Efficient Synthesis of 4-Fluoro-5-(perfluoroalkyl)pyrazoles from Organofluorosilicon Building Blocks[‡]

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A series of 4-fluoro-5-(perfluoroalkyl)pyrazoles has been prepared by heterocyclization of hemiperfluoroenones **3** or synthetic equivalents **1** and **2** with methylhydrazine. Compounds **1**–**3** were obtained by reaction of acylsilanes and perfluoroorganometallic reagents. The fluorinated pyrazoles could also be prepared in a one-pot reaction from the starting acylsilanes. This method is very general and has been applied to aromatic, aliphatic and carbohydrate derivatives, as well as to bis(pyrazole) derivatives. The reaction is completely regiospecific and the regiochemistry has been determined by HMBC correlations, ^{19}F-^{1}H and ^{1}H-^{1}H NOE and by comparison of chemical shifts and carbon-fluorine coupling constants of ring pyrazole carbon and fluorine atoms.

Introduction

Much attention has been devoted to the chemistry of heterocyclic compounds bearing fluorine atoms and/or polyfluoroalkyl groups, because they often have unique biological and physiological activities.[2] In particular, nitrogen-containing heterocyclic compounds play an important role in the medicinal and agrochemical fields.[3] Therefore, it is still of great significance to develop simple and effective methods for the synthesis of fluorine-containing azaheterocyclic compounds. Although there are good general reviews related to pyrazoles in the literature,[4] fluorine-containing pyrazoles have been less well studied.[5]

Previous papers in this series have demonstrated the versatility of the reaction of perfluoroorganometallic reagents with acylsilanes, leading to 1-(trialkylsilyl)perfluoroalkanols, 1-alkyl-1-(trialkylsilyloxy)perfluoro-1-alkenes and corresponding hemiperfluoroenones.[6] Treatment of these compounds with bis(nucleophiles) gave various nitrogen-containing heterocycles, such as imidazolidines/oxazolidines and diazepines/thiazepines.[7] This paper reports on a new series of pyrazoles bearing both a fluorine and a perfluoroalkyl substituent, in vicinal positions. These results demonstrate the usefulness and versatility of the chemistry of these mixed organofluorosilicon building blocks.[6,7]

4-Fluoropyrazoles have generally been prepared by treatment of hydrazines variously with fluoromalonaldehyde[8] or its bis(dialkyl acetals),[9] with β-fluorovinamidinium salts,[10] with 2,3,3-trifluoro-1-propenyl *p*-toluenesulfonates.[11] Irradiation of diazo derivatives gave also 4-fluoropyrazoles.[12] The synthesis of 4-fluoro-3-(perfluoroalkyl)pyrazoles has been reported starting from *N*-phenylsydnone and an excess of perfluoropropadiene,[13] from 1-perfluoroalkenyl phosphates[14] or from 2-fluoro-1,3-diketones and hydrazines.[15] In a preliminary paper, we mentioned the reaction of 1-(trimethylsilyl)perfluoroalkanols with methylhydrazine, giving good yields of polyfluorinated pyrazoles.[16]

Synthesis of Fluorinated Pyrazoles

Scheme 1 describes the overall process from perfluoroalkyl iodides and acylsilanes. Although a one-pot procedure from these compounds is possible, as shown later, most of the syntheses reported here used 1-(trialkylsilyl)perfluoroalkanols **1**, 1-alkyl-1-(trialkylsilyloxy)perfluoroalk-1-enes **2** and the corresponding hemiperfluoroenones **3** as starting materials. The reaction pathway (Scheme 1) indicates how, under the action of a base (here the hydrazine itself), alcohol **1** is transformed by a Brook rearrangement into the enoxysilane **2**. The latter reacts in situ with amine(here a hydrazine nitrogen moiety), giving the enone **3** by an S_N' substitution followed by the displacement of the amine by fluoride attack on the silicon atom. Then a Michael addition/elimination on the β-carbon atom by the nucleophilic function of the hydrazine gives an intermediate which is able to cyclize to 4-fluoropyrazoles **4** and/or **5** (Scheme 2). With suitable substituents on the silicon atom ($SiR^1_2R^2$ = TBS), enoxysilanes **2** can be isolated in high yields and, for some syntheses, the reaction sequence was begun with **2**. Hence, **1** and **2** act as synthetic equivalents of enones **3**. As previously mentioned, the better enone equivalent is alcohol **1** (R = Ar) for the aromatic series, and enoxysilane **2** (R = alkyl) for the aliphatic series.[6a,16]

[‡] Mixed Organofluorine−Organosilicon Chemistry, 11. − Part 10: Ref.[1]

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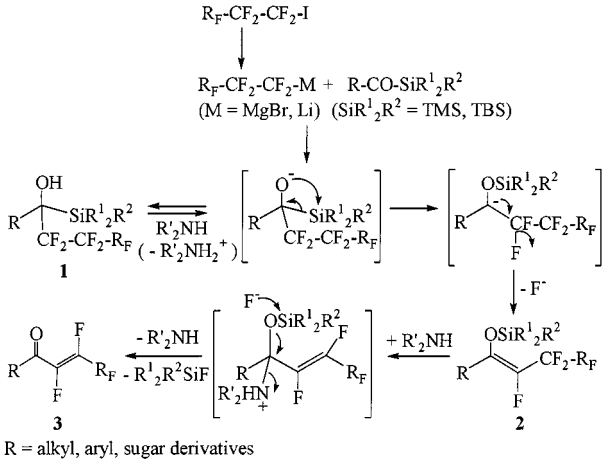
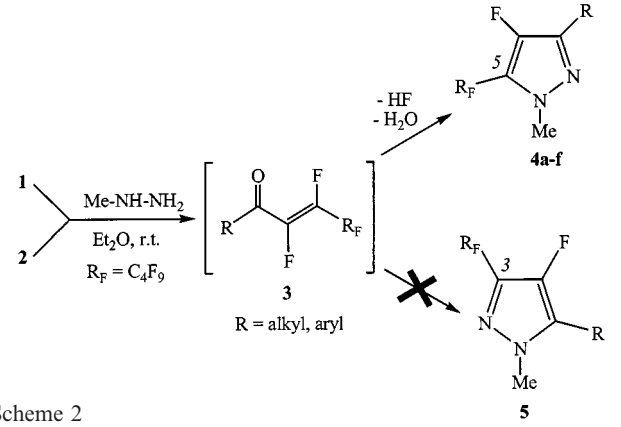


Scheme 1



Scheme 2

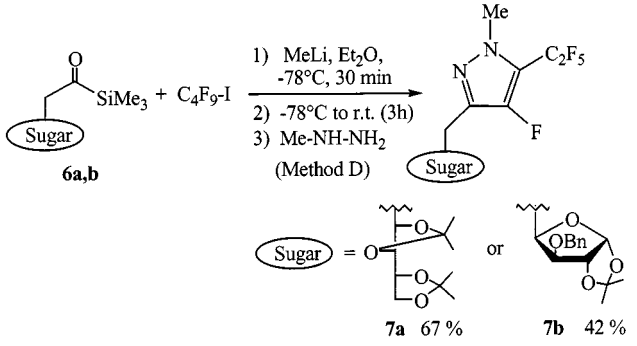
Pyrazoles **4a−f** were obtained under very mild and simple conditions, by mixing **1**, **2** or **3** (Method A, B, C, respectively) with methylhydrazine in ether (Scheme 2, Table 1). An excess of hydrazine was necessary to neutralize the hydrogen fluoride generated by the substitution. In the aromatic series, the reactions of alcohol **1** (R = Ar) and enone **3** (R = Ar) gave high yields of perfluoropyrazoles **4a−d** as single regioisomers. With aliphatic derivative **2** (R = *n*-C_5H_{11}), heterocyclization was quite efficient, but the yield of **4e** was lower (Table 1). A one-pot reaction (Method D) from acylsilane was also successfully performed and provided the pyrazole **4f** in good overall yield (69%).

This cyclocondensation was then extended to acylsilane derivatives of a racemic xylitol **6a** and a protected D-xylofuranose **6b**,[17] to give pyrazole rings attached to carbohydrate moieties (Scheme 3). The reaction was performed in a one-pot fashion (Method D) with moderate to good yields. The pyrazoles **7a** and **7b** were also obtained in two-step sequences (Method C) via the isolated intermediate enones, but the overall yields were equivalent to those resulting from the one-pot process.

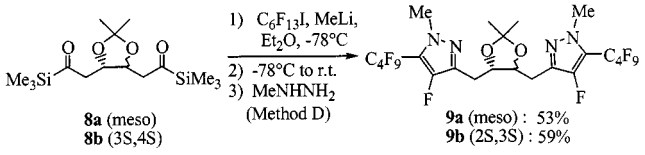
The one-pot procedure was also successfully applied to functionalized bis(acylsilanes) **8a** and **8b** (Scheme 4).[18] Bis-(pyrazole) derivatives **9a** and **9b** were obtained as single regioisomers, in good overall yields (53%, 59%), in the *meso* and the chiral series.

Table 1. Preparation of pyrazoles **4a−f**

Entry	Starting compound	R	Method	Pyrazole **4a-f**	Yield (%)
1	**1**	Ph	A	**4a**	95
2	**1**	p-Cl-Ph	A	**4b**	99
3	**1**	p-F-Ph	A	**4c**	74
4	**1**	p-OMe-Ph	A	**4d**	98
5	**3**	Ph	C	**4a**	95
6	**3**	p-Cl-Ph	C	**4b**	94
7	**3**	p-F-Ph	C	**4c**	89
8	**3**	p-OMe-Ph	C	**4d**	97
9	**2**	n-C_5H_{11}	B	**4e**	67
10	Acylsilane	n-C_8H_{17}	D	**4f**	69



Scheme 3



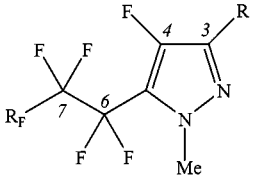
Scheme 4

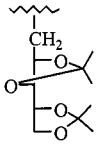
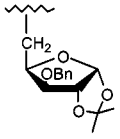
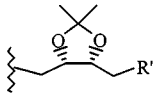
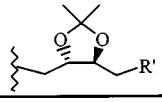
Structure of Fluorinated Pyrazoles

Only one regioisomer was observed, even in the crude mixtures (^{19}F and ^{1}H NMR). Signals between δ = −165 and −169 in the ^{19}F NMR spectra seem to correspond to 4-fluoropyrazoles.[15a] ^{13}C NMR spectroscopic data showed two doublets at δ ≈ 134−139 ($^{2}J_{C,F}$ = 4−10 Hz) and 147 ($^{1}J_{C,F}$ = 259−265 Hz), which were characteristic of C-3 and C-4 of the pyrazole ring, respectively (Table 2).

The major problem was to determine the regiochemistry. In principle, the heterocyclization of unsymmetrical bis-(electrophiles) **3** with methylhydrazine could give two regioisomers: the 5- and 3-(perfluoroalkyl)pyrazoles **4** and **5** (Scheme 2). Ishihara's group has already reported the synthesis of similar pyrazoles from fluorinated enol phosphates and hydrazines.[14] The authors claimed the formation of 3-(perfluoroalkyl)pyrazoles **5**, but no information was given about the determination of this regiochemistry. To confirm

Table 2. Selected ^{13}C, ^{19}F and ^{1}H chemical shifts and carbon-fluorine coupling constants of pyrazoles **4a−f**, **7a** and **7b**, and **9a** and **9b**



Cpd	R_F	R	Me-N	C3	C4	F6	F7	H1
4a	C_2F_5	Ph	40.2	137.0 $^2J_{C,F}$ 4.3	147.0 $^1J_{C,F}$ 265.3	-110.4	-123.8	3.87
4b	C_2F_5	p-Cl-Ph	40.3	135.9 $^2J_{C,F}$ 4.4	146.9 $^1J_{C,F}$ 265.3	-110.5	-123.7	3.97
4c	C_2F_5	p-F-Ph	40.2	136.1 $^2J_{C,F}$ 4.2	146.7 $^1J_{C,F}$ 263.8	-110.5	-123.7	4.00
4d	C_2F_5	p-MeO-Ph	40.1	136.9 $^2J_{C,F}$ 4.5	146.6 $^1J_{C,F}$ 263.6	-110.4	-123.7	3.95
4e	C_2F_5	n-C_5H_{11}	39.8	139.1 $^2J_{C,F}$ 9.0	147.4 $^1J_{C,F}$ 259.0	-110.4	-123.8	3.87
4f	C_2F_5	n-C_8H_{17}	39.6	139.0 $^2J_{C,F}$ 10.1	147.3 $^1J_{C,F}$ 259.7	-110.3	-123.7	3.83
7a	F		39.8	134.4	147.6 $^1J_{C,F}$ 259.9	-113.4	-85.5	3.87
7b	F		39.8	135.0	147.1 $^1J_{C,F}$ 259.4	-113.1	-85.3	3.84
9a	C_2F_5		39.6	134.5 $^2J_{C,F}$ 9.7	147.9 $^1J_{C,F}$ 260.8	-110.4	-123.7	3.89
9b	C_2F_5		39.9	134.5 $^2J_{C,F}$ 9.4	147.9 $^1J_{C,F}$ 260.6	-110.3	-123.7	3.90

the structures of pyrazoles **4a−f**, **7a** and 7**b**, and **9a** and **9b**, we recorded ^1H-^1H (COSY) and ^1H-^{13}C NMR spectra (HMQC, HMBC) for one member of each series (with particular attention paid to compounds **4f** and **9a**). Then, using ^{19}F, ^1H and ^{13}C NMR spectroscopic data (Table 2), we were able to produce reasonable assignments of the regiochemistry of all the pyrazoles. In its HMBC spectra (Figure 1), pyrazole **4f** showed an intense correlation ($^3J_{C5,MeN}$) between the C-5 and Me−N signals and a very weak one ($^4J_{C3,MeN}$) between the C-3 and Me−N signals.

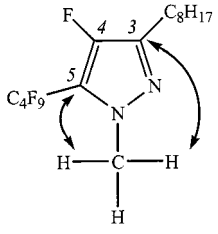


Figure 1. Selected HMBC correlations for compound **4f**

To confirm the regiochemistry of pyrazole **9a**, we performed three types of NMR experiments. Firstly, using HMBC spectra, we confirmed the presence of an intense correlation ($^3J_{C5,MeN}$) between the C-5 and Me−N signals

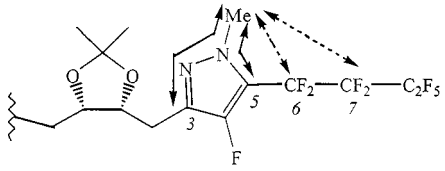


Figure 2. Selected HMBC correlations and ^1H-^{19}F NOE for compound **9a**

and a weak one ($^4J_{C3,MeN}$) between the C-3 and Me−N signals (Figure 2). Then we recorded ^1H-^{19}F NOE spectra. Irradiation of the N−Me protons at δ = 3.89 induced NOEs in the ^{19}F NMR spectrum on the adjacent fluorine atoms (6-F and 7-F), indicating a close relationship between the N−Me and the difluoromethylene groups (Figure 2).

Finally, we examined the homonuclear NOEs between the N−Me and α-methylene groups. Were we dealing with the 3-perfluoroalkyl regioisomer **10** (Figure 3), it would be possible to observe an NOE; if we had the 5-regioisomer **9a**, no NOE would be detected. Irradiation of the MeN group (δ = 3.89 in ^1H NMR) did not induce NOEs on the methylenic protons. This observation was a supplementary argument in favour of the 5-perfluoroalkyl isomer **9a**, even though it does not constitute a proof.

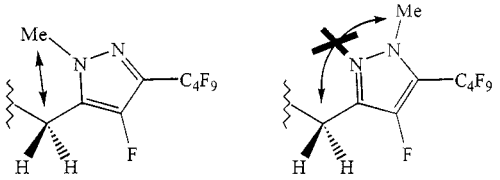
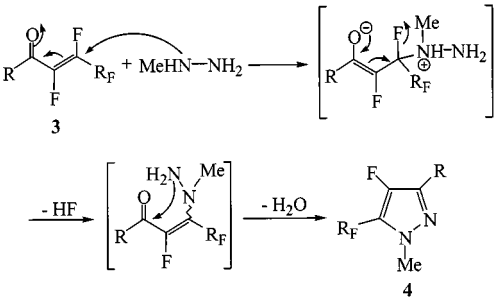


Figure 3. Selected ^{1}H-^{1}H NOE for pyrazoles **9a** and **10**

As shown in Table 2, we found for each member of the series (aromatic, aliphatic and sugar derivatives) close ^{13}C, ^{19}F and ^{1}H chemical shifts and carbon-fluorine coupling constants for the two annular carbon atoms (C-3 and C-4) and the two fluorine atoms (6-F and 7-F). These observations supported the regiochemical assignments for our 4-fluoro-5-(perfluoroalkyl)pyrazoles **4a−f**, **7a** and **7b**, and **9a** and **9b**.

Taking account of the high reactivity of enone **3** with amines, the substitution of the β-fluorine atom is initially induced by the N-1 atom of methylhydrazine, followed by cyclodehydration (Scheme 5).[4,19]



Scheme 5

Conclusion

We have developed a convenient synthetic method for the selective preparation of pyrazoles perfluoroalkylated at position 5 of the ring, starting from methylhydrazine and various equivalents for perfluoroenones **3**. This procedure was applied to pyrazoles **4a−f** and **7a** and **7b**, with a variety of substitution patterns (aromatic, aliphatic, and carbohydrate derivatives, various perfluoroalkyl chain lengths) and to bis-(pyrazoles) **9a** and **9b**. Electronic effects and the leaving group ability of fluorine activate substrates **1**, **2** and **3**, and dictate the regioselectivity of the reaction.

Experimental Section

Melting points are uncorrected. Optical rotations were determined with a Perkin−Elmer Model 241 polarimeter. FT-IR spectra were recorded with a MIDAC Corporation Spectrafile IR™ apparatus. ^{1}H, ^{13}C and ^{19}F spectra were recorded with a Bruker AC-250 or AC-500 with $CDCl_3$ as the solvent. Tetramethylsilane (δ = 0.00) or $CHCl_3$ (δ = 7.27) were used as internal standards for ^{1}H and ^{13}C NMR spectra, and $CFCl_3$ for ^{19}F NMR spectra. MS data were obtained with an AUTOSPEC (VG Instruments) apparatus at 70 eV in electron impact mode. Elemental analyses were performed with a Perkin−Elmer CHN 2400 apparatus. All reactions were monitored by TLC (Merck F 254 silica gel). Merck 9385 (40−63μm) silica gel was used for flash chromatography. All reactions were carried out under dry argon. THF was dried and freshly distilled from sodium/benzophenone. Ether (SDS Purex for analyses) was obtained from commercial sources and used without further purification. Aromatic and aliphatic acylsilanes and intermediates **1−3** were prepared according to the procedure reported in ref.[6] The acylsilane derivatives of racemic xylitol (**6a**) and of the protected D-xylofuranose (**6b**) were prepared according to the procedure reported in ref.[17]

Preparation of *meso*-3,4-*O*-Isopropylidene-1,6-bis(trimethylsilyl)hexane-1,6-dione (8a): The bis(acylsilane) **8a** was prepared by a multistep sequence involving treatment of 2-lithio-2-trimethylsilyl-1,3-dithiane with *meso*-1,3-butadiene diepoxide, acetalization and dethioketalization with iodine and calcium carbonate, according to the procedure described in ref.[18] − ^{1}H NMR: δ = 0.21 (s, 18 H, 2 $SiMe_3$), 1.37 (s, 6 H, 2 CH_3), 2.80 (dd, 2 H, $^2J_{H,H}$ = 17.2, $^3J_{H,H}$ = 5.0 Hz, 2 CH), 3.08 (ddd, 2 H, $^2J_{H,H}$ = 17.2, $^3J_{H,H}$ = 6.1, $^4J_{H,H}$ = 1.9 Hz, 2 CH), 4.07 (m, 2 H, 2 CH). − ^{13}C NMR: δ = −3.5 ($SiMe_3$), 26.9 (CH_3), 50.5 (CH_2), 75.8 (CH), 108.1 (C_4), 245.9 (CO). − IR (film): $\tilde{\nu}$ = 2986, 2959, 2901, 1644, 1406, 1372, 1250 cm^{-1}. − MS; *m/z*: 330 [M$^+$], 257, 230, 215, 186, 147, 131. − $C_{15}H_{30}O_4Si_2$: calcd. C 54.50, H 9.15; found C 54.74, H 8.91.

Preparation of (*S*,*S*)-3,4-*O*-Isopropylidene-1,6-bis(trimethylsilyl)hexane-1,6-dione (8b): The bis(acylsilane) **8b** was prepared by treatment of 2-lithio-2-trimethylsilyl-1,3-dithiane with *trans*-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol and dethioketalization with iodine and calcium carbonate, according to the procedure described in ref.[18] − ^{1}H NMR: δ = 0.21 (s, 18 H, 2 $SiMe_3$), 1.37 (s, 6 H, 2 CH_3), 2.79 (dd, 2 H, $^2J_{H,H}$ = 17.2, $^3J_{H,H}$ = 4.6 Hz, 2 CH), 3.08 (dd, 2 H, $^2J_{H,H}$ = 17.2, $^3J_{H,H}$ = 5.7, 2 CH), 4.08 (m, 2 H, 2 CH). − ^{13}C NMR: δ = −3.5 ($SiMe_3$), 26.9 (CH_3), 50.4 (CH_2), 75.7 (CH), 108.0 (C_4), 246.0 (CO). − IR (film): $\tilde{\nu}$ = 2959, 2901, 1644, 1406, 1372, 1250 cm^{-1}. − MS; *m/z*: 330 [M$^+$], 230, 186, 147, 113. − $C_{15}H_{30}O_4Si_2$: calcd. C 54.50, H 9.15; found C 54.61, H 9.23. − $[\alpha]_D^{21}$ = −56.4 (*c* = 0.52, $CHCl_3$).

General Procedures for the Synthesis of Pyrazoles

From 1-(Trialkylsilyl)perfluoroalkanol 1 (Method A): To a solution of **1** (0.6 mmol) in ether (5 mL) was added methylhydrazine (2 equiv., 1.2 mmol). The mixture was stirred at room temperature for 4 h and filtered. After solvent removal, compounds **4a−d** were purified by silica gel chromatography (petroleum ether/CH_2Cl_2, 70:30).

From 1-Alkyl-1-(trialkylsilyloxy)perfluoroalk-1-ene 2 (Method B): To a solution of **2** (0.2 mmol) in ether (2 mL) was added methylhydrazine (2 equiv., 0.4 mmol). The mixture was stirred at room temperature for one night and washed with water. After solvent removal, compound **4e** was purified by silica gel chromatography (petroleum ether/CH_2Cl_2, 90:10).

From Hemiperfluoroenone 3 (Method C): To a solution of **3** (0.6 mmol) in ether (5 mL) was added methylhydrazine (2 equiv., 1.2 mmol). The mixture was stirred at room temperature for 5 h and filtered. After solvent removal, compounds **4a−d** were purified by silica gel chromatography (petroleum ether/CH_2Cl_2, 70:30).

From Acylsilane and Perfluoroalkyl Iodide (One-Pot Reaction, Method D): To a solution of acylsilane (5.90 mmol, 1.0 equiv.) in ether (25 mL) was added freshly distilled perfluoroalkyl iodide (7.08 mmol, 1.2 equiv.). After cooling to −78 °C, a solution of

methyllithium (7.08 mmol, 1.2 equiv.) in ether was added dropwise. The mixture was stirred at −78 °C for 30 min and was then allowed to warm to room temperature (3 h). Methylhydrazine (29.50 mmol, 5 equiv.) was added and the resulting mixture was stirred overnight. After dilution with ether (50 mL) and hydrolysis with saturated aqueous NH_4Cl solution, the crude product was extracted with ether (5 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc/petroleum ether as eluent) to give pyrazoles **4f**, **7a** and **7b**, and **9a** and **9b**.

4-Fluoro-1-methyl-5-perfluorobutyl-3-phenylpyrazole (4a): ^{1}H NMR: δ = 3.95 (s, 3 H, CH_3−N), 7.7 (m, 5 H, Ph). − ^{13}C NMR: δ = 40.2 (s, CH_3), 112−117 (m, C_4F_9 + C-5), 119.3 (d, $^2J_{C,F}$ = 30.2 Hz, C-3), 127.9 (s, CH Ph), 129.1 (s, CH Ph), 133.2 (s, CH Ph), 141.8 (s, C_4 Ph), 147.0 (d, $^1J_{C,F}$ = 265.3 Hz, C-4). − ^{19}F NMR: δ = −81.5 (t, 3 F, $^3J_{F,F}$ = 9.4 Hz, CF_3), −110.5 (m, 2 F, CF_2), −123.7 (m, 2 F, CF_2), −126.5 (m, 2 F, CF_2), −164.4 (m, 1 F, F4). − IR (film): $\tilde{\nu}$ = 3010, 2970, 1590, 1450, 1350, 1220, 1140, 870 cm^{-1}. − MS; *m/z* (%): 394 (50) [M$^+$], 377, 225 (100), 182, 104, 77. − $C_{14}H_8F_{10}N_2$: calcd. C 42.66, H 2.07, N 7.11; found C 42.43, H 1.83, N 6.99.

3-(4′-Chlorophenyl)-4-fluoro-1-methyl-5-(perfluorobutyl)pyrazole (4b): ^{1}H NMR: δ = 3.97 (s, 3 H, CH_3−N), 7.40 (d, 2 H, $^3J_{H,H}$ = 8.0 Hz, Ar), 7.77 (d, 2 H, $^3J_{H,H}$ =8.0 Hz, Ar). − ^{13}C NMR: δ = 40.3 (s, CH_3), 105−125 (m, C_4F_9 + C-5), 127.2 (d, $^4J_{C,F}$ = 3.7 Hz, CH Ar), 128.1 (s, C_4 Ar), 129.0 (s, CH Ar), 134.5 (s, C_4 Ar), 135.9 (d, $^2J_{C,F}$ = 4.4 Hz, C-3), 146.9 (d, $^1J_{C,F}$ = 265.3 Hz, C-4). − ^{19}F NMR: δ = −81.4 (t, 3 F, $^3J_{F,F}$ = 9.4 Hz, CF_3), −110.5 (m, 2 F, CF_2), −123.7 (m, 2 F, CF_2), −126.5 (m, 2 F, CF_2), −165.3 (m, 1 F, F4). − IR (film): $\tilde{\nu}$ = 3000, 2980, 1580, 1540, 1450, 1430, 1350, 1310, 1230, 1020 cm^{-1}. − MS; *m/z* (%): 430 [M$^+$ + 2], 428 (65) [M$^+$], 262, 259 (100), 239, 216, 181, 129, 76.

4-Fluoro-3-(4′-fluorophenyl)-1-methyl-5-(perfluorobutyl)pyrazole (4c): ^{1}H NMR: δ = 4.00 (s, 3 H, CH_3−N), 7.14 (dd, 2 H, $^3J_{H,F}$ = 8.4, $^3J_{H,H}$ =8.4 Hz, Ar), 7.82 (dd, 2 H, $^3J_{H,H}$ =8.4, $^4J_{H,F}$ = 5.3 Hz, Ar). − ^{13}C NMR: δ = 40.2 (s, CH_3), 105−125 (m, C_4F_9 + C-5), 115.8 (d, $^2J_{C,F}$ = 22.0 Hz, CH Ar), 125.8 (s, C_4 Ar), 127.8 (d, $^3J_{C,F}$ = 5.8 Hz, CH Ar), 136.1 (d, $^2J_{C,F}$ = 4.2 Hz, C-3), 146.7 (d, $^1J_{C,F}$ = 263.8 Hz, C-4), 162.9 (d, $^1J_{C,F}$ = 247.8 Hz, C4′). − ^{19}F NMR: δ = −81.5 (t, 3 F, $^3J_{F,F}$ = 9.4 Hz, CF_3), −110.5 (m, 2 F, CF_2), −113.0 (m, 1 F, 4′-F), −123.7 (m, 2 F, CF_2), −126.5 (m, 2 F, CF_2), −164.9 (m, 1 F, 4-F). − IR (film): $\tilde{\nu}$ = 3000, 2980, 1610, 1600, 1580, 1450, 1350, 1310, 1230, 1050 cm^{-1}. − MS; *m/z* (%): 412 (75) [M$^+$], 395, 243 (100), 200, 122, 95. − $C_{14}H_7F_{11}N_2$: calcd. C 40.79, H 1.71, N 6.80; found C 40.74, H 1.53, N 6.74.

4-Fluoro-3-(4′-methoxyphenyl)-1-methyl-5-(perfluorobutyl)pyrazole (4d): ^{1}H NMR: δ = 3.83 (s, 3 H, CH_3−O), 3.95 (s, 3 H, CH_3−N), 6.95 (d, 2 H, $^3J_{H,H}$ = 9.0 Hz, Ar), 7.76 (d, 2 H, $^3J_{H,H}$ = 9.0 Hz, Ar). − ^{13}C NMR: δ = 40.1 (s, CH_3−N), 55.2 (s, CH_3−O), 110−120 (m, C_4F_9 + C-5), 114.2 (s, CH Ar), 122.3 (s, CH Ar), 127.4 (d, $^4J_{C,F}$ = 3.8 Hz, CH Ar), 136.9 (d, $^2J_{C,F}$ = 4.5 Hz, C-3), 146.6 (d, $^1J_{C,F}$ = 263.6 Hz, C-4), 159.9 (s, C-4′). − ^{19}F NMR: δ = −81.5 (t, 3 F, $^3J_{F,F}$ = 9.4 Hz, CF_3), −110.4 (m, 2 F, CF_2), −123.7 (m, 2 F, CF_2), −126.5 (m, 2 F, CF_2), −165.3 (m, 1 F, 4-F). − IR (film): $\tilde{\nu}$ = 3000, 2980, 1610, 1580, 1550, 1460, 1245, 1140 cm^{-1}. − MS; *m/z* (%): 424 (100) [M$^+$], 409, 381, 255, 212, 126, 107. − $C_{15}H_{10}F_{10}N_2O$: calcd. C 42.47, H 2.38, N 6.60; found C 42.12, H 2.17, N 6.44.

4-Fluoro-1-methyl-3-pentyl-5-(perfluorobutyl)pyrazole (4e): ^{1}H NMR: δ = 0.90 (t, 3 H, $^3J_{H,H}$ = 7 Hz, CH_3), 1.35 (m, 4 H, 2 CH_2), 1.65 (quint, 2 H, $^3J_{H,H}$ = 7 Hz, CH_2), 2.60 (t, 2 H, $^3J_{H,H}$ = 7 Hz, CH_2), 3.87 (s, 3 H, CH_3−N). − ^{13}C NMR: δ = 13.9 (s, CH_3), 22.3 (s, CH_2), 24.6 (s, CH_2), 28.1 (s, CH_2), 31.4 (s, CH_2), 39.8 (s, CH_3−N), 105−120 (m, C_4F_9 + C-5), 139.1 (d, $^2J_{C,F}$ = 9 Hz, C-3), 147.4 (d, $^1J_{C,F}$ = 259 Hz, C-4). − ^{19}F NMR: δ = −81.6 (t, 3 F, $^3J_{F,F}$ = 10 Hz, CF_3), −110.4 (m, 2 F, CF_2), −123.8 (m, 2 F, CF_2), −126.7 (m, 2 F, CF_2), −168.6 (m, 1 F, 4-F). − IR (film): $\tilde{\nu}$ = 2920, 2850, 1520, 1455, 1420, 1345, 1315, 1210, 1140 cm^{-1}. − MS; *m/z* (%): 388 (9) [M$^+$], 359, 345, 332 (100), 331, 317, 169, 162. − $C_{13}H_{14}F_{10}N_2$: calcd. C 40.22, H 3.63, N 7.22; found C 40.30, H 3.44, N 7.07.

4-Fluoro-1-methyl-3-octyl-5-(perfluorobutyl)pyrazole (4f): ^{1}H NMR: δ = 0.84 (t, 3 H, $^3J_{H,H}$ = 6.7 Hz, CH_3), 1.2−1.4 (m, 10 H, 5 CH_2), 1.61 (m, 2 H, CH_2), 2.56 (t, 2 H, $^3J_{H,H}$ = 7.8 Hz, CH_2), 3.83 (s, 3 H, CH_3−N). − ^{13}C NMR: δ = 13.9 (s, CH_3), 22.5 (s, CH_2), 24.5 (d, $^3J_{C,F}$ = 2.6 Hz, CH_2), 28.3 (s, CH_2), 29.07 (s, CH_2), 29.10 (s, CH_2), 29.12 (s, CH_2), 31.7 (s, CH_2), 39.6 (s, CH_3−N), 105−115 (m, 3 CF_2), 115.4 (td, $^2J_{C,F}$ = 30.7, $^2J_{C,F}$ = 20.1 Hz, C-5), 117.3 (qt, $^1J_{C,F}$ = 288.6, $^2J_{C,F}$ = 33.5 Hz, CF_3), 139.0 (d, $^2J_{C,F}$ = 10.1 Hz, C-3), 147.3 (d, $^1J_{C,F}$ = 259.7 Hz, C-4). − ^{19}F NMR: δ = −81.4 (t, 3 F, $^3J_{F,F}$ = 9.5 Hz, CF_3), −110.3 (m, 2 F, CF_2), −123.7 (m, 2 F, CF_2), −126.6 (m, 2 F, CF_2), −168.4 (m, 1 F, 4-F). − IR (film): $\tilde{\nu}$ = 2930, 2859, 1586, 1532, 1462, 1354, 1237 cm^{-1}. − MS; *m/z* (%): 430 (35) [M$^+$], 387, 345, 332 (100), 211, 162. − HRMS; *m/z* calcd. for $C_{16}H_{20}F_{10}N_2$ 430.1467; found 430.1466.

3-(1′-Deoxy-2′,3′,4′,5′-di-*O*-isopropylidenexylityl)-4-fluoro-1-methyl-5-(perfluoroethyl)pyrazole (7a): ^{1}H NMR: δ = 1.27 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 2.81 (dd, 1 H, $^2J_{H,H}$ = 14.9, $^3J_{H,H}$ = 6.1 Hz, H5′), 2.91 (dd, 1 H, $^2J_{H,H}$ = 14.9, $^3J_{H,H}$ = 4.9 Hz, 5′-H), 3.78 (m, 2 H, 1′-H), 3.89 (s, 3 H, CH_3−N), 3.95 (dd, 1 H, $^3J_{H,H}$ = 6.5, $^3J_{H,H}$ = 8.0 Hz, 3′-H), 4.05 (td, 1 H, $^3J_{H,H}$ = 6.8, $^3J_{H,H}$ = 4.5 Hz, 2′-H), 4.21 (m, 1 H, 4′-H). − ^{13}C NMR: δ = 25.3 (s, CH_3), 26.0 (s, CH_3), 26.9 (s, CH_3), 27.0 (s, CH_3), 28.6 (m, CH_2, C-1′), 39.8 (s, CH_3−N), 65.5 (s, CH_2, C-5′), 74.9 (s, CH, C-4′), 75.3 (s, CH, C-2′), 79.7 (s, CH, C-3′), 105−115 (m, CF_2), 109.6 (s, C_4 isopropylidene), 109.7 (s, C_4 isopropylidene), 118.4 (qt, $^1J_{C,F}$ = 286.5, $^2J_{C,F}$ = 38.4 Hz, CF_3), 134.4 (m, C-5), 134.6 (m, C-3), 147.6 (d, $^1J_{C,F}$ = 259.9 Hz, C-4). − ^{19}F NMR δ = −85.5 (m, 3 F, CF_3), −113.4 (m, 2 F, CF_2), −167.0 (m, 1 F, 4-F). − IR (film): $\tilde{\nu}$ = 2990, 1591, 1458, 1383, 1223, 1157, 1097, 1072, 982 cm^{-1}. − MS; *m/z* (%): 433 (29) [M$^+$], 331, 313, 271, 217, 201, 143 (100). − $C_{17}H_{22}F_6N_2O_4$: calcd. C 47.34, H 4.91, N 6.49; found C 47.64, H 5.04, N 6.19.

3-(3′-*O*-Benzyl-5′-deoxy-1′,2′-*O*-isopropylidene-α-D-xylofuranosyl)-4-fluoro-1-methyl-5-(perfluorethyl)pyrazole (7b): ^{1}H NMR: δ = 1.35 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 3.00 (dd, 1 H, $^2J_{H,H}$ = 14.9, $^3J_{H,H}$ = 7.2 Hz, 5′-H), 3.10 (dd, 1 H, $^2J_{H,H}$ = 14.9, $^3J_{H,H}$ = 6.8 Hz, 5′-H), 3.84 (s, 3 H, CH_3−N), 3.92 (d, 1 H, $^3J_{H,H}$ = 3.0 Hz, 3′-H), 4.49 (d, 1 H, $^2J_{H,H'}$ = 12.0 Hz, H_{Bn}), 4.54 (dt, 1 H, $^3J_{H,H}$ = 7.2, $^3J_{H,H}$ = 3.0 Hz, 4-H), 4.65 (d, 1 H, $^3J_{H,H}$ = 3.8 Hz, 2′-H), 4.68 (d, 1 H, $^2J_{H',H}$ = 12.0 Hz, H_{Bn}), 5.95 (d, 1 H, $^3J_{H,H}$ = 3.8 Hz, 1′-H), 7.3−7.4 (m, 5 H, H arom.). − ^{13}C NMR: δ = 23.5 (s, CH_2, C-5′), 26.2 (s, CH_3), 26.7 (s, CH_3), 39.8 (s, CH_3−N), 71.8 (s, CH_{2Bn}), 78.6 (s, CH, C-4′), 81.7 (s, CH, C-3′), 82.2 (s, CH, C-2′), 104.9 (s, CH, C-1′), 105−115 (m, CF_2), 111.5 (s, C_4 isopropylidene), 118.0 (qt, $^1J_{C,F}$ = 286.9, $^2J_{C,F}$ = 38.4 Hz, CF_3), 127.8−128.3 (3 C, CH arom.), 135.0 (m, C-5), 135.2 (m, C-3), 137.4 (s, C_4 arom.), 147.1 (d, $^1J_{C,F}$ = 259.4 Hz, C-4). − ^{19}F NMR: δ = −85.3 (m, 3 F, CF_3), −113.1 (m, 2 F, CF_2), −167.8 (m, 1 F, 4-F). − IR (film): $\tilde{\nu}$ = 2990, 1734, 1583, 1541, 1458, 1375, 1215, 1097, 972 cm^{-1}. − MS; *m/z* (%): 481 (60) [M$^+$], 422, 315, 231 (100), 162. − $C_{21}H_{22}F_6N_2O_4$: calcd. C 52.50, H 4.61, N 5.83; found C 52.31, H 4.86, N 5.54. − $[\alpha]_D^{21}$ = −46.6 (*c* = 0.73, $CHCl_3$).

1,4-Bis(4′-fluoro-1′-methyl-5′-perfluorobutyl-3′-pyrazoyl)-2,3-isopropylidenedioxybutane (*meso* Compound 9a): ^{1}H NMR: δ = 1.34 (s, 6 H, 2 CH_3), 2.87 (m, 4 H, 2 CH_2), 3.89 (s, 6 H, 2 CH_3−N), 4.10 (m, 2 H, 2 CH). − ^{13}C NMR: δ = 26.9 (s, CH_3), 28.1 (s, CH_2), 39.6 (s, CH_3−N), 78.3 (s, CH), 109.1 (s, C_4 isopropylidene), 104−112 (m, 2 CF_2), 112.5 (tt, $^1J_{C,F}$ = 258.3, $^2J_{C,F}$ = 34.4 Hz, CF_2), 115−116 (m, C-5′), 117.3 (qt, $^1J_{C,F}$ = 287.7, $^2J_{C,F}$ = 33.3 Hz, CF_3), 134.5 (d, $^2J_{C,F}$ = 9.7 Hz, C-3′), 147.9 (d, $^1J_{C,F}$ = 260.8 Hz, C-4′). − ^{19}F NMR: δ = −81.4 (t, 6 F, $^3J_{F,F}$ = 10.6 Hz, 2 CF_3), −110.4 (t, 4 F, $^3J_{F,F}$ = 11.9 Hz, 2 CF_2), −123.7 (m, 4 F, 2 CF_2), −126.5 (m, 4 F, 2 CF_2), −167.1 (m, 2 F, 4′-F). − IR (film): $\tilde{\nu}$ = 2934, 1462, 1352, 1321, 1207, 1136 cm^{-1}. − MS; *m/z* (%): 762 (3) [M^+], 747, 704, 687, 431, 413, 373, 345 (100), 331, 175. − HRMS; *m/z* calcd. for $C_{23}H_{18}F_{20}N_4O_2$ 762.1103; found 762.1094.

(*S*,*S*)-1,4-Bis(4′-fluoro-1′-methyl-5′-perfluorobutyl-3′-pyrazoyl)-2,3-isopropylidenedioxybutane (9b): ^{1}H NMR: δ = 1.35 (s, 6 H, 2 CH_3), 2.88 (m, 4 H, 2 CH_2), 3.90 (s, 6 H, 2 CH_3−N), 4.10 (m, 2 H, 2 CH). − ^{13}C NMR: δ = 27.0 (s, CH_3), 28.2 (s, CH_2), 39.9 (s, CH_3−N), 78.4 (s, CH), 109.2 (s, C_4 isopropylidene), 100−125 (m, C_4F_9 + C-5′), 134.5 (d, $^2J_{C,F}$ = 9.4 Hz, C-3′), 147.9 (d, $^1J_{C,F}$ = 260.6 Hz, C-4′). − ^{19}F NMR: δ = −81.4 (t, 6 F, $^3J_{F,F}$ = 9.5 Hz, 2 CF_3), −110.3 (m, 4 F, 2 CF_2), −123.7 (m, 4 F, 2 CF_2), −126.5 (m, 4 F, 2 CF_2), −167.1 (m, 2 F, 4′-F). − IR (film): $\tilde{\nu}$ = 2990, 2938, 1586, 1537, 1462, 1354, 1210 cm^{-1}. − MS; *m/z* (%): 762 (3) [M^+], 747, 431, 373, 345 (100), 331, 175, 162. − HRMS; *m/z* calcd. for $C_{23}H_{18}F_{20}N_4O_2$ 762.1103; found 762.1095. − $[\alpha]_D^{21}$ = −1.9 (*c* = 0.66, $CHCl_3$).

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[1] O. Lefebvre, T. Brigaud, C. Portella, *Tetrahedron* **1999**, *55*, 7233.
[2] [2a] J. T. Welch, *Tetrahedron* **1987**, *43*, 3123. − [2b] R. Filler, Y. Kobayashi, *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha and Elsevier Biomedical, Tokyo and New York, **1982**.
[3] For a review see: B. Roth, C. C. Cheng, *Prog. Med. Chem.* **1982**, *19*, 270.
[4] [4a] T. Eicher, S. Hauptmann in *The Chemistry of Heterocycles: Structure, Reactions, Syntheses and Applications*, Georg Thieme Verlag, Stuttgart, **1995**, p. 179. − [4b] J. Elguero in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt, **1984**, vol. 5, p. 169. − [4c] M. R. Grimmett in *Comprehensive Organic Chemistry* (Eds.: D. Barton, W. D. Ollis), Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt, **1979**, vol. 4, p. 357.
[5] [5a] J. Elguero, A. Fruchier, N. Jagerovic, A. Werner, *Org. Prep. Proc. Int.* **1995**, *27*, 33. − [5b] K. Burger, U. Wucherpfennig, E. Brunner, *Adv. Het. Chem.* **1994**, *60*, 1. − [5c] P. Bravo, D. Diliddo, G. Resnati, *Tetrahedron* **1994**, *50*, 8827. − [5d] X.-Q. Tang, C.-M. Hu, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2161. − [5e] I. I. Gerus, M. G. Gorbunova, V. P. Kukhar, *J. Fluorine Chem.* **1994**, *69*, 195. − [5f] M. Soufyane, C. Mirand, J. Lévy, *Tetrahedron Lett.* **1993**, *34*, 7737. − [5g] J.-P. Bouillon, C. Ates, Z. Janousek, H. G. Viehe, *Tetrahedron Lett.* **1993**, *34*, 5075. − [5h] B. C. Hamper, M. L. Kurtzweil, J. P. Beck, *J. Org. Chem.* **1992**, *57*, 5680.
[6] [6a] C. Portella, B. Dondy, *Tetrahedron Lett.* **1991**, *32*, 83. − [6b] B. Dondy, P. Doussot, C. Portella, *Synthesis* **1992**, 995. − [6c] B. Dondy, C. Portella, *J. Org. Chem.* **1993**, *58*, 6671. − [6d] P. Doussot, C. Portella, *J. Org. Chem.* **1993**, *58*, 6675.
[7] B. Dondy, P. Doussot, M. Iznaden, M. Muzard, C. Portella, *Tetrahedron Lett.* **1994**, *35*, 4357.
[8] [8a] C. Reichardt, K. Halbritter (Schering A. −G.), *Ger. Offen.* **1970**, 2016990; *Chem. Abstr.* **1972**, *76*, 46229. − [8b] C. Reichardt, K. Halbritter, *Liebigs Ann. Chem.* **1975**, 470.
[9] H. Molines, C. Wakselman, *J. Org. Chem.* **1989**, *54*, 5618.
[10] X. Shi, T. Ishihara, H. Yamanaka, J. T. Gupton, *Tetrahedron Lett.* **1995**, *36*, 1527.
[11] K. Funabiki, T. Ohtsuki, T. Ishihara, H. Yamanaka, *Chem. Lett*. **1995**, 239.
[12] J. Vilarrasa, C. Galvez, M. Calofell, *An. Quim.* **1975**, *71*, 631.
[13] G. B. Blackwell, R. N. Haszeldine, D. R. Taylor, *J. Chem. Soc., Perkin Trans.1* **1982**, 2207.
[14] [14a] T. Ishihara, Y. Okada, M. Kuroboshi, T. Shinozaki, T. Ando, *Chem. Lett*. **1988**, 819. − [14b] T. Ishihara (Mitsui Toatsu Chemicals, Inc.), *Jpn. Kokai Tokkyo Koho JP* **1989**, 0122855; *Chem. Abstr.* **1989**, *111*, 134144.
[15] [15a] C. L. Bumgardner, J. C. Sloop, *J. Fluorine Chem.* **1992**, *56*, 141. − [15b] T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecka, J. M. Miyashino, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347.
[16] B. Dondy, P. Doussot, C. Portella, *Tetrahedron Lett.* **1994**, *35*, 409.
[17] R. Plantier-Royon, C. Portella, *Tetrahedron Lett.* **1996**, *37*, 6113.
[18] Bis(acylsilanes) **8a** and **8b** were each prepared by a multi-step sequence according to the procedure described in: J.-P. Bouillon, C. Portella, *Tetrahedron Lett.* **1997**, *38*, 6595..
[19] W.-D. Rudorf, M. Augstin, *J. Prakt. Chem.* **1978**, *320*, 585.

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