PERFLUOROALKYLATION OF 6-IODOPURINES BY TRIMETHYL(PERFLUOROALKYL)SILANES. SYNTHESIS OF 6-(PERFLUOROALKYL)PURINE BASES, NUCLEOSIDES AND ACYCLIC NUCLEOTIDE ANALOGUES

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Dedicated to the memory of Dr Miroslav Protiva.

A CuI/KF mediated perfluoroalkylation reaction of various 9-substituted 6-iodopurines **1** with trimethyl(trifluoromethyl)silane or heptafluoropropyl(trimethyl)silane was used for the synthesis of the corresponding 6-(trifluoromethyl)- and 6-(heptafluoropropyl)purine derivatives (purine bases, nucleosides and acyclic nucleotide analogues) in moderate to good yields.

Key words: Purines; Nucleosides; Cross-coupling reactions; Trifluoromethylation; Perfluoroalkylation; Cuprates; Fluorinated compounds; Cytostatic activity.

Purine bases modified in the 6-position and their nucleoside and nucleotide derivatives and analogues possess a broad spectrum of biological activity. The cytotoxicity of 6-methylpurine and its nucleosides is well known[1], while a promising cytostatic activity of 6-(alkylamino)purine derivatives (as cytokinines analogues) has been recently discovered[2]. Many 6-(alkylamino)purine nucleosides are important adenosine receptors antagonists[3] and acyclic nucleotide analogues derived from 6-[(di)alkylamino]purines are strong antivirals, antineoplastic agents and immunomodulators[4].

Fluorinated analogues of natural compounds exert interesting biological activity[5]. Also fluorinated derivatives of nucleosides have been studied, in particular antineoplastic 5-fluorouracil[6] and its nucleosides, antiviral 5-(trifluoromethyl)uracil nucleosides[7], antitumor 2-fluoroadenine nucleosides[8], as well as nucleosides with fluorinated sugar moiety[9]. Reactive 2- and 6-fluoropurine derivatives are good starting compounds for nucleophilic substitution reactions[10]. 2-Trifluoromethyl-[11] and 8-trifluoromethyl-

purine[12] derivatives are easily prepared by heterocyclization of 5,6-diaminopyrimidines or 4-aminoimidazole-5-carboxylic acid derivatives by trifluoroacetates and are reported to possess interesting antirhinovirus, vasodepressor, platelet aggregation inhibitory, phosphodiesterase inhibitory and antitumor activity. 2-(Trifluoromethyl)adenosine analogues were also prepared[13] by trifluoromethylation of 2-iodoadenosines by trifluoromethylzinc bromide and CuBr in DMF/HMPA. 6-Fluoroalkylated purines are quite rare in the literature. 6-(Trifluoromethyl)purine and 2-amino-6-(trifluoromethyl)purine were prepared by multistep cyclization procedures[14] starting from ethyl 4,4,4-trifluoro-3-oxobutanoate in low overall yields (3 and 6%, respectively). Trifluoromethylation of protected 6-iodopurine riboside with trifluoromethyl iodide and copper metal in HMPA gave[15] the 6-(trifluoromethyl)purine derivative in moderate yield; the final 6-(trifluoromethyl)purine riboside was reported to exhibit a moderate cytotostatic activity. Except for the above mentioned example, biological activity of any 6-(fluoroalkyl)purine derivative has not been published so far.

In this paper we report on the attempts to develop a versatile trifluoromethylation and perfluoroalkylation of 6-halopurines, the use of that methodology for the synthesis of 6-(trifluoromethyl)- and 6-(perfluoroalkyl)purine bases, nucleosides and acyclic nucleotide analogues, as well as on the biological activity of the products.

RESULTS AND DISCUSSION

In the last decade, with the development of the cross-coupling methodology, many 6-*C*-substituted purines have been prepared[16]. Thus, 6-halopurine derivatives react with alkyl(aryl)zinc or tin reagents[16a–16e], trialkylaluminum[16f] or alkylcuprates[16g,16h] to give the 6-alkylpurine derivatives. Also reverse approach based on the reaction of purine-6-zinc iodide with aryl or vinyl halides has recently been described[17].

For the synthesis of the 6-(perfluoroalkyl)purine derivatives, our first attempts focussed on the application of the copper-mediated cross-coupling reactions[15,18] of 6-iodopurines with perfluoroalkyl iodides. In a model experiment, we treated perfluorobutyl iodide (as an example of a stable, cheap and high-boiling perfluoroalkyl iodide) with 6-iodo-9-(tetrahydropyran-2-yl)purine and copper in DMF at 120 °C for 24 h (conditions analogous to the published procedures[18]); however, no reaction took place. Though the problem certainly consists in the activity of the copper metal

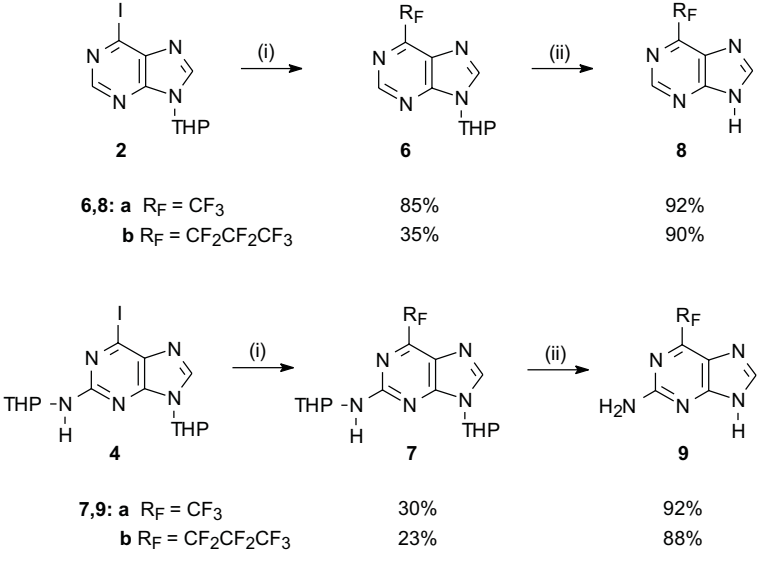
used, the lack of reactivity was not overcome even with the use of the activated copper[18a].

For the systematic structure–activity relationship studies of a series of target 6-(perfluoroalkyl)purine derivatives, there was a need to develop a facile, reproducible synthetic method for the perfluoroalkylation of purines using commercially available reagents. Therefore we investigated the copper(I) iodide/potassium fluoride mediated cross-coupling reactions[19] of trimethyl(perfluoroalkyl)silanes with 6-halopurines. In the general procedure, the 6-halopurine derivative was treated with trimethyl(perfluoroalkyl)silane (aproximately 1.5 equivalent), KF and CuI in a mixture of DMF and *N*-methylpyrrolidin-2-one (NMP) in a septum-sealed glass vial at 60 °C for 20 h. The first experiments designed to evaluate the reactivity of a series of 6-halopurine derivatives towards trimethyl(trifluoromethyl)silane (**1a**) revealed that all the 6-chloropurine derivatives (6-chloropurine, 6-chloro-9-(tetrahydropyran-2-yl)purine, 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purine and their 2-amino derivatives), as well as the 6-iodopurine bases (6-iodopurine and 2-amino-6-iodopurine) are entirely unreactive, whereas the use of the 9-(tetrahydropyran-2-yl)- (THP) protected 6-iodopurine **2** afforded the 6-trifluoromethyl derivative **6a** in 85% yield. Therefore, we selected 9-substituted/protected 6-iodopurines as suitable starting materials.

The THP-protected 6-iodopurine[17] **2** and the protected 6-iodopurine phosphonate[16e] **3** were known. The bis(THP)-protected 2-amino-6-iodopurine **4** was prepared by the reaction of 2-amino-6-iodopurine with 3,4-dihydro-2*H*-pyran in DMF catalyzed by HCl in 63% yield, analogously to the procedure[20] published for its 6-chloro analogue. Since it was known that partial hydrolysis of the trifluoromethyl function took place[15] during alkali mediated deacetylation of some trifluoromethylated nucleosides, we selected acidolabile protecting groups for the protection of the nucleoside hydroxy functions. Thus the known 2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine was iododeaminated[21] using a standard procedure (reflux with diiodomethane and isoamyl nitrite in acetonitrile) to give the 6-iodopurine nucleoside **5** in 36% yield.

For the synthesis of the 6-perfluoroalkylated purine bases we used the reaction of trimethyl(trifluoromethyl)silane (**1a**) and heptafluoropropyl-(trimethyl)silane (**1b**) with the THP-protected 6-iodopurines **2** and **4** (Scheme 1). The trifluoromethylation of the protected 6-iodopurine **2** proceeded smoothly to give the product **6a** in 85% yield, while in the same reaction of the protected 2-amino-6-iodopurine **4**, though the conversion was quantitative, the yield of the product **7a** was much lower (27%) due to unidentified degradative side reactions. The perfluoropropylation of the com-

pounds **2** and **4** was much slower and even the use of a higher excess of the silane reagent **1b** and longer reaction time (48 h) did not bring good yields. Despite the fact that the conversion was not quantitative and in addition to the degradation products also some starting compounds were present in the reaction mixture, the products **6b** and **7b** were isolated in moderate yields (35 and 23%, respectively) by column chromatography. The THP-protected derivatives **6** and **7** were easily deprotected by treatment with wet Dowex 50 (H^+) in methanol to give the perfluoroalkylpurine bases **8** and **9** in good yields (*ca* 90%).

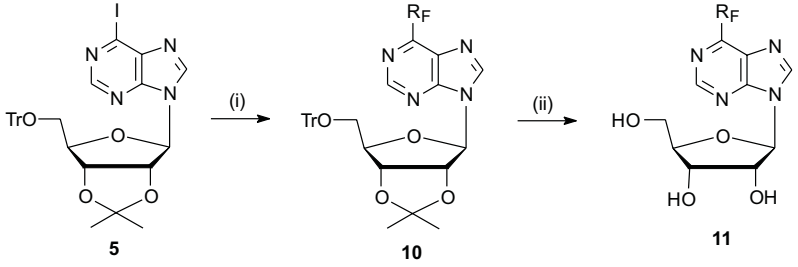


(i) R_FSiMe_3, KF, CuI, DMF/NMP, 60 °C, 20 h; (ii) Dowex 50 (H^+), H_2O, reflux, 1 h
THP = tetrahydropyran-2-yl

SCHEME 1

An analogous perfluoroalkylation of the protected 6-iodopurine ribonucleoside **5** was quite facile and the products **10a** and **10b** were isolated in acceptable yields of 75 and 47%, respectively (Scheme 2). The most difficult step was the deprotection due to the instability of the nucleosidic bond in the 6-perfluoropurine ribosides that easily cleaved to give the purine bases. The attempted deprotection using wet Dowex 50 (H^+) in refluxing methanol led to the deglycosylated purines **6** as major products (after 3 h, the degradation to the bases **6** was already quantitative). Therefore, milder con-

ditions using refluxing 80% acetic acid were used. Even under these conditions some deglycosylation occurred but it was slower than in the former method. The optimum yields of the deprotected nucleosides **11** (*ca* 30%) were achieved after 1 h treatment (the conversion being aproximately 50%) followed by column chromatography.



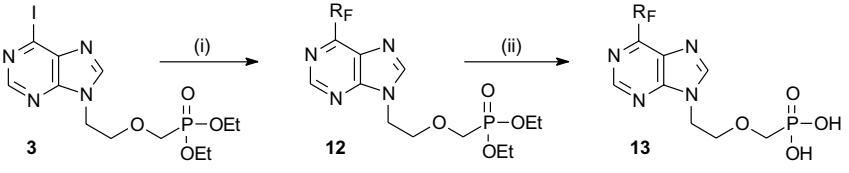
5 **10** **11**

10,11: **a**	$R_F = CF_3$	75%	35%
b	$R_F = CF_2CF_2CF_3$	47%	30%

(i) R_FSiMe_3, KF, CuI, DMF/NMP, 60 °C, 20 h; (ii) 80% AcOH, reflux, 1 h

SCHEME 2

The perfluoroalkylation of the 9-[2-(diethoxyphosphonylmethoxy)-ethyl]-6-iodopurine (**3**) proceeded in a similar manner as in the above mentioned cases to give the perfluoroalkylated products **12** in 92 and 46%, respectively (Scheme 3). The standard procedure using bromo(trimethyl)-silane (TMSBr) in acetonitrile[22] was used for the cleavage of the phosphonate esters. The isolation of the free phosphonates was quite complicated. Due to the absence of basic functions in the molecule, it was impossible to use the standard combination of Dowex 50 (H^+) followed by Dowex 1 (AcO^-) ion-exchange chromatography[22]. Chromatography on



3 **12** **13**

12,13: **a**	$R_F = CF_3$	92%	82%
b	$R_F = CF_2CF_2CF_3$	46%	31%

(i) R_FSiMe_3, KF, CuI, DMF/NMP, 60 °C, 20 h; (ii) TMSBr, acetonitrile

SCHEME 3

DEAE Sephadex, followed by deionization on Dowex 50 (H^+) afforded the free phosphonates **13** as extremely hygroscopic solids.

All new compounds were fully characterized by ^1H and ^{19}F NMR (^{13}C NMR was also recorded for at least one example of each class of compounds), MS and HR-MS and/or microanalysis. Since the melting points found for the known compounds **8a**, **9a** and **11a** differed from the published values quite significantly, these compounds were also fully characterized. For the assignment of the NMR signals, standard 2D techniques were used. ^1H-^1H spin network was determined by COSY spectra. Carbon connectivities based on one-bond and three-bond ^1H-^{13}C correlation were established by inverse techniques HMQC and HMBC spectra, respectively. The bis(THP)-protected 2-aminopurines **4** and **7** were isolated, characterized and used as diastereomeric mixtures. They were chromatographically homogeneous but splitting of some carbon signals was observed in ^{13}C NMR spectra. Due to their strong hygroscopicity, the free phosphonates **13** could not be characterized by microanalysis. Therefore, a combination of electrophoresis and TLC (purity evidence) and HR-MS were used for the characterization.

In conclusion, the perfluoroalkylation methodology presented in this paper was successfully used for the preparation of 6-(trifluoromethyl)- and 6-(heptafluoropropyl)purine derivatives (purine bases, nucleosides and acyclic nucleotide analogues). It is the most effective alternative approach for the trifluoromethylation of 2-unsubstituted 6-iodopurines; their heptafluoropropylation, as well as both perfluoroalkylations of the protected 2-amino-6-iodopurine **4** offered lower, but still acceptable, yields of the perfluoroalkylated products. In comparison with the Kobayashi approach[15], this method avoids the use of expensive gaseous CF_3I and toxic HMPA, as well as the preparation of highly activated copper metal. The limitations are the necessity to use 6-iodopurines as starting compounds (6-chloropurines are unreactive) and the accessibility of the starting trialkyl(perfluoroalkyl)silanes which, with the exception of the commercially available compounds **1a** and **1b**, must be prepared[23] from perfluoroalkyl iodides, chlorotrimethylsilane and hexaethylphosphorous triamide.

The 6-(perfluoroalkyl)purines **8**, **9**, **11** and **13** were tested for their cytostatic[24] (inhibition of the cell growth in the following cell cultures: (i) mouse leukemia L1210 cells (ATCC CCL 219); (ii) murine L929 cells (ATCC CCL 1) and (iii) human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2)) and antiviral[25] activity (DNA viruses: HSV-1, HSV-2, CMV, VZV and vaccinia virus, and retroviruses: HIV-1, HIV-2 and MSV). In accord with the qualitative literature data[15], compound **11a** exhibited a promising cytostatic activ-

ity; it will be a subject of further detailed study and the results will be published elsewhere. None of the other tested compounds exhibited any considerable activity in any of the assays.

EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40 °C/2kPa and compounds were dried at 60 °C/2kPa over P_2O_5. Melting points were determined on a Kofler block and are uncorrected. Paper electrophoresis was performed on a paper Whatman No. 3 MM at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogencarbonate (TEAB) at pH 7.5 and the electrophoretical mobilities are referenced to uridine 3′-phosphate. NMR spectra were measured on a Bruker AMX-3 400 (400 MHz for ^{1}H, 100.6 MHz for ^{13}C and 376.5 MHz for ^{19}F nuclei), Bruker DRX 500 (500 MHz for ^{1}H, 125.7 MHz for ^{13}C and 470.59 MHz for ^{19}F) and Varian Gemini 300HC (300.075 MHz for ^{1}H and 75.462 MHz for ^{13}C) spectrometers. TMS was used as internal standard for the ^{1}H and ^{13}C NMR spectra; $CFCl_3$ was an internal standard for ^{19}F NMR spectra. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix) or EI (electron energy 70 eV) techniques. DMF was distilled from P_2O_5, degassed *in vacuo* and stored over molecular sieves under Ar. Acetonitrile was refluxed with CaH_2 and distilled. Trimethyl(trifluoromethyl)silane (**1a**) and heptafluoropropyl(trimethyl)silane (**1b**) were purchased from Fluka.

6-Iodo-9-(tetrahydropyran-2-yl)-2-[(tetrahydropyran-2-yl)amino]purine (**4**)

A mixture of 2-amino-6-iodopurine[26] (3 g, 11.5 mmol), 4.5 M HCl in DMF (0.1 ml, 0.45 mmol) and DMF (100 ml) was stirred at 60 °C under Ar and 3,4-dihydro-2*H*-pyran (5.3 ml, 58 mmol) was added dropwise within 10 min through a septum. The stirring at 60 °C was continued for another 6 h and then the solvent was evaporated *in vacuo* (*ca* 100 Pa, bath temperature 40 °C). The dark red oily residue was dissolved in ethyl acetate (100 ml) and extracted with saturated aqueous $Na_2S_2O_3$ (100 ml). The aqueous layer was washed with ethyl acetate (100 ml) and the combined organic layers were dried with $MgSO_4$ and evaporated. Column chromatography of the residue on silica gel (150 g, ethyl acetate–light petroleum 1 : 1) and crystallization of the crude product from dichloromethane–heptane afforded the product **4** as yellowish powder, yield 3.1 g (63%), m.p. 132–134 °C. FAB MS, *m/z* (rel.%): 430 (55) [M + H]; 346 (90) [M + H – THP]; 304 (15) [M + 2 H – I]; 262 (55) [M + H – 2 THP]; 220 (22) [M + H – I – THP]; 136 (30) [M + H – I – 2 THP]; 85 (100) [THP]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.45–2.10 (m, 12 H); 3.60–3.80 (m, 2 H); 3.95–4.05 (m, 1 H); 4.10–4.20 (m, 1 H); 5.32–5.41 (m, 1 H); 5.53–5.63 (m, 1 H); 5.68–5.77 (m, 1 H); 7.98 (s, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): 23.32, 23.38, 25.50, 25.83, 32.02, 32.38 (all CH_2); 67.02, 69.24 (CH_2O); 80.54, 80.61, 82.13, 82.69 (OCHN); 123.35 (C-5); 140.00, 140.20 (C-8); 149.45, 149.66 (C-4); 157.77, 157.85 (C-2). For $C_{15}H_{20}IN_5O_2$ (429.3) calculated: 41.97% C, 4.70% H, 29.56% I, 16.31% N; found: 42.01% C, 4.69% H, 29.62% I, 16.61% N.

6-Iodo-9-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)purine (**5**)

A mixture of 2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine[27] (9.6 g, 17.5 mmol), CH_2I_2 (24 ml), i-AmONO (12 ml) and acetonitrile (135 ml) was refluxed for 8 h and then allowed to stand

overnight at room temperature. The mixture was then taken down *in vacuo* (*ca* 100 Pa, bath temperature *ca* 40 °C), the residue was treated with saturated aqueous $Na_2S_2O_3$ (250 ml) and extracted with ethyl acetate (3 × 250 ml). The collected organic phases were dried over $MgSO_4$ and evaporated. Column chromatography of the residue on silica gel (400 g, ethyl acetate–light petroleum 1 : 2) and crystallization from dichloromethane–heptane afforded the product **5** as yellowish powder, yield 4.2 g (36%), m.p. 70–73 °C. FAB MS, *m/z* (rel.%): 661 (1.5) [M + H]; 401 (4), 243 (100) [Tr]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.40 (s, 3 H, CH_3); 1.63 (s, 3 H, CH_3); 3.27 (m, 2 H, H-5′); 4.59 (m, 1 H, H-4′); 4.96 (dd, 1 H, *J*(2′,3′) = 6.2, *J*(4′,3′) = 2.3, H-3′); 5.47 (dd, 1 H, *J*(1′,2′) = 1.9, *J*(3′,2′) = 6.2, H-2′); 6.14 (d, 1 H, *J*(2′,1′) = 1.9, H-1′); 7.18–7.31 (m, 15 H, H-arom.); 8.23 (s, 1 H, H-8); 8.47 (s, 1 H, H-2). For $C_{32}H_{29}IN_4O_4$ (660.5) calculated: 58.19% C, 4.43% H, 19.21% I, 8.48% N; found: 58.51% C, 4.80% H, 18.60% I, 8.17% N.

Trifluoromethylation of 6-Iodopurine Derivatives. General Procedure

A mixture of the iodopurine derivative **2**–**5** (1 mmol), CF_3SiMe_3 (206 µl, 1.4 mmol), KF (82 mg, 1.4 mmol), CuI (304 mg, 1.6 mmol), DMF (1 ml) and NMP (1 ml) was stirred in a 5 ml glass vial at 60 °C for 24 h. After cooling to room temperature the solvents were evaporated under low pressure (*ca* 100 Pa, bath temperature *ca* 40 °C) and the residue was chromatographed on a column of silica gel (50 g) using a suitable solvent. The products were chromatographically homogeneous (TLC, HPLC).

9-(Tetrahydropyran-2-yl)-6-(trifluoromethyl)purine (**6a**). Colourless crystals, m.p. 84–89 °C (CH_2Cl_2–cyclohexane); yield 85%, eluent ethyl acetate–light petroleum 1 : 1. EI MS, *m/z* (rel.%): 272 (15) [M]; 244 (8); 189 (20) [M + H – THP]; 119 (8) [M – THP – CF_3]; 85 (100) [THP]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.50–2.30 (m, 6 H); 3.82 (dt, 1 H, *J* = 11.5, 2.6, OCH_2-a); 4.22 (m, OCH_2-b); 5.86 (dd, 1 H, *J* = 10.4, 2.3, NCHO); 8.48 (s, 1 H, H-8); 9.09 (s, 1 H, H-2). ^{19}F NMR (376.5 MHz, $CDCl_3$): –66.67 (s, CF_3). For $C_{11}H_{11}F_3N_4O$ (272.2) calculated: 48.53% C, 4.07% H, 20.94% F, 20.58% N; found: 48.56% C, 4.08% H, 20.56% F, 20.24% N.

9-(Tetrahydropyran-2-yl)-2-[(tetrahydropyran-2-yl)amino]-6-(trifluoromethyl)purine (**7a**). Oil, yield 27%, eluent ethyl acetate–light petroleum 1 : 1. FAB MS, *m/z* (rel.%): 372 (20) [M + H]; 288 (100) [M + H – THP]; 204 (62) [M + H – 2 THP]; 85 (81) [THP]. ^{1}H NMR (500 MHz, $CDCl_3$): 1.50–2.15 (m, 12 H); 3.65–3.70 (m, 1 H); 3.73–3.81 (m, 1 H); 4.00–4.07 (d, 1 H, *J* = 11.5); 4.15–4.21 (m, 1 H); 5.39–5.48 (m, 1 H); 5.64–5.71 (m, 1 H); 5.84–5.94 (brm, 1 H, NH); 8.12 (s, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): 23.41, 25.53, 25.90, 30.39, 32.06, 32.44 (all CH_2); 67.17, 69.36 (CH_2O); 80.69, 80.76, 82.25, 82.72 (OCHN); 121.23 (q, ^1J(F,C) = 274.9, CF_3); 125.00 (C-5); 142.73, 142.91 (C-8); ≈146 (brd, C-6); 155.44, 155.61 (C-4); 158.32 (C-2). ^{19}F NMR (376.5 MHz, $CDCl_3$): –67.45 (s, CF_3). For $C_{16}H_{20}F_3N_5O_2 \cdot 1/3\ H_2O$ (377.4) calculated: 50.93% C, 5.52% H, 15.10% F, 18.56% N; found: 51.25% C, 5.47% H, 14.66% F, 18.29% N.

9-(2,3-O-Isopropylidene-5-O-trityl-β-D-ribofuranosyl)-6-(trifluoromethyl)purine (**10a**). Foam, yield 75%, eluent ethyl acetate–light petroleum 1 : 2. FAB MS, *m/z* (rel.%): 603 (8) [M + H]; 243 (100) [Tr]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.40 (s, 3 H, CH_3); 1.64 (s, 3 H, CH_3); 3.28–3.31 (m, 2 H, H-5′); 4.62 (ddd, 1 H, *J* = 2.5, 2.7, 4.9, H-4′); 4.98 (dd, 1 H, *J*(2′,3′) = 6.2, *J*(4′,3′) = 2.5, H-3′); 5.49 (dd, 1 H, *J*(1′,2′) = 2.3, *J*(3′,2′) = 6.2, H-2′); 6.22 (d, 1 H, *J*(2′,1′) = 2.3, H-1′); 7.15–7.32 (m, 15 H, H-arom.); 8.34 (s, 1 H, H-8); 8.94 (s, 1 H, H-2). ^{19}F NMR (376.5 MHz, $CDCl_3$): –59.58 (s, CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): 26.05, 27.81 (CH_3); 64.62 (C-5′); 82.04, 84.91, 87.56 (C-2′, C-3′, C-4′); 92.73 (C-1′); 115.18 (CMe_2); 121.23 (q, ^1J(F,C) = 274.4, CF_3); 128.47–129.21 (m, C-arom.); 131.51 (C-5); 146.04 (q, ^2J(F,C) = 36.5, C-6); 147.13 (C-8);

152.50 (C-2); 153.45 (C-4). For $C_{33}H_{29}F_3N_4O_4$ (602.6) calculated: 66.77% C, 4.85% H, 9.46% F, 9.30% N; found: 66.58% C, 5.17% H, 8.92% F, 8.92% N.

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-(trifluoromethyl)purine (**12a**). Oil, yield 92%, eluent ethyl acetate. FAB MS, *m/z* (rel.%): 405 (16) [M + Na]; 383 (100) [M + H]. ^{1}H NMR (500 MHz, $CDCl_3$): 1.28 (t, 6 H, $J(CH_3,CH_2)$ = 7.0, CH_3); 3.79 (d, 2 H, J(P,CH) = 8.0, PCH_2); 4.01 (t, 2 H, $J(1',2')$ = 4.7, H-2′); 4.08 (dq, 4 H, $J(CH_3,CH_2) \approx J$(P,OCH_2) ≈ 7, $POCH_2$); 4.57 (t, 2 H, $J(2',1')$ = 4.7, H-1′); 8.45 (s, 1 H, H-8); 9.08 (s, 1 H, H-2). ^{19}F NMR (376.5 MHz, $CDCl_3$): –66.67 (s, CF_3). ^{13}C NMR (125 MHz, $CDCl_3$): 17.05 (d, ^3J(P,C) = 5.5, CH_3); 44.45 (C-1′); 63.12 (d, ^2J(P,C) = 6.8, $POCH_2$); 66.00 (d, ^1J(P,C) = 166, PCH_2); 71.24 (d, ^3J(P,C) = 6.8, C-2′); 121.42 (q, ^1J(F,C) = 274, CF_3); 130.64 (C-5); 145.74 (q, ^2J(F,C) = 37.3, C-6); 149.03 (C-8); 152.49 (C-2); 154.44 (C-4). For $C_{13}H_{18}F_3N_4O_4P$ (382.3) calculated: 40.84% C, 4.75% H, 14.91% F, 14.66% N; found: 40.45% C, 4.77% H, 15.13% F, 14.44% N.

Heptafluoropropylation of 6-Iodopurine Derivatives. General Procedure

A mixture of the iodopurine derivative **2**–**5** (1 mmol), $CF_3CF_2CF_2SiMe_3$ (350 µl, 1.7 mmol), KF (82 mg, 1.4 mmol), CuI (304 mg, 1.6 mmol), DMF (1 ml) and NMP (1 ml) was stirred in a 5 ml glass vial at 60 °C for 48 h. After cooling to room temperature the solvents were evaporated under low pressure (*ca* 100 Pa, bath temperature *ca* 40 °C) and the residue was chromatographed on a column of silica gel (50 g) using a suitable solvent. The products were chromatographically homogeneous (TLC, HPLC).

6-(Heptafluoropropyl)-9-(tetrahydropyran-2-yl)purine (**6b**). Colourless crystals, m.p. 58–60 °C (CH_2Cl_2–cyclohexane); yield 35%, eluent ethyl acetate–light petroleum 1 : 1. EI MS, *m/z* (rel.%): 372 (12) [M]; 289 (17) [M + H – THP]; 169 (8) [$CF_2CF_2CF_3$]; 85 (100) [THP]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.60–2.30 (m, 6 H); 3.82 (dt, 1 H, J = 11.6, 2.5, OCH_2-a); 4.22 (m, OCH_2-b); 5.88 (dd, 1 H, J = 10.5, 2.3, NCHO); 8.50 (s, 1 H, H-8); 9.13 (s, 1 H, H-2). ^{19}F NMR (376.5 MHz, $CDCl_3$): –80.54 (t, J = 9.3, CF_3); –114.71 (tq, J = 9.3, 4.5, CF_2-2″); –126.54 (t, J = 4.5, CF_2-1″). ^{13}C NMR (75 MHz, $CDCl_3$): 23.25, 25.47, 32.50 (CH_2-2′,3′,4′); 69.63 (CH_2-5′); 83.53 (CH-1′); 105–125 (complex multiplet, $CF_2CF_2CF_3$); 132.97 (C-5); 140–144 (complex multiplet, C-6); 146.07 (C-8); 152.68 (C-2); 153.79 (C-4). Exact mass (EI HRMS) found: 372.0815; calculated for $C_{13}H_{11}F_7N_4O$: 372.0821. For $C_{13}H_{11}F_7N_4O$ (372.2) calculated: 41.97% C, 2.98% H, 35.73% F, 15.05% N; found: 42.56% C, 3.11% H, 35.00% F, 14.95% N.

6-(Heptafluoropropyl)-9-(tetrahydropyran-2-yl)-2-[(tetrahydropyran-2-yl)amino]purine (**7b**). Oil, yield 23%, eluent ethyl acetate–light petroleum 1 : 1. FAB MS, *m/z* (rel.%): 472 (21) [M + H]; 388 (100) [M + H – THP]; 304 (89) [M + H – 2 THP]; 85 (70) [THP]. ^{1}H NMR (500 MHz, $CDCl_3$): 1.50–2.10 (m, 12 H); 3.60–3.80 (m, 2 H); 3.97–4.04 (m, 1 H); 4.13–4.20 (m, 1 H); 5.34–5.41 (m, 1 H); 5.66 (brt, 1 H); 5.84 (brm, 1 H, NH); 8.11 (s, H-8). ^{19}F NMR (376.5 MHz, $CDCl_3$): –81.09 (brs, CF_3); –115.67 (brs, CF_2-2″); –127.19 (brs, CF_2-1″). Exact mass (FAB HRMS) found: 472.1572; calculated for $C_{18}H_{21}F_7N_5O_2$ [M + H]: 472.1583.

6-(Heptafluoropropyl)-9-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)purine (**10b**). Foam, yield 47%, eluent ethyl acetate–light petroleum 1 : 2. FAB MS, *m/z* (rel.%): 703 (14) [M + H]; 243 (100) [Tr]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.41 (s, 3 H, CH_3); 1.65 (s, 3 H, CH_3); 3.31 (d, 2 H, J(4′,5′) = 5.1, H-5′); 4.61 (m, 1 H, ΣJ = 12.4, H-4′); 4.98 (dd, 1 H, $J(2',3')$ = 6.2, $J(4',3')$ = 2.5, H-3′); 5.48 (dd, 1 H, $J(1',2')$ = 2.2, $J(3',2')$ = 6.2, H-2′); 6.22 (d, 1 H, $J(2',1')$ = 2.2, H-1′); 7.1–7.4 (m, 15 H, H-arom.); 8.35 (s, 1 H, H-8); 8.98 (s, 1 H, H-2). ^{19}F NMR (376.5 MHz, $CDCl_3$): –81.05 (t, J = 9.0, CF_3); –115.05 (q, J = 9.0, CF_2-2″); –126.92 (brs, CF_2-1″). Exact mass (FAB HRMS) found: 703.2138; calculated for $C_{35}H_{30}F_7N_4O_4$ [M + H]: 703.2155.

9-[2-(Diethoxyphosphonylmethoxy)ethyl]-6-(heptafluoropropyl)purine (**12b**). Oil, yield 46%, eluent ethyl acetate. FAB MS, *m/z* (rel.%): 483 (100) [M + H]. ^{1}H NMR (500 MHz, $CDCl_3$): 1.30 (t, 6 H, $J(CH_3,CH_2)$ = 7.0, CH_3); 3.82 (d, 2 H, J(P,CH) = 8.1, PCH_2); 4.03 (t, 2 H, J(1′,2′) = 4.7, H-2′); 4.10 (dq, 4 H, $J(CH_3,CH_2) \approx J(P,OCH_2) \approx 7$, $POCH_2$); 4.59 (t, 2 H, J(2′,1′) = 4.7, H-1′); 8.49 (s, 1 H, H-8); 9.14 (s, 1 H, H-2). ^{19}F NMR (376.5 MHz, $CDCl_3$): –73.46 (t, J = 9.2, CF_3); –107.55 (tq, J = 9.2, 4.5, CF_2-2″); –119.45 (t, J = 4.5, CF_2-1″). ^{13}C NMR (125 MHz, $CDCl_3$): 16.74 (d, ^3J(P,C) = 4.7, CH_3); 44.18 (C-1′); 62.96 (d, ^2J(P,C) = 6.0, $POCH_2$); 65.60 (d, ^1J(P,C) = 166.8, PCH_2); 70.93 (d, ^3J(P,C) = 9.2, C-2′); 105–120 (complex multiplet, $CF_2CF_2CF_3$); 132.10 (C-5); 145.28 (t, ^2J(F,C) = 26.9, C-6); 148.94 (C-8); 152.10 (C-2); 153.96 (C-4).

Deprotection of the THP-Protected Bases **6** and **7**. General Procedure

A mixture of the THP-protected base **6** or **7** (0.6–1.5 mmol), Dowex 50 X 8 (H^+) (*ca* 300 mg), methanol (10 ml) and water (1 ml) was refluxed for 1 h, then filtered while hot and the resin was washed with a mixture of 35% aqueous NH_3 (1 ml) and methanol (10 ml). The combined filtrates were evaporated and the residue codistilled with toluene. Crystallization of the residue from methanol/toluene with an addition of heptane afforded the free bases **8** and **9**.

6-(Trifluoromethyl)purine (**8a**). Colourless crystals, m.p. 217–219 °C (toluene) (ref.[14] 254–255 °C (sublimed)); yield 92%. EI MS, *m/z* (rel.%): 188 (100) [M]; 119 (95) [M – CF_3]. ^{1}H NMR (500 MHz, $CDCl_3$): 8.84 (s, 1 H, H-8); 9.09 (s, 1 H, H-2). ^{19}F NMR (470.59 MHz, $CDCl_3$): –64.59 (s, CF_3). For $C_6H_3F_3N_4$ (188.1) calculated: 38.31% C, 1.61% H, 30.30% F, 29.78% N; found: 38.26% C, 1.40% H, 30.43% F, 29.40% N.

6-(Heptafluoropropyl)purine (**8b**). Colourless crystals, m.p. 162–165 °C (toluene–heptane); yield 90%. EI MS, *m/z* (rel.%): 288 (100) [M]; 269 (15) [M – F]; 169 (96) [$CF_2CF_2CF_3$]; 142 (20); 119 (38) [M – $CF_2CF_2CF_3$]. ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (s, 1 H, H-8); 9.16 (s, 1 H, H-2); 14.14 (brs, NH). ^{19}F NMR (376.5 MHz DMSO-d_6): –80.50 (t, J = 8.7, CF_3); –113.98 (brs, CF_2-2″); –126.76 (t, J = 4.5, CF_2-1″). ^{13}C NMR (75 MHz, DMSO-d_6): 105–125 (m, $CF_2CF_2CF_3$); 149.53 (C-8); 151.74 (C-2); the quaternary carbon signals of C-4,5,6 were very weak. Exact mass (EI HRMS) found: 288.0273; calculated for $C_8H_3F_7N_4$: 288.0246. For $C_8H_3F_7N_4$ (288.1) calculated: 33.35% C, 1.05% H, 46.16% F, 19.45% N; found: 33.72% C, 1.08% H, 45.85% F, 19.33% N.

2-Amino-6-(trifluoromethyl)purine (**9a**). Yellowish crystals, m.p. 282–283 °C (toluene) (ref.[14] 360 °C (ethanol)); yield 92%. EI MS, *m/z* (rel.%): 203 (100) [M]; 134 (35) [M – CF_3]. ^{1}H NMR (500 MHz, DMSO-d_6): 6.88 (brs, 1 H, NH); 8.27 (s, 1 H, H-8). ^{19}F NMR (376.5 MHz, DMSO-d_6): –65.11(s, CF_3). ^{13}C NMR (75 MHz, DMSO-d_6): 120.99 (q, ^1J(F,C) = 274.3, CF_3); ≈121 (very weak s, C-5); ≈143 (very weak m, C-6); 144.24 (C-8); 157.98 (C-4); 160.04 (C-2). For $C_6H_4F_3N_5$ (203.1) calculated: 35.47% C, 1.98% H, 34.48% N; found: 35.73% C, 2.18% H, 33.96% N.

2-Amino-6-(heptafluoropropyl)purine (**9b**). Yellowish crystals, m.p. 213-216 °C (toluene–heptane); yield 90%. EI MS, *m/z* (rel.%): 303 (100) [M]. ^{1}H NMR (400 MHz, DMSO-d_6): 6.92 (brs, 2 H, NH_2); 8.24 (s, 1 H, H-8); 13.03 (brs, 1 H, NH). ^{19}F NMR (376.5 MHz, DMSO-d_6): –79.37 (brs, CF_3); –113.05 (brd, J = 7.2, CF_2-2″); –126.76 (brs, CF_2-1″). ^{13}C NMR (75 MHz, DMSO-d_6): 105–125 (m, $CF_2CF_2CF_3$); 124.20 (C-5); 143.10 (weak m, C-6); 143.78 (C-8); 156.91 (C-4); 159.93 (C-2). Exact mass (EI HRMS) found: 303.0362; calculated for $C_8H_4F_7N_5$:

303.0355. For $C_8H_4F_7N_5$ (303.1) calculated: 31.70% C, 1.33% H, 23.10% N; found: 31.54% C, 1.37% H, 22.79% N.

Deprotection of Nucleosides **10**. General Procedure

A mixture of the protected nucleoside **10** (0.8–1.3 mmol) and 80% aqueous AcOH (20 ml) was refluxed for 1 h, evaporated *in vacuo* and codistilled with toluene (20 ml). The residue was chromatographed on a column of silica gel (50 g, ethyl acetate–methanol 9 : 1). The products were crystallized from i-PrOH–heptane.

9-(β-D-Ribofuranosyl)-6-(trifluoromethyl)purine (**11a**). Colourless crystals, m.p. 145–148 °C (i-PrOH–heptane–cyclohexane) (ref.[15] 176 °C (i-PrOH–i-Pr_2O)); yield 35%. FAB MS, *m/z* (rel.%): 321 (18) [M + H]; 189 (100) [M – Rf]. ^{1}H NMR (500 MHz, DMSO-d_6): 3.60–3.63 and 3.71–3.75 (2 × m, 2 × 1 H, H-5′); 4.02 (ddd, 1 H, *J*(3′,4′) = 3.8, *J*(5′a,4′) = 3.8, *J*(5′b,4′) = 4.0, H-4′); 4.23 (ddd, 1 H, *J*(2′,3′) = 5.1, *J*(OH,3′) = 5.2, *J*(4′,3′) = 3.8, H-3′); 4.62 (ddd, 1 H, *J*(1′,2′) = 5.0, *J*(3′,2′) = 5.1, *J*(OH,2′) = 5.6, H-2′); 5.13 (t, 1 H, *J*(5′,OH) = 5.4, 5′-OH); 5.29 (d, 1 H, *J*(3′,OH) = 5.2, 3′-OH); 5.62 (d, 1 H, *J*(2′,OH) = 5.7, 2′-OH); 6.13 (d, 1 H, *J*(2′,1′) = 5.0, H-1′); 9.12 and 9.18 (2 × s, 2 × 1 H, H-2 and H-8). ^{19}F NMR (376.5 MHz, DMSO-d_6): –64.49 (s, CF_3). ^{13}C NMR (75 MHz, DMSO-d_6): 60.91 (C-5′); 70.00 (C-3′); 74.01 (C-2′); 85.71 (C-4′); 88.10 (C-1′); 120.82 (q, ^1J(F,C) = 274.5, CF_3); 130.12 (C-5); 142.90 (q, ^2J(F,C) = 36.8, C-6); 147.96 (C-8); 151.65 (C-2); 153.64 (C-4). Exact mass (FAB HRMS) found: 321.0846; calculated for $C_{11}H_{12}F_3N_4O_4$ [M + H]: 321.0810. For $C_{11}H_{11}F_3N_4O_4$ (320.2) calculated: 41.26% C, 3.46% H, 17.80% F, 17.50% N; found: 41.50% C, 3.51% H, 17.61% F, 17.88% N.

6-(Heptafluoropropyl)-9-(β-D-ribofuranosyl)purine (**11b**). Colourless crystals, m.p. 89–92 °C (i-PrOH–heptane); yield 30%. FAB MS, *m/z* (rel.%): 421 (18) [M + H]; 289 (100) [M – Rf]. ^{1}H NMR (400 MHz, $CDCl_3$): 3.83 and 4.00 (2 × brs, 2 × 1 H, H-5′); 4.38 (brs, 1 H, H-4′); 4.54 (brs, 1 H, H-3′); 4.92 (brs, 1 H, H-2′); 6.04 (d, 1 H, *J*(2′,1′) = 6.4, H-1′); 8.51 (s, 1 H, H-8); 9.10 (s, 1 H, H-2). ^{19}F NMR (376.5 MHz, $CDCl_3$): –80.56 (t, *J* = 8.1, CF_3); –114.77 (brd, *J* = 8.4, CF_2-2″); –126.49 (brs, CF_2-1″). Exact mass (FAB HRMS) found: 421.0683; calculated for $C_{13}H_{12}F_7N_4O_4$ [M + H]: 421.0746. For $C_{13}H_{11}F_7N_4O_4$ (420.2) calculated: 37.16% C, 2.64% H, 31.65% F, 13.33% N; found: 37.17% C, 2.66% H, 31.73% F, 13.70% N.

Deprotection of Phosphonates **12**. General Procedure

A mixture of the phosphonate diesters (0.5–1.2 mmol), TMSBr (1 ml) and acetonitrile (5 ml) was stirred overnight at ambient temperature, then evaporated and codistilled with toluene (10 ml). The residue was dissolved in a mixture of water (5 ml) and triethylamine (1 ml) and, after standing at room temperature for 10 min, evaporated *in vacuo*. The residue was applied on a column of DEAE-Sephadex A-25 (≈50 ml), washed with water and eluted with a linear gradient 0.01–1 M aqueous TEAB (1 l each; detection at 260 nm). The appropriate product-containing fractions were evaporated and the residue deionized on a Dowex 50 X 8 (H^+) column (≈50 ml, eluent water). Evaporation and/or freeze-drying of the appropriate aqueous fractions afforded the free phosphonates as extremely hygroscopic compounds; any attempts to crystallize them failed.

9-[2-(Phosphonomethoxy)ethyl]-6-(trifluoromethyl)purine (**13a**). Yield 82%, E_{Up} 0.95. FAB MS, *m/z* (rel.%): 327 (28) [M + H]; 162 (100). ^{1}H NMR (400 MHz, DMSO-d_6): 3.60 (d, 2 H, *J*(P,CH) = 8.6, PCH_2); 3.95 (t, 2 H, *J*(1′,2′) = 5.0, H-2′); 4.54 (t, 2 H, *J*(2′,1′) = 5.0, H-1′); 8.86 (s, 1 H, H-8); 9.13 (s, H-2). ^{19}F NMR (376.5 MHz, DMSO-d_6): –64.37 (s, CF_3). Exact mass (FAB HRMS) found: 327.0452; calculated for $C_9H_{11}F_3N_4O_4P$ [M + H]: 327.0470.

6-(Heptafluoropropyl)-9-[2-(phosphonomethoxy)ethyl]purine (**13b**). Yield 31%, E_{Up} 0.86. FAB MS, *m/z* (rel.%): 449 (16) [M + Na]; 427 (100) [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): 3.63 (d, 2 H, *J*(P,CH) = 8.4, PCH_2); ≈4.0 (hidden in a H_2O signal, H-2′); 4.55 (t, 2 H, *J*(2′,1′) = 5.2, H-1′); 8.86 (s, 1 H, H-8); 9.18 (s, H-2). ^{19}F NMR (376.5 MHz, DMSO-d_6): –79.30 (t, *J* = 8.7, CF_3); –112.46 (q, *J* = 8.7, CF_2-2″); –125.37 (brs, CF_2-1″). ^{13}C NMR (75 MHz, DMSO-d_6): 43.10 (C-1′); 66.14 (d, ^{1}*J*(P,C) = 159.3, PCH_2); 69.58 (d, ^{3}*J*(P,C) = 10.8, C-2′); 105–120 (complex multiplet, $CF_2CF_2CF_3$); 132.20 (C-5); 142.19 (m, C-6); 150.29 (C-8); 151.30 (C-2); 153.82 (C-4). Exact mass (FAB HRMS) found: 427.0395; calculated for $C_{11}H_{11}F_7N_4O_4P$ [M + H]: 427.0406.

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