_m), 133.4 (d, $^2J(^{13}C,^{19}F) = 14$ Hz; C_p), 132.5 (s; C_i), 124.9 (s; C_o), 27.2 (s; CH_3), 20.3 ppm (d, $^2J(^{13}C,^{19}F) = 12$ Hz; CCH_3); ^{19}F NMR (282.38 MHz, $CDCl_3$): $\delta = -191.1$ ppm (s, $^1J(^{19}F,^{29}Si) = 297$ Hz); $^{29}Si\{^1H\}$ NMR (59.63 MHz, $CDCl_3$): $\delta = 14.2$ ppm (d, $^1J(^{29}Si,^{19}F) = 297$ Hz); IR (KBr): $\tilde{\nu} = 2092$ (CN), 732 cm^{-1} (CS); HR-MS: *m/z*: calcd for $C_{15}H_{22}FN^{32}S^{28}Si$: 295.1221; found 295.1227; elemental analysis calcd (%) for $C_{15}H_{22}FN^{32}S^{28}Si$ (295.49): C 60.9, H 7.5, N 4.7; found C 61.1, H 7.4, N 4.5.

Di-*tert*-butylfluoro(4-isocyanatophenyl)silane (4b): A solution of 4-(di-*tert*-butylfluorosilanyl)phenylamine (1.44 g, 5.7 mmol) in toluene (20 mL) was added dropwise to a 20% solution of phosgene in toluene (30 mL, 57 mmol) at 0 °C.[13] The reaction mixture was then heated at reflux for 4 h. After the solution had been cooled to room temperature, the volatiles were removed in vacuo to afford **4b** as a green-brown oil that solidified (1.42 g, 5.1 mmol, 89%). ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.56$ (d, $^3J(^1H,^1H) = 7.5$ Hz, 2H; H_m), 7.12 (d, $^3J(^1H,^1H) = 7.5$ Hz, 2H; H_o), 1.05 ppm (s, 18H; CH_3); $^{13}C\{^1H\}$ NMR (75.48 MHz, $CDCl_3$): $\delta = 135.2$ (d, $^3J(^{13}C,^{19}F) = 4$ Hz; C_m), 134.7 (s; C_i), 131.3 (d, $^2J(^{13}C,^{19}F) = 15$ Hz; C_p), 125.1 (s; C_o), 27.3 (s; CH_3), 20.2 ppm (d, $^2J(^{13}C,^{19}F) = 12$ Hz; CCH_3); ^{19}F NMR (282.38 MHz, $CDCl_3$): $\delta = -191.2$ ppm (s, $^1J(^{19}F,^{29}Si) = 298$ Hz); $^{29}Si\{^1H\}$ NMR (59.63 MHz, $CDCl_3$): $\delta = 14.2$ ppm (d, $^1J(^{29}Si,^{19}F) = 298$ Hz); IR (KBr): $\tilde{\nu} = 2263$ (C≡N), 1469 cm^{-1} (C=O); HR-MS: *m/z*: calcd for $C_{15}H_{22}OFN^{28}Si$: 279.1449; found 279.1423; elemental analysis calcd (%) for $C_{15}H_{22}FNOSi$ (279.43): C 64.5, H 7.9, N 5.0; found C 64.0, H 7.9, N 4.7.

1-[4-(Di-*tert*-butylfluorosilanyl)phenyl]pyrrole-2,5-dione (5): A two-necked flask fitted with a dropping funnel and a reflux condenser was charged with maleic anhydride (0.47 g, 4.8 mmol) and diethyl ether (20 mL).[14] The mixture was stirred magnetically until all of the maleic anhydride had dissolved. A solution of 4-(di-*tert*-butylfluorosilanyl)phenylamine (1.22 g, 4.8 mmol) in diethyl ether (5 mL) was then added by means of a dropping funnel to give a viscous suspension. This was stirred at room temperature for 1 h and then cooled to 10 °C. A cream-colored powder was precipitated, which was collected by filtration and used for subsequent reactions without further purification. ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.78$ (d, $^3J(^1H,^1H) = 7$ Hz, 2H; H_m), 7.65 (d, $^3J(^1H,^1H) = 7$ Hz, 2H; H_o), 6.69 (d, $^3J(^1H,^1H) = 13$ Hz, 1H; CH), 6.36 (d, $^3J(^1H,^1H) = 13$ Hz, 1H; CH), 1.05 ppm (s, 18H; CH_3); ^{19}F NMR (282.38 MHz, $CDCl_3$): $\delta = -191.2$ ppm (s, $^1J(^{19}F,^{29}Si) = 297$ Hz); $^{29}Si\{^1H\}$ NMR (59.63 MHz, $CDCl_3$): $\delta = 14.2$ ppm (d, $^1J(^{29}Si,^{19}F) = 297$ Hz).

A 50 mL flask was charged with acetic anhydride (5 mL) and anhydrous sodium acetate (0.5 g).[14] The acid (1.48 g, 4.2 mmol), obtained as described above, was added, and the resulting mixture was heated over a steam bath for 30 min to dissolve the suspended solids. After the reaction mixture had been cooled to room temperature, it was poured into iced water (50 mL) to precipitate the product, which was separated by filtration and washed with ice-cold water (3 × 10 mL) and with petroleum ether (20 mL, b.p. 30–60 °C). Recrystallization from *n*-hexane gave **5** as yellow needles (1.05 g, 3.16 mmol, 75%). M.p. 125–126 °C; ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.69$ (d, $^3J(^1H,^1H) = 7.5$ Hz, 2H; H_m), 7.38 (d, $^3J(^1H,^1H) = 7.5$ Hz, 2H; H_o), 6.85 (s, 2H; CH), 1.05 ppm (s, 18H; CH_3); $^{13}C\{^1H\}$ APT-NMR (75.48 MHz, $CDCl_3$): $\delta = 169.5$ (s; CO), 134.8 (d, $^3J(^{13}C,^{19}F) = 5$ Hz; C_m), 134.4 (s; CH), 133.7 (d, $^2J(^{13}C,^{19}F) = 15$ Hz; C_p), 132.6 (s; C_i), 124.8 (s; C_o), 27.4 (s; CH_3), 20.4 ppm (d, $^2J(^{13}C,^{19}F) = 12$ Hz; CCH_3); ^{19}F NMR (282.38 MHz, $CDCl_3$): $\delta = -191.2$ ppm (s, $^1J(^{19}F,^{29}Si) = 299$ Hz); $^{29}Si\{^1H\}$ NMR (59.63 MHz, $CDCl_3$): $\delta = 14.2$ ppm (d, $^1J(^{29}Si,^{19}F) = 299$ Hz); IR (KBr): $\tilde{\nu} = 1709$ cm^{-1} (C=O); HR-MS: *m/z*: calcd for $C_{18}H_{24}O_2FN^{28}Si$: 333.1555; found 333.1554; elemental analysis calcd (%) for $C_{18}H_{24}FNO_2Si$ (279.43): C 64.8, H 7.3, N 4.2; found C 64.5, H 7.3, N 4.0.

Di-*tert*-butyl{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}fluorosilane (2c): At −78 °C under magnetic stirring, a solution of *t*-butyllithium in

pentane (46.5 mL, 1.5 mol L^{-1}) was added to a solution of (4-bromobenzyloxy)(*tert*-butyl)dimethylsilane[15] (10 g, 33.2 mmol) in diethyl ether (200 mL). After the reaction mixture had been stirred for 30 min at −78 °C, the suspension obtained was added dropwise over a period of 30 min to a cooled (−78 °C) solution of di-*tert*-butyldifluorosilane (7.16 g, 39.7 mmol, 1.2 equiv) in diethyl ether (150 mL). The reaction mixture was allowed to warm to room temperature over a period of 12 h and then hydrolyzed with saturated aqueous NaCl solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×200 mL). The combined organic layers were dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to afford **2c** as a yellowish oil (12.4 g, 98%). It was used for subsequent reactions without further purification. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.57 (d, $^3J(^1H,^1H)$ = 7.8 Hz, 2H; H_m), 7.34 (d, $^3J(^1H,^1H)$ = 7.8 Hz, 2H; H_o), 4.76 (s, 2H; CH_2), 1.05 (s, 18H; CCH_3), 0.95 (s, 9H; CCH_3) 0.11 ppm (s, 6H; $SiCH_3$); ^{13}C{^{1}H} NMR (100.63 MHz, $CDCl_3$): δ = 142.7 (s; C_i), 133.8 (d, $^3J(^{13}C,^{19}F)$ = 4 Hz; C_m), 131.7 (d, $^2J(^{13}C,^{19}F)$ = 14 Hz; C_p), 125.1 (s; C_o), 64.7 (s; CH_2), 27.3 (s; CH_3), 26.1 (s; CCH_3), 25.9 (s; CH_3) 20.2 (d, $^2J(^{13}C,^{19}F)$ = 12 Hz; CCH_3), −5.0 ppm (s; $SiCH_3$); ^{19}F NMR (188.29 MHz, C_6D_6): δ = −189.9 ppm (s, $^1J(^{19}F,^{29}Si)$ = 298 Hz); HR-MS: *m/z*: calcd for $C_{21}H_{39}OF^{28}Si_2$: 382.2523; found 382.2528; elemental analysis calcd (%) for $C_{21}H_{39}FOSi_2$ (382.70): C 65.9, H 10.3; found C 66.1, H 9.8.

4-(Di-*tert*-butylfluorosilanyl)benzyl alcohol (3c): A catalytic amount of concentrated aqueous HCl was added to a suspension of **2c** (12 g, 31.4 mmol) in methanol (300 mL).[16] The reaction mixture was stirred for 18 h at room temperature and then the solvent and the volatiles were removed under reduced pressure. The residue was redissolved in diethyl ether (200 mL) and the solution was washed with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether (3×200 mL). The combined organic layers were dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to afford **3c** as a yellowish oil (7.7 g, 91%) that solidified (m.p. 82 °C). ^{1}H NMR (400.13 MHz, C_6D_6): δ = 7.67 (d, $^3J(^1H,^1H)$ = 7.7 Hz, 2H; H_m), 7.55 (d, $^3J(^1H,^1H)$ = 7.7 Hz, 2H; H_o), 4.33 (d, $^3J(^1H,^1H)$ = 4.6 Hz, 2H; CH_2), 1.21 (t, $^3J(^1H,^1H)$ = 4.6 Hz; OH), 1.11 ppm (s, 18H; CCH_3); ^{13}C{^{1}H} NMR (100.63 MHz, C_6D_6): δ = 143.0 (s; C_i), 134.0 (d, $^3J(^{13}C,^{19}F)$ = 4 Hz; C_m), 132.2 (d, $^2J(^{13}C,^{19}F)$ = 14 Hz; C_p), 125.9 (s; C_o), 64.4 (s; CH_2), 27.2 (s; CH_3), 20.0 ppm (d, $^2J(^{13}C,^{19}F)$ = 12 Hz; CCH_3); ^{19}F NMR (188.29 MHz, C_6D_6): δ = −189.2 ppm (s, $^1J(^{19}F,^{29}Si)$ = 298 Hz); IR (KBr): $\tilde{\nu}$ = 3296 cm^{-1} (OH); HR-MS: *m/z*: calcd for $C_{15}H_{25}OF^{28}Si$: 268.1653; found 268.1650; elemental analysis calcd (%) for $C_{15}H_{25}FOSi$ (268.44): C 67.1, H 9.4; found C 67.1, H 9.3.

4-(Di-*tert*-butylfluorosilyl)benzaldehyde (6): A solution of the alcohol **3c** (5.18 g, 19.3 mmol) in dichloromethane (100 mL) was added dropwise to a stirred ice-cooled solution of pyridinium chlorochromate (10.4 g, 48.2 mmol) in dry dichloromethane (250 mL).[17] After the reaction mixture had been stirred for 30 min at 0 °C and for 2.5 h at room temperature, anhydrous diethyl ether (250 mL) was added and the supernatant solution was decanted from the black gum-like material. The insoluble material was washed thoroughly with diethyl ether and the combined organic phases were passed through a short pad of silica gel. The solvents were removed in vacuo to yield aldehyde **6** as a yellowish oil (4.93 g, 18.5 mmol, 96%), the NMR, IR, and mass spectra of which were in accordance with the data reported in the literature.[6]

4-(Di-*tert*-butylfluorosilyl)benzoic acid (7): At room temperature, 1 M aqueous $KMnO_4$ (45 mL) was added to a mixture of **6** (2.0 g, 7.47 mmol), *tert*-butanol (45 mL), dichloromethane (5 mL), and 1.25 M $NaH_2PO_4{\cdot}H_2O$ buffer (30 mL) at pH 4.0–4.5.[18] After the mixture had been stirred for 25 min, it was cooled to 5 °C, whereupon excess $KMnO_4$ was added. The reaction was then quenched by the addition of saturated aqueous Na_2SO_3 solution (20 mL). Upon addition of 2 N HCl (37.5%), all of the MnO_2 dissolved. The resulting solution was extracted with diethyl ether (3× 150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a white solid, which was purified by recrystallization from Et_2O/*n*-hexane to give **7** (1.95 g, 93%, m.p. 203 °C). ^{1}H NMR (200.13 MHz, C_6D_6): δ = 8.08 (d, $^3J(^1H,^1H)$ = 8.1 Hz, 2H; H_m), 7.56 (d, $^3J(^1H,^1H)$ = 8.1 Hz, 2H; H_o), 0.96 ppm (d, $^4J(^1H,^1H)$ = 1.1 Hz, 18H; CCH_3); ^{13}C{^{1}H} NMR (100.63 MHz, C_6D_6): δ = 171.8 (s; COOH), 140.8 (d, $^2J(^{13}C,^{19}F)$ = 13 Hz; C_p), 133.9 (d, $^3J(^{13}C,^{19}F)$ = 4 Hz; C_m), 130.4 (s; C_i), 129.1 (s; C_o), 27.0 (s; CCH_3), 19.9 ppm (d, $^2J(^{13}C,^{19}F)$ = 12 Hz; CCH_3); ^{19}F NMR (188.29 MHz, C_6D_6): δ = −188.4 ppm (s, $^1J(^{19}F,^{29}Si)$ = 300 Hz); HR-MS: *m/z*: calcd for $[C_{15}H_{25}O_2F^{28}Si]^-$: 281.1379; found 281.1367; elemental analysis calcd (%) for $C_{15}H_{23}FO_2Si$ (282.43): C 63.8, H 8.2; found C 63.7, H 8.2.

2,5-Dioxopyrrolidin-1-yl 4-(di-*tert*-butylfluorosilyl)benzoate (8a): At room temperature, 1-ethyl-3-(3′-diaminopropyl)carbodiimide hydrochloride (EDCI) (0.65 g, 3.39 mmol) was added to a solution of the carboxylic acid **7** (0.87 g, 3.08 mmol) and 1-hydroxysuccinimide (HO-Su) in dimethylformamide (10 mL).[19] The reaction was monitored by thin-layer chromatography and the mixture was stirred until the starting material had been fully consumed. The addition of water led to the deposition of a precipitate, which was collected by filtration. The filtrate was extracted with diethyl ether. The organic layer was washed with saturated NaCl solution (30 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate in vacuo gave a residue, which was recrystallized from *n*-hexane to provide **8b** as colorless needles (0.96 g, 2.53 mmol, 82%). M.p. 43–44 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.11 (d, $^3J(^1H,^1H)$ = 8.0 Hz, 2H; H_m), 7.75 (d, $^3J(^1H,^1H)$ = 8.0 Hz, 2H; H_o), 2.89 (s, 4H; CH_2), 1.07 ppm (s, 18H; CCH_3); ^{13}C{^{1}H} NMR (100.63 MHz, $CDCl_3$): δ = 169.1 (s; CO), 161.8 (s; COO), 142.8 (d, $^2J(^{13}C,^{19}F)$ = 14 Hz; C_p), 134.2 (d, $^3J(^{13}C,^{19}F)$ = 4 Hz; C_m), 129.1 (s; C_i), 125.8 (s; C_o), 27.1 (s; CCH_3), 25.6 (s; CH_2), 20.1 ppm (d, $^2J(^{13}C,^{19}F)$ = 12 Hz; CCH_3); ^{19}F NMR (188.29 MHz, $CDCl_3$): δ = −188.9 ppm (s, $^1J(^{19}F,^{29}Si)$ = 298 Hz); HR-MS: *m/z*: calcd for $C_{19}H_{26}O_4NF^{28}Si$: 379.1609; found 379.1601; elemental analysis calcd (%) for $C_{19}H_{26}FNO_4Si$ (379.49): C 60.1, H 6.9, N 3.7; found C 60.2, H 6.8, N 3.4.

Pentafluorophenyl 4-(di-*tert*-butylfluorosilyl)benzoate (8b): 1,3-Dicyclohexylcarbodiimide (DCC) (0.4 g, 19.4 mmol) was added to a mixture of acid **7** (0.5 g, 1.77 mmol) and pentafluorophenol (0.36 g, 1.94 mmol) in dioxane (10 mL).[20] The reaction mixture was stirred for 1 h at room temperature. The dicyclohexylurea formed was filtered off and the filtrate was concentrated in vacuo. Recrystallization of the residue from *n*-hexane yielded **8b** (0.59 g, 1.3 mmol, 74%) as a white solid. M.p. 87 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.18 (d, $^3J(^1H,^1H)$ = 8.0 Hz, 2H; H_m), 7.80 (d, $^3J(^1H,^1H)$ = 8.0 Hz, 2H; H_o), 1.07 ppm (s, 18H; CCH_3); ^{13}C{^{1}H} NMR (100.63 MHz, $CDCl_3$): δ = 162.6 (s; COO), 142.6 (d, $^2J(^{13}C,^{19}F)$ = 14 Hz; C_p), 140.0, 139.5, 137.9 (m; C_{arom}, C_6F_5), 134.3 (d, $^3J(^{13}C,^{19}F)$ = 4 Hz; C_m), 129.3 (s; C_i), 127.8 (s; C_o), 125.3 (m; C_{arom}, C_6F_5), 27.1 (s; CCH_3), 20.1 ppm (d, $^2J(^{13}C,^{19}F)$ = 12 Hz; CCH_3); ^{19}F NMR (188.29 MHz, $CDCl_3$): δ = −152.8 (d, $^3J(^{19}F,^{19}F)$ = 17 Hz, 2F; F_o), −158.3 (t, $^3J(^{19}F,^{19}F)$ = 21 Hz, 1F; F_p), −162.8 (dt, $^3J(^{19}F,^{19}F)$ = 17 Hz, $^3J(^{19}F,^{19}F)$ = 21 Hz, 2F; F_m), −188.9 ppm (s, $^1J(^{19}F,^{29}Si)$ = 298 Hz, 1F; SiF); HR-MS: *m/z*: calcd for $[C_{21}H_{22}O_2F_6{}^{28}Si-C_4H_9]^+$: 391.0584; found 391.0564; elemental analysis calcd (%) for $C_{21}H_{22}F_6O_2Si$ (448.47): C 56.2, H 4.9; found C 56.5, H 5.3.

General procedure for the labeling of SiFA compounds 3a–8b (Table 2)

a) Preparation of $[^{18}F]F^-$/Kryptofix 2.2.2./K^+ complex for SiFA labeling: No-carrier-added (nca) aqueous [^{18}F]fluoride (5000–18000 MBq), which had been prepared by the $^{18}O(p,n)^{18}F$ nuclear reaction on an enriched [^{18}O]water (95%) target, was passed through a QMA cartridge (Waters, pre-activated with 1 N K_2CO_3 (5 mL) and water (10 mL)) and eluted with a solution of 1 N K_2CO_3 (10 μL) and Kryptofix 2.2.2. (10 mg) in CH_3CN/H_2O (900 μL:50 μL). The water was then completely removed from the mixture by co-evaporation with CH_3CN (2×1 mL) using a stream of nitrogen at 80 °C. The "dried" $[^{18}F]F^-$/Kryptofix 2.2.2./K^+ complex was dissolved in acetonitrile or DMSO (400–1000 μL) and this stock solution was used for labeling.

b) Preparation of $[n\mathrm{Bu_4N}]^{18}F$ using $[n\mathrm{Bu_4N}]HCO_3$ for SiFA labeling: Aqueous [^{18}F]fluoride (5000–18000 MBq), which had been prepared by the $^{18}O(p,n)^{18}F$ nuclear reaction on enriched [^{18}O]water (95%), was loaded onto a Chromafix PS-HCO_3 (GE Healthcare Europe) cartridge and eluted with a mixture of acetonitrile (800 μL) and aqueous tetrabutylammonium hydrogencarbonate solution (200 μL) (c = 0.075 mmol mL^{-1}, ABX, Radeberg, Germany). It was then azeotropically dried using acetonitrile (2×1 mL, stream of nitrogen, 80 °C). The "dried"

[nBu$_4$N][^{18}F] complex was dissolved in acetonitrile or DMSO (400–1000 μL) and this stock solution was used for labeling.

General procedure for the labeling of SiFA compounds: In a small Eppendorf tube (2 mL), the SiFA compound (for the amount, see Table 2) was dissolved in acetonitrile or DMSO, and then "dried" $^{18}F^-$ (in acetonitrile or DMSO, see Table 2) was added to give a total volume of 50–500 μL. The mixture was kept at room temperature for the appropriate time (Table 2), then diluted with water and passed over a pre-conditioned small reversed-phase solid-phase cartridge (10 mg HLB or SepPak light C-18, Waters). The cartridge was washed with water and eluted with acetonitrile, DMSO, or in the case of **5** for RSA labeling with ethanol (250 μL), to yield the SiFA compound for further labeling.

HPLC conditions: For the analysis of the reaction mixtures and quality control, Agilent series 1200 HPLCs equipped with multi-wavelength UV detectors and Raytest radioactivity detectors (Straubenhardt, Germany) were used. The columns used for the quality control of the labeled [^{18}F]**3a**–**8b** were Chromolith Performance RP-18 (100×4.6 mm) (Merck, Darmstadt, Germany) (flow rate: 4 mL min^{-1}; gradient from 100% water + 0.1% TFA to 100% acetonitrile + 0.1% TFA as eluent in 5 min). A Superdex 75 size-exclusion column (GE Healthcare Europe), eluted with 10 mM phosphate buffer at pH 7.2 (flow rate 1 mL min^{-1}), was used for the purification of the ^{18}F-labeled RSA.

Derivatization of RSA: Rat serum albumin (RSA) was labeled in a model experiment in order to investigate the in vivo stability, the distribution, and the metabolism of the SiFA compound **5**. RSA was dissolved in phosphate buffer (50 mM, pH 8) at a concentration of 10 mg mL^{-1} (150 nmol mL^{-1}). A 75 mM 2-iminothiolane stock solution was prepared by dissolving the derivatizing reagent (2.0 mg) in DMF (200 μL). An aliquot of the freshly prepared stock solution (10 μL, 10 equiv) was added to the protein solution (5 mg, 500 μL) and the mixture was allowed to react at room temperature for 1 h. The derivatized protein was purified on a Nap-5 column (equilibration buffer: PB 50 mM, pH 6.5) and was obtained in quantitative yield. The degree of sulfhydryl modification was determined by Ellman's assay, which revealed approximately two sulfhydryl groups per albumin molecule.

^{18}F Labeling of derivatized RSA with [^{18}F]5: The sulfhydryl-functionalized protein (5 mg) in phosphate buffer (1.0 mL, 50 mM, pH 6.5), as obtained from the protein derivatization step, was added to [^{18}F]**5** (250 μL of the aforementioned solution in ethanol) and the mixture was allowed to react at room temperature for 30 min without stirring. For purification, the mixture was applied to a gel-chromatography FPLC column (Superdex 75). The fraction containing the product (t_R = 14.9 min) was collected, sterile filtered, and used for the animal experiment.

Animal experiment: A male CD rat, housed according to German animal protection laws and protocols of the local committee, was used for the in vivo evaluation. The experiment was performed under inhalation anesthesia (oxygen 1.2 mL min^{-1}, isofluran 1.5 vol%) and with appropriate warming to prevent hypothermia. 6.5 MBq of [^{18}F]albumin was intravenously administered via a lateral tail vein. List mode data were acquired over 180 min using a Siemens Inveon 120 small animal PET system (Siemens Preclinical Imaging, Knoxville, TN, USA) and divided into temporal frames of increasing length varying from 10 s to 30 min for the assessment of temporal changes in regional tracer accumulation. Tomographic volumes were created using two iterations of 3D OSEM followed by 18 iterations of 3D MAP iterative reconstruction,[27] yielding a transaxial spatial resolution of approximately 1.4 mm.

[1] a) S. E. Snyder, M. Kilbourn, *Handbook of Radiopharmaceuticals Radiochemistry and Applications: Chemistry of Fluorine-18 Radiopharmaceuticals* (Eds.: M. Welch, C. S. Redvanly), Wiley, New York, **2003**; b) L. Cai, S. Lu, V. W. Pike, *Eur. J. Org. Chem.* **2008**, 2853–2873.

[2] For recent reviews, see: a) S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501–1516; b) R. Schirrmacher, C. Wängler, E. Schirrmacher, *Mini-Rev. Org. Chem.* **2007**, *4*, 317–329; c) P. Blower, *J. Dalton Trans.* **2006**, 1705–1711; d) R. Ting, M. J. Adam, T. J. Ruth, D. M. Perrin, *J. Am. Chem. Soc.* **2005**, *127*, 13094–13095; e) L. Mu, A. Höhne, P. A. Schubiger, S. M. Ametamey, K. Graham, L. E. Cyr, L. Dinkelborg, T. Stellfeld, A. Srinivasan, U. Voigtmann, U. Klar, *Angew. Chem.* **2008**, *120*, 5000–5003; *Angew. Chem. Int. Ed.* **2008**, *47*, 4922–4925.

[3] J. Marik, S. H. Hausner, L. A. Fix, K. J. Gagnon, J. L. Sutcliffe, *Bioconjugate Chem.* **2006**, *17*, 1017–1021.

[4] J. Marik, J. L. Sutcliffe, *Tetrahedron Lett.* **2006**, *47*, 6681–6684.

[5] M. Glaser, E. Arstad, *Bioconjugate Chem.* **2007**, *18*, 989–993.

[6] R. Schirrmacher, G. Bradtmöller, E. Schirrmacher, O. Thews, J. Tillmanns, T. Siessmeier, H.-G. Buchholz, P. Bartenstein, B. Wängler, C. M. Niemeyer, K. Jurkschat, *Angew. Chem.* **2006**, *118*, 6193–6197; *Angew. Chem. Int. Ed.* **2006**, *45*, 6047–6050.

[7] E. Schirrmacher, B. Wängler, M. Cypryk, G. Bradtmöller, M. Schäfer, M. Eisenhut, K. Jurkschat, R. Schirrmacher, *Bioconjugate Chem.* **2007**, *18*, 2085–2089.

[8] G. Bradtmöller, K. Jurkschat, M. Schürmann, *Acta Crystallogr. Sect. E* **2006**, *62*, o1393–o1394.

[9] M. C. Haberecht, H. Vitze, H.-W. Lerner, M. Bolte, *Acta Crystallogr. Sect. E* **2004**, *60*, o329–o330.

[10] a) A. Heppeler, S. Froidevaux, A. N. Eberle, H. R. Maecke, *Curr. Med. Chem.* **2000**, *7*, 971–994; G. Vaidyanathan, M. R. Zalutsky, *Int. J. Rad. Appl. Instrum. B* **1992**, *19*, 275–281; b) L. W. Herman, A. J. Fischmann, R. G. Tompkins, R. N. Hanson, C. Byon, H. W. Strauss, D. R. Elmaleh, *Nucl. Med. Biol.* **1994**, *21*, 1005–1010; c) Y. S. Chang, J. M. Jeong, Y. S. Lee, H. W. Kim, G. B. Rai, S. J. Lee, D. S. Lee, J. K. Chung, M. C. Lee, *Bioconjugate Chem.* **2005**, *16*, 1329–1333; d) B. De Bruin, B. Kuhnast, F. Hinnen, L. Yaouancq, M. Amessou, L. Johannes, A. Samson, R. Boisgard, B. Tavitian, F. Dolle, *Bioconjugate Chem.* **2005**, *16*, 406–411; e) L. Lang, W. C. Eckelman, *Appl. Radiat. Isot.* **1997**, *48*, 169–173; f) F. Dollé, F. B. L. Hinnen, R. Boisgard, A. F. R. M. Sanson, B. Tavitian, *J. Labelled Compd. Radiopharm.* **2003**, *46*, S15–S17; g) M. Berndt, J. Pietzsch, F. Wuest, *Nucl. Med. Biol.* **2007**, *34*, 5–15; h) R. R. Flawel, P. Kothar, M. Bar-Dagan, M. Synan, S. Vallabhajosula, J. M. Friedman, T. W. Muir, G. Ceccarini, *J. Am. Chem. Soc.* **2008**, *130*, 9106–9112; i) F. Wuest, M. Berndt, R. Bergmann, J. van den Hoff, J. Pietzsch, *Bioconjugate Chem.* **2008**, *19*, 1202–1210.

[11] a) A. Mustafa, W. Asker, S. Khattab, S. M. A. D. Zayed, *J. Org. Chem.* **1961**, *26*, 787–792; b) R. A. Abramovitch, L. Floch, *Heterocycles* **1981**, *15*, 391; c) M. Augustin, W. Müller, *J. Prakt. Chem. (Leipzig)* **1985**, *327*, 789–798.

[12] A. Brikh, C. Morin, *J. Organomet. Chem.* **1999**, *581*, 82–86.

[13] B. Rempfer, H. Oberhammer, N. Aunert, *J. Am. Chem. Soc.* **1986**, *108*, 3893–3897.

[14] J. R. Pratt, W. D. Massey, F. H. Pinkerton, S. F. Thames, *J. Org. Chem.* **1975**, *40*, 1090–1094.

[15] R. B. Weisenfeld, *J. Org. Chem.* **1986**, *51*, 2434–2436.

[16] M. P. Cava, A. A. Deana, K. Muth, M. J. Mitchell, *Org. Synth. Coll. Vol. 5*, **1973**, 944–945.

[17] M. Nassal, *Liebigs Ann. Chem.* **1983**, *9*, 1510–1523.

[18] P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, **1994**.

[19] K. Ito, H. Tanaka, *Chem. Pharm. Bull.* **1977**, *25*, 1732–1739.

[20] R. J. Heffner, J. Jiang, M. M. Joullie, *J. Am. Chem. Soc.* **1992**, *114*, 10181–10189.

[21] F. Fujisaki, M. Oishi, K. Sumoto, *Chem. Pharm. Bull.* **2007**, *55*, 124–127.

[22] L. A. Babadzhanova, N. V. Kirij, Y. L. Yagupolskii, W. Tyrra, D. Naumann, *Tetrahedron* **2005**, *61*, 1813–1819.

[23] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467.

[24] G. M. Sheldrick, SHELXL-97, University of Göttingen, Göttingen (Germany), **1997**.

[25] *International Tables for Crystallography, Vol. C*, Kluwer Academic, Dordrecht, **1992**.

[26] G. M. Sheldrick, SHELXTL Release 5.1, Software Reference Manual, Bruker AXS, Inc., Madison, Wisconsin, USA, **1997**.

[27] E. U. Mumcuoglu, R. Leahy, S. R. Cherry, Z. Zhou, *IEEE Trans. Med. Imag.* **1994**, *13*, 687–701.

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