ARTICLE

OBC
www.rsc.org/obc

The first synthesis and cytostatic activity of novel 6-(fluoromethyl)purine bases and nucleosides†

Peter Šilhár, Radek Pohl, Ivan Votruba and Michal Hocek*

Centre for New Antivirals and Antineoplastics, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nam. 2, CZ-16610, Prague 6, Czech Republic. E-mail: hocek@uochb.cas.cz; Fax: +420 220183559; Tel: +420 220183324

Received 8th June 2005, Accepted 9th June 2005
First published as an Advance Article on the web 4th July 2005

Two alternative approaches to the synthesis of novel 6-(fluoromethyl)purine bases and nucleosides are described either by direct deoxyfluorination or by multistep functional group transformations starting from 6-(hydroxymethyl)purines. 6-(Fluoromethyl)purine ribonucleoside displayed significant cytostatic effects.

Introduction

Several types of purines bearing C-substituents in the position 6 are biologically active (Chart 1). 6-Aryl and 6-hetarylpurine,[1] 6-trifluoromethylpurine,[2] as well as 6-(hydroxymethyl)purine[3] ribonucleosides display significant cytostatic activity. 6-Methylpurine, as well as its ribonucleoside, are highly cytotoxic[4] and its liberation by purine nucleoside phosphorylases from its non-toxic deoxyribonucleoside was proposed as a novel principle in the gene therapy of cancer.[5] Fluoromethyl is a simple isosteric derivative of methyl group and fluorine is often used as surrogate for oxygen in biologically active compounds. Hydrophobic nucleobase surrogates, including fluorinated and trifluoromethylated (het)aromatics, are[6] very promising tools in chemical biology (*e.g.*, extension of the genetic alphabet, *etc.*). The biological activities and other applications of the above mentioned important classes of compounds imply that the missing logical members of the series, 6-(fluoromethyl)purines, are of great interest both in medicinal chemistry and chemical biology. Surprisingly, these simple compounds have, to the best of our knowledge, never been reported.

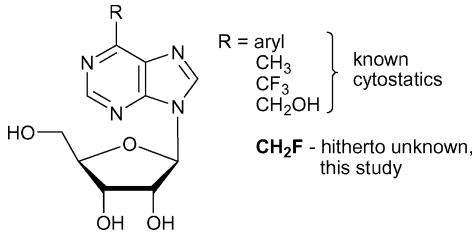
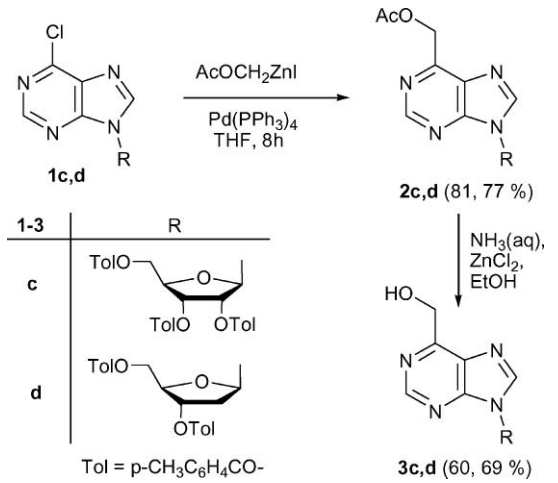


Chart 1 Cytostatic 6-substituted purine ribonucleosides.

There are scarce references to other halomethylpurines. 6-(Chloromethyl)purine was synthesized in low yield from 6-methylpurine-*N*-oxide or by chlorination of 6-methylpurine with NCS, followed by partial reduction of the intermediate 6-(trichloromethyl)purine.[7] Analogously, bromination of 6-methylpurine with NBS afforded 6-(dibromomethyl)- and 6-(tribromomethyl)purine that could be partially hydrogenated to 6-(bromomethyl)purine.[7] A multistep synthesis of 6-(iodomethyl)purine ribonucleoside[8] was based on Finkelstein reaction of NaI with 6-(mesyloxymethyl)purine which was prepared *via* 6-(hydroxymethyl)purine from purine ribonucleoside by photoaddition of methanol in moderate yield.

Results and discussion

Recently, we have reported[3] a facile and efficient synthesis of 6-(hydroxymethyl)purines by Pd-catalyzed cross-coupling reactions of 6-halopurines and (acyloxymethyl)zinc iodides followed by deprotection. Here, we wish to report the first synthesis of 6-(fluoromethyl)purines starting from these now easily available intermediates either by direct deoxyfluorinations or by multistep procedures. 6-(Hydroxymethyl)purines bases protected in position 9 or nucleosides protected in the glycon part were needed for the fluorinations. The protected bases **3a**,**b** were prepared by a previously reported method.[3] In nucleoside derivatives, the procedures and protecting groups have to be modified in order to enable selective deacylation of the acyloxymethyl group at the purine in presence of the acyl-protected sugar part. Therefore, we have used a combination of (acetyloxymethyl)zinc iodide for cross-coupling reactions and a more stable toluoyl protecting group for protection of the nucleosides. The protected (acetyloxymethyl)purine nucleosides **2c**,**d** were obtained in good yields but their deacetylation by NH_3–EtOH was not fully selective and the desired sugar-protected 6-(hydroxymethyl)purine nucleosides **3c**,**d** were isolated in moderate yields of *ca.* 30–35% besides a mixture of partially and fully deprotected nucleosides. Interestingly, an addition of $ZnCl_2$ (1.2 eq.) significantly enhanced the selectivity of deacylation to give the key intermediates **3c**,**d** in acceptable yields of 60 and 69%, respectively and *ca.* 20% of starting material was recovered (Scheme 1).



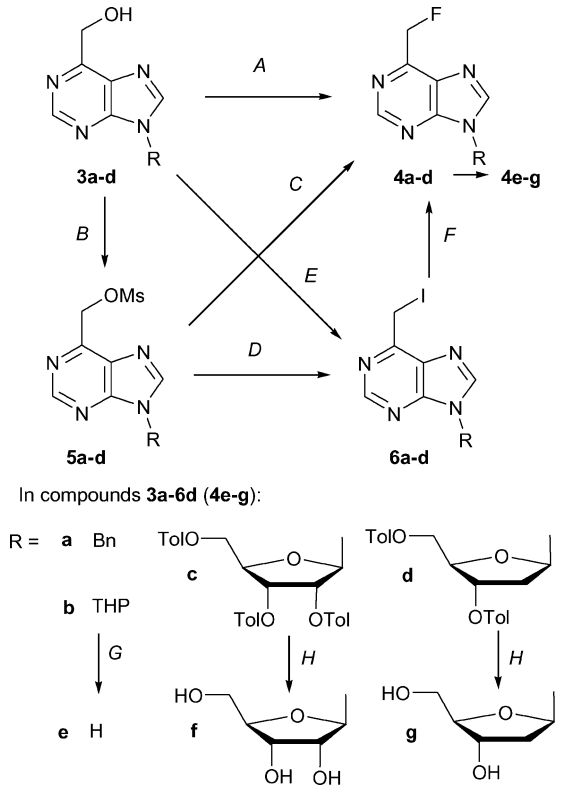
Scheme 1

At first we have tried direct deoxyfluorinations of hydroxymethyl group with various commercially available fluorinating

† Electronic supplementary information (ESI) available: NMR spectra of compounds **4**. See http://dx.doi.org/10.1039/b508122j

DOI: 10.1039/b508122j

agents (step A, Scheme 2, Table 1). Thus, deoxyfluorination with (diethylamino)sulfur trifluoride (DAST)[9] gave only low yield of product **4b** (entry 1, Table 1). Slightly better results were obtained with the use of perfluor-1-butanesulfonyl fluoride[10] with Hünig's base in methylene chloride (entries 4, 5; Table 1) but not with DBU in toluene (entries 2, 3). Next, we tried Deoxo-Fluor[11] ([bis-(2-methoxyethyl)amino]sulfur trifluoride) as a mild and thermally stable reagent to afford the desired products **4a**–**d** in better yields of 41–46% (entry 6–9, Table 1). Notably, in the reactions with perfluorbutanesulfonyl fluoride in presence of Hünig's base (but not DBU in toluene) or with Deoxo-Fluor (1.5 eq.) the unreacted starting alcohol **3a**–**d** was recovered in the yields of 30–35% and 13–20%, respectively, and re-used. Therefore even this very simple and straightforward one-step but rather moderately yielding procedure is relatively efficient.



Scheme 2 Yields of the particular steps are given in Table 1. A: (i) DAST, CH_2Cl_2; (ii) $C_4F_9SO_2F$, DBU, toluene; (iii) $C_4F_9SO_2F$, $^iPr_2EtN$, CH_2Cl_2 or (iv) Deoxo-Fluor, CH_2Cl_2. B: Ms_2O, $^iPr_2EtN{\cdot}CH_2Cl_2$, DMAP (cat.), 2 h. C: $Et_3N{\cdot}3HF$, $^iPr_2EtN$, DCE, 80 °C, 12 h. D: NaI, acetone, rt, 1.5 h. E: I_2, PPh_3, THF or CH_2Cl_2, rt, 30 min. F AgF, THF, rt, 10 h G Dowex 50WX8 (H^+), EtOH, 70 °C, 1.5 h. H: NaOMe (0.2 eq), MeOH, rt.

An alternative way to prepare the desired fluoromethyl derivatives is to perform multi-step sequences, *via* transformation of hydroxy groups to a suitable leaving group for nucleophilic substitutions (Scheme 2). Thus, substitution of mesylates,[12] tosylates[13] or triflates[14] by fluoride proceeded in moderate to good yields. The mesylates **5a**–**d** were prepared in very good yields from **3a**–**d** and Ms_2O under standard conditions (step B). Unfortunately, in our hands a substitution of mesyloxy group in derivatives **5a**,**b** by fluoride anion from $Et_3N{\cdot}3HF$ (step C, Scheme 2) proceeded with low yields (entries 14, 15; Table 1). Therefore we have turned our efforts to 6-(iodomethyl)purines. These intermediates were prepared either by direct deoxyiodination of hydroxymethylpurines **3** or by Finkelstein[15] reaction of mesylates **5**. Model deoxyiodination of 6-(hydroxymethyl)purines **3a**,**b** (step E, Scheme 2) by the use of I_2 and PPh_3[16] proceeded in acceptable yields of 68 and 79%, respectively. On the other hand the Finkelstein reactions of mesylates **5a**–**d** (step D, entries 16–19, Table 1) gave the iodomethyl derivatives **6a**–**d** in nearly quantitative yields. The total yields of the two-step and direct iodination are comparable. The direct method is shorter but in the two-step sequence the isolation of products is more convenient. The final nucleophilic substitution of the iodo derivatives was acomplished by making use of AgF[17] (step F). It was very efficient because of the higher insolubility of the resulting AgI than the starting AgF in THF. The reactions gave the desired 6-(flurometyl)purines **4a**–**d** in very good yields of 72–84%. In comparison, the multistep

Table 1 Yields of the particular steps of the synthesis

Entry	Step	Starting compound	Product	Reagent	Yield (%)[b]
1	A (i)	**3b**	**4b**	DAST	18
2	A (ii)	**3a**	**4a**	$C_4F_9SO_2F$	13
3	A (ii)	**3b**	**4b**	$C_4F_9SO_2F$	13
4	A (iii)	**3a**	**4a**	$C_4F_9SO_2F$	31
5	A (iii)	**3b**	**4b**	$C_4F_9SO_2F$	23
6	A (iv)	**3a**	**4a**	Deoxo-Fluor	42
7	A (iv)[a]	**3b**	**4b**	Deoxo-Fluor	46
8	A (iv)	**3c**	**4c**	Deoxo-Fluor	41
9	A (iv)	**3d**	**4d**	Deoxo-Fluor	43
10	B	**3a**	**5a**	Ms_2O	93
11	B	**3b**	**5b**	Ms_2O	96
12	B	**3c**	**5c**	Ms_2O	90
13	B	**3d**	**5d**	Ms_2O	95
14	C	**5a**	**4a**	$Et_3N{\cdot}HF$	18 (17)
15	C	**5b**	**4b**	$Et_3N{\cdot}HF$	14 (13)
16	D	**5a**	**6a**	NaI	95 (88)
17	D	**5b**	**6b**	NaI	95 (91)
18	D	**5c**	**6c**	NaI	98 (88)
19	D	**5d**	**6d**	NaI	94 (89)
20	E	**3a**	**6a**	I_2–PPh_3	68
21	E	**3b**	**6b**	I_2–PPh_3	79
22	F	**6a**	**4a**	AgF	77 (68)
23	F	**6b**	**4b**	AgF	72 (66)
24	F	**6c**	**4c**	AgF	84 (74)
25	F	**6d**	**4d**	AgF	81 (72)
26	G	**4b**	**4e**	H^+–EtOH	70
27	H	**4c**	**4f**	MeONa	82
28	H	**4d**	**4g**	MeONa	79

[a] In the presence of $^iPr_2EtN$. [b] Values in parentheses are overall yields from **3a**–**d**.

Table 2 Cytostatic and ADA inhibitory activity of title compounds

Compound	IC_{50}/μmol l^{-1} [a]		
	HL60	CCRF-CEM	ADA
4a	NA[b]	NA	NA
4e	NA	NA	NA
4f	1.54 (±0.11)	0.70 (±0.04)	NA
4g	NA	NA	NA

[a] Values are means of four experiments, standard deviation is given in parentheses. [b] NA = not active (inhibition of cell growth at 10 μM was lower than 30%).

sequence *via* iodomethyl derivatives gives the fluoromethylpurines **4a**–**d** in relatively good total yields of 66–74% from **3a**–**d**. On the other hand the direct deoxyfluorinations offers somewhat lower yields (41–46%) but saves 1–2 steps.

Standard deprotection of 6-(fluoromethyl)purine intermediates **4b**–**d** was used to prepare the final free 6-(fluoromethyl)purine base and nucleosides **4e**–**g** (Scheme 2, entries 26–28, Table 1). The THP protective group in position 9 of purine is easily cleavable under mild acidic conditions. Thus compound **4b** was deprotected using Dowex 50 × 8 (H^+ form)[18] in ethanol to afford free base **4e** in 70% of yield. The ester groups in **4c**,**d** were cleaved by NaOMe in methanol at rt[19] to give free nucleosides **4f**,**g** in about 80% yield.

Title 6-(fluoromethyl)purines and nucleosides **4a**,**e**–**g**, were subjected for biological activity screening. *In vitro* cytostatic activity tests (inhibition of cell growth) were performed using the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 219); human promyelocytic leukemia HL60 cells (ATCC CCL 240); human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2); and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). Adenosine deaminase (ADA) inhibition was studied[20] on calf intestinal adenosine aminohydrolase (EC 3.5.4.4.). The results are summarized in Table 2.

The only active compound of this series was the 6-(fluoromethyl)purine ribonucleoside (**4f**) that exerted significant antiproliferative activity against HL-60 and CCRF-CEM (IC_{50} = 1.54 and 0.70 μmol l^{-1}, respectively) but no considerable effect against L1210 and HeLa S3 cell-lines. The other tested compounds were entirely inactive. The cytostatic effect of **4f** is somewhat lower than that of the corresponding 6-(hydroxymethyl)purine ribonucleoside[3] and is comparable to that of 6-(trifluoromethyl)purine ribonucleoside.[2] Unlike the 6-(hydroxymethyl)purine ribonucleoside[3] compound **4f** does not inhibit ADA. Therefore it can be concluded that in terms of their biological activity the 6-(fluoromethyl)purine nucleosides are analogues of 6-methylpurine[4] nucleosides.

In conclusion, two alternative approaches to the synthesis of novel 6-(fluoromethyl)purine bases and nucleosides either by direct deoxyfluorination or by multistep functional group transformation of 6-(hydroxymethyl)purines have been developed. The multistep sequence gives higher total yields, while the direct approach obviously saves time. Ribonucleoside **4f** shows promising cytostatic effects which invite further research in this field. Application of this methodology to the synthesis of series of modified nucleoside and nucleotide analogues, their biological activity screening and DNA polymerase assays are underway. This methodology may also be adopted for the synthesis of other types of fluoromethyl(het)aromatics as hydrophobic nucleobase surrogates.

Experimental

General

Starting materials: 9-benzyl-6-(hydroxymethyl)purine,[3] 6-(hydroxymethyl)-9-(tetrahydropyran-2-yl)purine,[3] 6-chloro-9-(2-deoxy-3,5-di-*O*-toluoyl-β-D-*erythro*-pentofuranosyl)purine.[21] All preparations of (acyloxymethyl)zinc iodides and cross-coupling reactions were conducted under argon atmosphere. THF was dried and distilled from sodium–benzophenone. NMR spectra were recorded on Bruker Avance 400 MHz spectrometer (^{1}H at 400, ^{13}C at 100.6 MHz), a Bruker Avance (500 MHz for ^{1}H and 125.8 MHz for ^{13}C). Chemical shifts (in ppm, δ scale) were referenced to TMS as internal standard. For spectra, refer to the supplementary information. The assignment of carbons was based on C,H-HSQC and C,H-HMBC experiments. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured at 25 °C on a Autopol IV (Rudolph Research Analytical) polarimeter, $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). Cytostatic activity tests were performed as described in ref.[1a] ADA inhibition assay was performed by standard technique ref.[20]

6-Chloro-9-(2,3,5-*O*-toluoyl-β-D-ribofuranosyl)purine (1c). New compound prepared in analogy to published method.[22] Anal. calcd for $C_{34}H_{29}ClN_4O_7$: C, 63.70; H, 4.56; Cl, 5.53; N, 8.74; found: C, 63.61; H, 4.45; Cl, 5.54; N, 8.63. ^{1}H NMR (400 MHz, $CDCl_3$): 2.38 and 2.42 (2 × s, 9H, CH_3-Tol); 4.65 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.0, H-5′b); 4.83 (ddd, 1H, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 4.0, 3.1, H-4′); 4.92 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.1, H-5′a); 6.20 (dd, 1H, $J_{3',2'}$ = 5.8, $J_{3',4'}$ = 4.7, H-3′); 6.37 (t, 1H, $J_{2',3'}$ = 5.8, $J_{2',1'}$ = 5.3, H-2′); 6.45 (d, 1H, $J_{1',2'}$ = 5.3, H-1′); 7.16, 7.23 and 7.25 (3 × m, 3 × 2H, H-*m*-Tol); 7.80, 7.91 and 7.96 (3 × m, 3 × 2H, H-*o*-Tol); 8.27 (s, 1H, H-8); 8.62 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.70 and 21.74 (CH_3-Tol); 63.15 (CH_2-5′); 71.31 (CH-3′); 73.73 (CH-2′); 81.23 (CH-4′); 87.33 (CH-1′); 125.50, 125.92 and 126.45 (C-*i*-Tol); 129.25, 129.29 and 129.35 (CH-*m*-Tol); 129.70 and 129.86 (CH-*o*-Tol); 132.30 (C-5); 143.84 (CH-8); 144.34, 144.66 and 144.80 (C-*p*-Tol); 151.32 (C-4); 151.53 (C-6); 152.28 (CH-2); 165.15, 165.36 and 166.12 (CO-Tol).

Preparation of (acetyloxymethyl)zinc iodide

A solution of iodomethyl acetate[23] (2.00 g, 10 mmol) in THF (5 ml) was added at 0–5 °C to the suspension of zinc dust (1.31 g, 20 mmol) in THF (4 ml), which was preactivated with dibromoethane (20 μl) and trimethylsilyl chloride (20 μl). Reaction mixture was stirred 1 h at 0–5 °C. After settling down of non-reacted zinc, a clear solution was obtained. The concentration of (acetyloxymethyl)zinc iodide has been determined by complexometric titration of Zn(II) ions in hydrolyzed aliquot (average value approx. 1.0 mmol ml^{-1}).

General procedure for cross-couplings of (acetyloxymethyl)zinc iodide with 6-chloropurine nucleosides 1c,d

A solution of (acetyloxymethyl)zinc iodide (1.7 ml, *ca.* 1.5 mmol) in THF was added at rt to a solution of a 6-chloropurine nucleoside (**1c** or **1d**, 0.5 mmol), $Pd(PPh_3)_4$ (29 mg, 5%) in THF (1 ml) and stirred at rt for 8 h. The reaction was quenched with 1 M NaH_2PO_4 (30 ml) and extracted with $CHCl_3$ (3 × 30 ml). Collected organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude oily product was purified on silica gel (hexanes–ethyl acetate 3 : 1–1 : 1).

6-(Acetyloxymethyl)-9-(2,3,5-tri-*O*-toluoyl-β-D-ribofuranosyl)-purine (2c). Yield: 81% as white foam. Exact mass (FAB HR MS) found: 679.2415; calcd for $C_{37}H_{35}N_4O_9$: 679.2404. FAB MS *m/z* (%): 679 (MH^+, 1); 487 (10); 193 (4); 151 (5); 119 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 2.21 (s, 3H, CH_3-Ac); 2.38 and 2.42 (2 × s, 9H,CH_3-Tol); 4.66 (dd, 1H, J_{gem} = 12.2, $J_{5'b,4'}$ = 4.1, H-5′b); 4.82 (td, 1H, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 4.1, 3.1, H-4); 4.89 (dd, 1H, J_{gem} = 12.2, $J_{5'a,4'}$ = 3.1, H-5′a); 5.60 (s, 2H, O–CH_2); 6.20 (dd, 1H, $J_{3',2'}$ = 5.8, $J_{3',4'}$ = 4.6, H-3′); 6.38 (t, 1H, $J_{2',3'}$ = 5.8, $J_{2',1'}$ = 5.5, H-2′); 6.48 (d, 1H, $J_{1',2'}$ = 5.5,

H-1′); 7.16, 7.22 and 7.26 (3 × m, 3 × 2H, H-*m*-Tol); 7.81, 7.91 and 7.99 (3 × m, 3 × 2H, H-*o*-Tol); 8.23 (s, 1H, H-8); 8.85 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.80 (CH_3-Ac); 21.70 and 21.73 (CH_3-Tol); 62.42 (O-CH_2); 63.41 (CH_2-5′); 71.39 (CH-3′); 73.66 (CH-2′); 81.06 (CH-4′); 86.84 (CH-1′); 125.60, 125.99 and 126.56 (C-*i*-Tol); 129.22, 129.26 and 129.34 (CH-*m*-Tol); 129.77, 129.86 and 129.88 (CH-*o*-Tol); 132.35 (C-5); 143.41 (CH-8); 144.24, 144.59 and 144.71 (C-*p*-Tol); 151.27 (C-4); 152.65 (CH-2); 155.69 (C-6); 165.15, 165.37 and 166.18(CO-Tol); 170.74 (CO-Ac). IR (CCl_4): ν = 3039, 1755, 1733, 1612, 1598, 1498, 1410, 1377, 1334, 1266, 1226, 1179, 1125, 1113, 1092, 1021, 643 cm^{-1}.

6-(Acetyloxymethyl)-9-(2-deoxy-3,5-di-*O*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (2d). Yield: 77% as white crystals (mp 111–112 °C). Anal. calcd for $C_{29}H_{28}N_4O_7$: C, 63.96; H, 5.18; N, 10.29; found: C, 63.99; H, 5.18; N, 10.15. FAB MS *m/z* (%): 545 (M^+, 2), 353 (2), 193 (40), 151 (29), 119 (100), 91 (40). ^{1}H NMR (400 MHz, $CDCl_3$): 2.22 (s, 3H, CH_3-Ac); 2.41 and 2.45 (2 × s, 2 × 3H, CH_3-Tol); 2.86 (ddd, 1H, J_{gem} = 14.1, $J_{2'b,1'}$ = 5.8, $J_{2'b,3'}$ = 2.1, H-2′b); 3.18 (ddd, 1H, J_{gem} = 14.2, $J_{2'a,1'}$ = 8.4, $J_{2'a,3'}$ = 6.3, H-2′a); 4.63–4.70 (m, 2H, H-5′b and H-4′); 4.78 (dd, 1H, J_{gem} = 13.2, $J_{5'a,4'}$ = 5.2, H-5′a); 5.61 (s, 2H, O-CH_2); 5.83 (dt, 1H, $J_{3',2'a}$ = 6.3, $J_{3',4'}$ = 2.2, $J_{3',2'b}$ = 2.1, H-3′); 6.60 (dd, 1H, $J_{1',2'a}$ = 8.4, $J_{1',2'b}$ = 5.8, H-1′); 7.23 and 7.29 (2 × m, 2 × 2H, H-*m*-Tol); 7.90 and 7.98 (2 × m, 2 × 2H, H-*o*-Tol); 8.25 (s, 1H, H-8); 8.89 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.78 (CH_3-Ac); 21.69 and 21.75 (CH_3-Tol); 37.78 (CH_2-2′); 62.43 (O–CH_2); 63.89 (CH_2-5′); 75.02 (CH-3′); 83.14 (CH-4′); 84.92 (CH-1′); 126.32 and 126.59 (C-*i*-Tol); 129.26 (CH-*m*-Tol); 129.61 and 129.79 (CH-*o*-Tol); 132.29 (C-5); 143.00 (CH-8); 144.17 and 144.55 (C-*p*-Tol); 151.03 (C-4); 152.38 (CH-2); 155.54 (C-6); 165.90 and 166.11 (CO-Tol); 170.75 (CO-Ac). IR (CCl_4): ν = 3039, 1755, 1728, 1613, 1597, 1496, 1409, 1376, 1333, 1267, 1226, 1178, 1100, 1021 cm^{-1}.

General procedure for deacetylation of nucleosides 2c,d

Aqueous ammonia (25%, 0.4 ml, 6 mmol) was added to the mixture of 6-(acetyloxymethyl)purine nucleoside **2** (1 mmol) and $ZnCl_2$ (164 mg, 1.2 mmol) in EtOH (25 ml). Reaction mixture was stirred for 12–20 h at rt, adsorbed on silica gel and chromatographed (hexanes–ethyl acetate 1 : 1–1 : 2).

6-(Hydroxymethyl)-9-(2,3,5-tri-*O*-toluoyl-β-D-ribofuranosyl)-purine (3c). Yield: 60% as white solid. Exact mass (FAB HR MS) found: 673.2313; calcd for $C_{35}H_{33}N_4O_8$: 673.2298. FAB MS *m/z* (%): 637 (MH^+, 4); 487 (5); 151 (4); 119 (100). ^{1}H NMR (500 MHz, DMSO-d_6): 2.34, 2.38 and 2.39 (3 × s, 3 × 3H,CH_3-Tol); 4.63 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.8, H-5′b); 4.78 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.6, H-5′a); 4.85 (ddd, 1H, $J_{4',3'}$ = 5.7, $J_{4',5'}$ = 4.8, 3.6, H-4); 4.89 (d, 2H, $J_{CH2,OH}$ = 6.3, CH_2–OH); 5.46 (t, 1H, $J_{OH,CH2}$ = 6.3, OH); 6.23 (dd, 1H, $J_{3',2'}$ = 6.0, $J_{3',4'}$ = 5.7, H-3′); 6.51 (dd, 1H, $J_{2',3'}$ = 6.0, $J_{2',1'}$ = 4.7, H-2′); 6.66 (d, 1H, $J_{1',2'}$ = 4.7, H-1′); 7.25, 7.30 and 7.31 (3 × m, 3 × 2H, H-*m*-Tol); 7.76, 7.85 and 7.87 (3 × m, 3 × 2H, H-*o*-Tol); 8.76 (s, 1H, H-2); 8.79 (s, 1H, H-8). ^{13}C NMR (125.8 MHz, DMSO-d_6): 21.36, 21.37 and 21.39 (CH_3-Tol); 60.14 (CH_2-OH); 63.19 (CH_2-5′); 70.76 (CH-3′); 72.91 (CH-2′); 79.59 (CH-4′); 86.75 (CH-1′); 125.75, 126.07 and 126.72 (C-*i*-Tol); 129.45, 129.52, 129.60 and 129.62 (CH-Tol); 131.81 (C-5); 144.06, 144.57 and 144.69 (C-*p*-Tol); 145.59 (CH-8); 150.61 (C-4); 152.07 (CH-2); 160.36 (C-6); 164.66, 164.86 and 165.59(CO-Tol). IR (CCl_4): ν = 3445, 1727, 1612, 1588, 1498, 1412, 1336, 1267, 1180, 1126, 1114, 1093, 691, 645 cm^{-1}.

6-(Hydroxymethyl)-9-(2-deoxy-3,5-di-*O*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (3d). Yield: 69% as white solid. Exact mass (FAB HR MS) found: 503.1906; calcd for $C_{27}H_{27}N_4O_6$: 503.1931. FAB MS *m/z* (%): 503 (MH^+, 60), 353 (10), 151 (100), 119 (90). ^{1}H NMR (400 MHz, MeOD): 2.38 and 2.42 (2 × s, 2 × 3H, CH_3-Tol); 2.88 (ddd, 1H, J_{gem} = 14.3, $J_{2'b1'}$ = 6.4, $J_{2'b3'}$ = 3.1, H-2′b); 3.46 (ddd, 1H, J_{gem} = 14.3, $J_{2'a1'}$ = 7.4, $J_{2'a3'}$ = 6.7, H-2′a); 4.58–4.66 (m, 2H, H-5′b and H-4′); 4.77 (m, 1H, H-5′a); 5.02 (d, 1H, J_{gem} = 15.0, O-CH_2b); 5.06 (d, 1H, J_{gem} = 15.0, O–CH_2a); 5.93 (dt, 1H, $J_{3'2'b}$ = 6.7, $J_{3'2'a}$ = 3.1, $J_{3'4'}$ = 2.8, H-3′); 6.60 (dd, 1H, $J_{1'2'a}$ = 7.4, $J_{1'2'b}$ = 6.4, H-1′); 7.21 and 7.32 (2 × m, 2 × 2H, H-*m*-Tol); 7.82 and 7.98 (2 × m, 2 × 2H, H-*o*-Tol); 8.57 (s, 1H, H-8); 8.78 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, MeOD): 21.62 and 21.67 (CH_3-Tol); 37.61 (CH_2-2′); 61.46 (O-CH_2); 65.00 (CH_2-5′); 76.46 (CH-3′); 84.32 (CH-4′); 86.83 (CH-1′); 128.08 and 128.14 (C-*i*-Tol); 130.22 and 130.35 (CH-*m*-Tol); 130.67 and 130.83 (CH-*o*-Tol); 132.71 (C-5); 145.49 and 145.82 (C-*p*-Tol); 146.13 (CH-8); 152.01 (C-4); 153.20 (CH-2); 160.82 (C-6); 167.43 and 167.64 (CO-Tol). IR ($CHCl_3$): ν = 3458, 1721, 1612, 1603, 1585, 1495, 1410, 1336, 1269, 1179, 1121, 1102, 1020, 691, 646 cm^{-1}.

Typical procedure for deoxyfluorinations with DAST and Deoxo-Fluor (step A)

6-(Hydroxymethyl)purine **3** (0.5 mmol) was dissolved in CH_2Cl_2 (5 ml) under Ar atmosphere and cooled to −20 °C. Deoxo-Fluor (0.5–1 mmol) was then added and the reaction mixture was allowed to warm to rt and stirred for 10 h. Reaction was quenched with 5% $NaHCO_3$ and extracted with $CHCl_3$. Organic phase was drying over $MgSO_4$ concetrated and chromatographed on silica gel (hexanes–ethyl acetate 2 : 1 to 1: 1).

Typical procedure for deoxyfluorinations with perfluorbutane-1-sulfonyl fluoride (step A)

Perfluorobutane-1-sulfonyl fluoride (0,75–1 mmol) was added to a solution of 6-(hydroxymethyl)purine **3** (0.5 mmol) in toluene or CH_2Cl_2 (4 ml) in presence of base (DBU or ^{i}Pr$_2$NEt; 0,83–1,1 mmol). The reaction mixture was stirred for 12–32 h. Reaction was quenched with 5% $NaHCO_3$ and extracted with $CHCl_3$. Organic phases were dried over $MgSO_4$ concentrated and chromatographed on silica gel (hexanes–ethyl acetate 2 : 1 to 1 : 1).

Typical procedure for reactions of 6-(methanesulfonyloxymethyl)purines 5 with $Et_3N{\cdot}3HF$ (step C)

Hünig's base (^{i}Pr$_2$EtN; 188 µl, 1.1 mmol) and $Et_3N.3HF$ (82 µl, 0.5 mmol) were added to a solution of 6-(methanesulfonyloxymethyl)purine **5** (0.5 mmol) in 1,2-dichlorethane (10 ml). Reaction mixture was stirred for 12–20 h at 80 °C. After starting material was consumed, the reaction mixture was chromatographed on a column of silica gel (hexanes–ethyl acetate 1 : 1).

Typical procedure for reactions of 6-(iodomethyl)purines 6 with AgF (step F)

A solution of a 6-(iodomethyl)purine **6** (0.2 mmol) in THF (5 ml) was stirred with AgF (33 mg, 0.26 mmol) for 10 h at rt with exclusion of light. After the reaction was complete, the solids were filtered off and washed with ethyl acetate. Volatiles were evaporated *in vacuo* and crude product was chromatographed on silica gel (hexanes–ethyl acetate 2 : 1–1 : 1).

9-Benzyl-6-(fluoromethyl)purine (4a). Yield: 42% with Deoxo-Fluor (step A), 68% *via* 6-(iodomethyl)purine **6a** (steps B, D, F). White crystals, mp 64–65 °C. Anal. calcd for $C_{13}H_{11}FN_4$: C, 64.45; H, 4.58; F, 7.84; N, 23.13; found: C, 64.08; H, 4.60; F, 7.77; N, 22.68. Exact mass (FAB HR MS) found: 243.1038; calcd for $C_{13}H_{12}FN_4$: 243.1046. FAB MS *m/z* (%): 243.1 (MH^+, 22); 225 (7); 91 (100). ^{1}H NMR (500 MHz, $CDCl_3$): 5.48 (s, 2H, CH_2-Ph); 5.90 (d, 2H, $J_{H,F}$ = 46.7, CH_2-F); 7.30–7.40 (m, 5H, Ph); 8.10 (s, 1H, H-8); 9.04 (d, 1H, $J_{H,F}$ = 0.8, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): 47.41 (CH_2-Ph); 80.97 (d, $J_{C,F}$ = 172, CH_2-F); 127.88, 128.75 and 129.22 (CH-Ph); 131.41 (C-5); 134.82 (C-*i*-Ph); 145.01 (CH-8); 152.02 (C-4); 152.61 (CH-2); 154.52

(d, $J_{C,F}$ = 18, C-6). ^{19}F NMR (188.2 MHz, $CDCl_3$): −225.38 (t, $J_{F,H}$ = 46.7). IR (CCl_4): ν = 3035, 1599, 1500, 1407, 1331, 1211, 1030 cm^{-1}.

6-(Fluoromethyl)-9-(tetrahydropyran-2-yl)purine (4b). Yield: 46% with Deoxo-Fluor (step A), 66% *via* 6-(iodomethyl)purine **6b** (steps B, D, F). White crystals, mp 71–72 °C. Exact mass (FAB HR MS) found: 237.1146; calcd for $C_{11}H_{14}FN_4O$: 237.1152. FAB MS *m/z* (%): 236 (M^+, 11); 149 (33); 85 (100). ^{1}H NMR (500 MHz, $CDCl_3$): 1.65–1.87 and 2.04–2.21 (m, 6H, CH_2-THP); 3.81 (dt, 1H, J = 11.8 and 2.6, bCH_2-O-THP); 4.20 (ddt, 1H, J = 11.8, 4.5 and 1.7, aCH_2-O-THP); 5.83 (dd, 1H, J = 10.4 and 2.5, CH-O-THP); 5.88 and 5.91 (dd, 1H, $J_{H,F}$ = 46.7, J_{gem} = 12.6, CH_2-F); 8.34 (s, 1H, H-8); 9.00 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): 22.68, 24.79 and 31.81 (CH_2-THP); 68.87 (CH_2-O-THP); 80.89 (d, $J_{C,F}$ = 172, CH_2-F); 82.09 (CH-O-THP); 131.57 (C-5); 143.04 (CH-8); 151.14 (C-4); 152.39 (CH-2); 154.47 (d, $J_{C,F}$ = 18, C-6). IR (CCl_4): ν = 2949, 2857, 1601, 1588, 1496, 1410, 1332, 1210, 1088, 1047, 645 cm^{-1}.

6-(Fluoromethyl)-9-(2,3,5-tri-*O*-toluoyl-β-D-ribofuranosyl)-purine (4c). Yield: 41% with Deoxo-Fluor (step *A*), 70% *via* 6-(iodomethyl)purine **6c** (steps B, D, F). White foam. Exact mass (FAB HR MS) found: 639.2228; calcd for $C_{35}H_{32}FN_4O_7$: 639.2255. FAB MS *m/z* (%): 639 (M^+, 2); 621 (2); 487 (10); 119 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 2.38, 2.42 and 2.43 (3 × s, 3 × 3H, CH_3-Tol); 4.66 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.1, H-5′b); 4.83 (td, 1H, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 4.1, 3.1, H-4); 4.91 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.1, H-5′a); 5.86 (d, 2H, $J_{H,F}$ = 46.6, CH_2-F); 6.22 (dd, 1H, $J_{3',2'}$ = 5.8, $J_{3',4'}$ = 4.6, H-3′); 6.40 (t, 1H, $J_{2',3'}$ = 5.8, $J_{2',1'}$ = 5.4, H-2′); 6.49 (d, 1H, $J_{1',2'}$ = 5.4, H-1′); 7.16, 7.23 and 7.26 (3 × m, 3 × 2H, H-*m*-Tol); 7.81, 7.92 and 7.98 (3 × m, 3 × 2H, H-*o*-Tol); 8.27 (s, 1H, H-8); 8.88 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.71 and 21.75 (CH_3-Tol); 63.30 (CH_2-5′); 71.37 (CH-3′); 73.68 (CH-2′); 80.79 (d, $J_{C,F}$ = 173, CH_2-F); 81.11 (CH-4′); 87.00 (CH-1′); 125.57, 125.98 and 126.52 (C-*i*-Tol); 129.24, 129.29 and 129.35 (CH-*m*-Tol); 129.76 and 129.88 (CH-*o*-Tol); 132.11 (d, $J_{C,F}$ = 1, C-5); 143.86 (CH-8); 144.29, 144.63 and 144.76 (C-*p*-Tol); 151.55 (C-4); 152.69 (CH-2); 154.98 (d, $J_{C,F}$ = 18, C-6); 165.18, 165.39 and 166.17 (CO-Tol). IR (CCl_4): ν = 3039, 1732, 1612, 1601, 1579, 1498, 1410, 1333, 1266, 1209, 1179,1126, 1113, 1092, 1020, 643 cm^{-1}.

6-(Fluoromethyl)-9-(2-deoxy-3,5-di-*O*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (4d). Yield: 43% with Deoxo-Fluor (step *A*), 72% *via* 6-(iodomethyl)purine **6d** (steps B, D, F). White foam. Exact mass (FAB HR MS) found: 505.1883; calcd for $C_{27}H_{26}FN_4O_5$: 505.1887. FAB MS *m/z* (%): 505 (MH^+, 2); 487 (1); 153 (11); 119 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 2.38 and 2.42 (2 × s, 2 × 3H, CH_3-Tol); 2.88 (ddd, 1H, J_{gem} = 14.2, $J_{2'b,1'}$ = 5.8, $J_{2'b,3'}$ = 2.2, H-2′b); 3.20 (ddd, 1H, J_{gem} = 14.2, $J_{2'a,1'}$ = 8.3, $J_{2'a,3'}$ = 6.4, H-2′a); 4.64–4.70 (m, 2H, H-5′b and H-4′); 4.80 (dd, 1H, J_{gem} = 13.3, $J_{5'a,4'}$ = 5.1, H-5′a); 5.85 (dt, 1H, $J_{3',2'}$ = 6.4, 2.2 $J_{3',4'}$ = 2.4, H-3′); 5.86 (d, 2H, $J_{H,F}$ = 46.6, CH_2-F); 6.62 (dd, 1H, $J_{1'2'}$ = 8.3, 5.8, H-1′); 7.22 and 7.29 (2 × m, 2 × 2H, H-*m*-Tol); 7.89 and 7.98 (2 × m, 2 × 2H, H-*o*-Tol); 8.29 (s, 1H, H-8); 8.93 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.68 and 21.75 (CH_3-Tol); 37.85 (CH_2-2′); 63.86 (CH_2-5′); 75.03 (CH-3′); 80.82 (d, $J_{C,F}$ = 173, CH_2-F); 83.25 (CH-4′); 85.02 (CH-1′); 126.33 and 126.57 (C-*i*-Tol); 129.29 and 129.32 (CH-*m*-Tol); 129.61 and 129.82 (CH-*o*-Tol); 132.17 (d, $J_{C,F}$ = 3, C-5); 143.46 (CH-8); 144.25 and 144.61 (C-*p*-Tol); 151.38 (C-4); 152.44 (CH-2); 154.79 (d, $J_{C,F}$ = 18, C-6); 165.94 and 166.12 (CO-Tol). IR (CCl_4): ν = 3039, 1727, 1613, 1601, 1588, 1497, 1408, 1332, 1267, 1210, 1178,1100, 1021 cm^{-1}.

6-(Fluoromethyl)-9*H*-purine (4e). 6-(Fluoromethyl)-9-(tetrahydropyran-2-yl)purine **4b** (92 mg, 0.389 mmol) was dissolved in ethanol (10 ml) and Dowex 50 WX8 (H^+ form) (*ca.* 20 mg) was added. This suspension was stirred for 1 h at 75 °C. After a complete deprotection of starting material, the reaction mixture was filtered and Dowex was washed with NH_3–EtOH. Volatiles were evaporated *in vacuo*. Crude product was chromatographed on silica gel (hexanes–ethyl acetate 1 : 2–0 : 1) and crystallized from ethyl acetate–hexanes to afford 42 mg (70%) of white solid (mp 204–205 °C). Anal. calcd for $C_6H_5FN_4$: C, 47.37; H, 3.31; F, 12.49; N, 36.83; found: C, 47.02; H, 3.29; F, 12.59; N, 36.48. FAB MS *m/z* (%): 153 (MH^+, 100); 134 (37); 121 (8). ^{1}H NMR (400 MHz, $CDCl_3$): 5.85 (d, 2H, $J_{H,F}$ = 46.6, CH_2-F); 8.59 (s, 1H, H-8); 8.92 (d, 1H, $J_{H,F}$ = 1.0, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 82.80 (d, $J_{C,F}$ = 169, CH_2-F); 127.14 (C-5); 148.09 (CH-8); 153.06 (CH-2); 153.29 (C-6); 158.22 (C-4). ^{19}F NMR (188.2 MHz, $CDCl_3$): − 223.82 (t, $J_{F,H}$ = 46.6). IR (KBr): ν = 3100, 1601, 1479, 1440, 1397, 1328, 1107, 795, 644 cm^{-1}.

6-(Fluoromethyl)-9-(β-D-ribofuranosyl)purine (4f). A methanolic solution of MeONa (*c* = 1 M; 35 µl, 0,035 mmol) was added to a solution of 6-(fluoromethyl)purine ribonucleoside **4c** (110 mg, 0,172 mmol) in methanol (10 ml). After a complete deprotection of starting material (16 h, monitoring by TLC), the reaction mixture was adsorbed on silica gel and chromatographed (ethyl acetate–methanol 1 : 0–9 : 1) to give 40 mg (82%) of white solid (crystalization from MeOH–EtOAc–heptane, mp 184–185 °C). $[\alpha]_D^{20}$ = −29.5 (*c* = 3.59, MeOH). Anal. calcd for $C_{11}H_{13}FN_4O_4$: C, 46.48; H, 4.61; F, 6.68; N, 19.71; found: C, 46.22; H, 4.45; F, 7.03; N, 19.46. Exact mass (FAB HR MS) found: 285.1002; calcd for $C_{11}H_{14}FN_4O_4$: 285.0999. FAB MS *m/z* (%): 285 (MH^+, 15); 257 (3); 153 (16). ^{1}H NMR (400 MHz, DMSO-d_6): 3.58 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.9, $J_{5'b,4'}$ = 4.1, H-5′b); 3.70 (dt, 1H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.2, $J_{5'a,4'}$ = 4.1, H-5′a); 3.99 (q, 1H, $J_{4',5'}$ = 4.1, $J_{4',3'}$ = 3.8, H-4′); 4.20 (bq, 1H, $J_{3',2'}$ = 5.1, $J_{3',OH}$ = 5.0, $J_{3',4'}$ = 3.8, H-3′); 4.63 (q, 1H, $J_{2',OH}$ = 5.7, $J_{2',1'}$ = 5.6, $J_{2',3'}$ = 5.1, H-2′); 5.10 (t, 1H, $J_{OH,5'}$ = 5.9, 5.2, OH-5′); 5.26 (d, 1H, $J_{OH,3'}$ = 5.0, OH-3′); 5.56 (d, 1H, $J_{OH,2'}$ = 5.7, OH-2′); 5.84 (d, 2H, $J_{H,F}$ = 46.6, CH_2-F); 6.07 (d, 1H, $J_{1'2'}$ = 5.6, H-1′); 8.90 (s, 1H, H-8); 8.99 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 61.36 (CH_2-5′); 70.42 (CH-3′); 73.94 (CH-2′); 80.71 (d, $J_{C,F}$ = 167, CH_2-F); 85.90 (CH-4′); 87.87 (CH-1′); 131.97 (d, $J_{C,F}$ = 2, C-5); 145.74 (CH-8); 151.76 (C-4); 152.08 (CH-2); 153.62 (d, $J_{C,F}$ = 17, C-6). ^{19}F NMR (100.6 MHz, DMSO-d_6): −216.76 (t, $J_{F,H}$ = 46.6). IR (KBr): ν = 3382, 3285, 1603, 1585, 1501, 1417, 1405, 1331, 1211, 1119, 1089, 1048, 797, 649 cm^{-1}.

6-(Fluoromethyl)-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-purine (4g). Prepared from 6-(fluoromethyl)purine 2′-deoxynucleoside **4d** (133 mg, 0.264 mmol) by procedure described above (see preparation of **4f**). Yield: 56 mg (79%) of white solid (crystalization from MeOH–EtOAc–heptane, mp 142–143 °C). $[\alpha]_D^{20}$ = −4.3 (*c* = 4.55, MeOH). Anal. calcd for $C_{11}H_{13}FN_4O_3$: C, 49.25; H, 4.88; F, 7.08; N, 20.89; found: C, 49.17; H, 4.81; F, 7.28; N, 20.63. Exact mass (FAB HR MS) found: 269.1057; calcd for $C_{11}H_{14}FN_4O_3$: 269.1050. FAB MS *m/z* (%): 269 (MH^+, 35); 251 (5); 153 (100); 135 (18). ^{1}H NMR (400 MHz, DMSO-d_6): 2.37 (ddd, 1H, J_{gem} = 13.3, $J_{2'b,1'}$ = 6.4, $J_{2'b,3'}$ = 3.7, H-2′b); 2.80 (ddd, 1H, J_{gem} = 13.3, $J_{2'a,3'}$ = 7.1, $J_{2'a,1'}$ = 5.9, H-2′a); 3.53 (ddd, 1H, J_{gem} = 11.8, $J_{5'b,OH}$ = 5.5, $J_{5'b,4'}$ = 4.7, H-5′b); 3.63 (dt, 1H, J_{gem} = 11.8, $J_{5'a,OH}$ = 5.5, $J_{5'a,4'}$ = 5.2, H-5′a); 3.90 (td, 1H, $J_{4',5'}$ = 5.2, 4.7, $J_{4',3'}$ = 3.1, H-4′); 4.46 (dq, 1H, $J_{3',2'}$ = 7.1, 3.7, $J_{3',OH}$ = 4.1, $J_{3',4'}$ = 3.1, H-3′); 4.98 (t, 1H, $J_{OH,5'}$ = 5.5, OH-5′); 5.37 (d, 1H, $J_{OH,3'}$ = 4.1, OH-3′); 5.83 (d, 2H, $J_{H,F}$ = 46.7, CH_2-F); 6.50 (t, 1H, $J_{1'2'}$ = 6.4, 5.9, H-1′); 8.86 (s, 1H, H-8); 8.97 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 39.44 (CH_2-2′); 61.65 (CH_2-5′); 70.73 (CH-3′); 80.69 (d, $J_{C,F}$ = 167, CH_2-F); 83.99 (CH-1′); 88.21 (CH-4′); 131.99 (C-5); 145.71 (CH-8); 151.46 (C-4); 151.97 (CH-2); 153.47 (d, $J_{C,F}$ = 17, C-6). ^{19}F NMR (188.2 MHz, DMSO-d_6): −216.69 (t, $J_{F,H}$ = 46.7). IR (KBr): ν = 3371, 3212, 1598, 1500, 1450, 1398, 1342, 1331, 1207, 1102, 1060, 1027, 751, 645 cm^{-1}.

General procedure for preparation of 6-(methanesulfonyloxymethyl)purines (5)

A solution of 6-(hydroxymethyl)purine **3** (1 mmol) in CH_2Cl_2 (2 ml) was added to a mixture of methanesulfonic anhydride (209 mg, 1.2 mmol), Et_3N (0.2 ml, 1.4 mmol) and 4-(dimethylamino)pyridine (5 mg) in CH_2Cl_2 (8 ml). After consumption of starting material (2 h), the reaction mixture was directly applied on a column of silica gel and product was eluted with hexanes–ethyl acetate 1 : 1–1 : 3.

9-Benzyl-6-(methanesulfonyloxymethyl)purine (5a). Yield: 93% as white solid. Exact mass (FAB HR MS) found: 319.0859; calcd for $C_{14}H_{15}N_4O_3S$: 319.0865. FAB MS *m/z* (%): 319 (MH^+, 100); 225 (25); 91 (76). ^{1}H NMR (400 MHz, $CDCl_3$): 3.24 (s, 3H, CH_3-S); 5.47 (s, 2H, CH_2-N); 5.76 (s, 2H, CH_2-O); 7.30–7.41 (m, 5H, Ph); 8.10 (s, 1H, H-8); 9.03 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 38.44 (CH_3-S); 47.51 (CH_2-N); 66.63 (CH_2-O); 127.94, 128.81 and 129.25 (CH-Ph); 131.89 (C-5); 134.70 (C-*i*-Ph); 145.23 (CH-8); 152.06 (C-4); 152.47 (C-6); 152.65 (CH-2). IR ($CHCl_3$): ν = 3033, 1600, 1501, 1406, 1357, 1333, 1177, 1030, 961, 646, 526, 507 cm^{-1}.

6-(Methanesulfonyloxymethyl)-9-(tetrahydropyran-2-yl)purine (5b). Yield: 96% as white foam. Exact mass (FAB HR MS) found: 313.0976 calcd for $C_{12}H_{17}N_4O_4S$: 313.0971. FAB MS *m/z* (%): 313 (MH^+,11); 229 (93); 135 (38); 85 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 1.65–1.88 and 2.02–2.22 (m, 6H, CH_2-THP); 3.24 (s, 3H, CH_3-S); 3.80 (td, 1H, J = 11.7 and 2.7, bCH_2-O-THP); 4.20 (ddt, 1H, J = 11.7, 4.2 and 1.8, aCH_2-O-THP); 5.73 and 5.77 (2 × d, 2 × 1H, J_{gem} = 13.3, CH_2-O); 5.83 (dd, 1H, J = 10.3 and 2.5, CH-O-THP); 8.35 (s, 1H, H-8); 9.00 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.67, 24.79 and 31.81 (CH_2-THP); 38.44 (CH_3-S); 66.60 (CH_2-O); 68.89 (CH_2-O-THP); 82.22 (CH-O-THP); 132.01 (C-5); 143.33 (CH-8); 151.22 (C-4); 152.43 (C-6); 152.45 (CH-2). IR ($CHCl_3$): ν = 2951, 2861, 1602, 1496, 1407, 1357, 1334, 1177, 1087, 1045, 959, 526, 508 cm^{-1}.

6-(Methanesulfonyloxymethyl)-9-(2,3,5-tri-*O*-toluoyl-β-D-ribofuranosyl)purine (5c). Yield: 90% as white foam. Exact mass (APCI HR MS) found: 715.2083 calcd for $C_{36}H_{34}N_4O_{10}S$: 715.2074. FAB MS *m/z* (%): 715 (MH^+, 5); 487 (10); 228 (4); 119 (100). ^{1}H NMR (500 MHz, $CDCl_3$): 2.38 and 2.43 (2 × s, 9H,CH_3-Tol); 3.21 (s, 3H, CH_3-S); 4.67 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.2, H-5′b); 4.83 (td, 1H, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 4.2, 3.1, H-4′); 4.90 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.1, H-5′a); 5.72 (s, 2H, CH_2-O); 6.20 (dd, 1H, $J_{3',2'}$ = 5.8, $J_{3',4'}$ = 4.7, H-3′); 6.38 (t, 1H, $J_{2',3'}$ = 5.8, $J_{2',1'}$ = 5.4, H-2′); 6.48 (d, 1H, $J_{1',2'}$ = 5.4, H-1′); 7.16, 7.23 and 7.26 (3 × m, 3 × 2H, H-*m*-Tol); 7.80, 7.91 and 7.98 (3 × m, 3 × 2H, H-*o*-Tol); 8.27 (s, 1H, H-8); 8.88 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): 21.71 and 21.75 (CH_3-Tol); 38.46 (CH_3-S); 63.33 (CH_2-5′); 66.48 (CH_2-O); 71.35 (CH-3′); 73.67 (CH-2′); 81.12 (CH-4′); 87.06 (CH-1′); 125.53, 125.94 and 126.51 (C-*i*-Tol); 129.25, 129.29 and 129.35 (CH-*m*-Tol); 129.76, 129.87 and 129.88 (CH-*o*-Tol); 132.65 (C-5); 144.11 (CH-8); 144.32, 144.66 and 144.80 (C-*p*-Tol); 151.61 (C-4); 152.74 (CH-2); 152.91 (C-6); 165.18, 165.38 and 166.16 (CO-Tol). IR ($CHCl_3$): ν = 1727, 1612, 1601, 1499, 1410, 1359, 1336, 1267, 1179, 1126, 1114, 1093, 1020, 964, 839, 643, 526, 508 cm^{-1}.

6-(Methanesulfonyloxymethyl)-9-(2-deoxy-3,5-di-*O*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (5d). Yield: 95% as white solid. Exact mass (FAB HR MS) found: 581.1717 calcd for $C_{28}H_{29}N_4O_8S$: 581.1706. FAB MS *m/z* (%): 581 (MH^+,6); 353 (2); 229 (26); 135 (48); 119 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 2.41 and 2.45 (2 × s, 2 × 3H, CH_3-Tol); 2.88 (ddd, 1H, J_{gem} = 14.2, $J_{2'b,1'}$ = 5.9, $J_{2'b,3'}$ = 2.3, H-2′b); 3.20 (ddd, 1H, J_{gem} = 14.2, $J_{2'a,1'}$ = 8.3, $J_{2'a,3'}$ = 6.4, H-2′a); 3.23 (s, 3H, CH_3-S); 4.64–4.70 (m, 2H, H-4′ and H-5′b); 4.79 (dd, 1H, J_{gem} = 13.4, $J_{5'a,4'}$ = 5.3, H-5′a); 5.72 (s, 2H, CH_2-O); 5.84 (dt, 1H, $J_{3',2'}$ = 6.4, 2.3, $J_{3',4'}$ = 2.3, H-3′); 6.60 (dd, 1H, $J_{1'2'}$ = 8.3, 5.9, H-1′); 7.22 and 7.29 (2 × m, 2 × 2H, H-*m*-Tol); 7.89 and 7.98 (2 × m, 2 × 2H, H-*o*-Tol); 8.29 (s, 1H, H-8); 8.93 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.69 and 21.75 (CH_3-Tol); 37.83 (CH_2-2′); 38.45 (CH_3-S); 63.86 (CH_2-5′); 66.50 (CH_2-O); 74.98 (CH-3′); 83.27 (CH-4′); 85.11 (CH-1′); 126.30 and 126.56 (C-*i*-Tol); 129.29 and 129.32 (CH-*m*-Tol); 129.61 and 129.81 (CH-*o*-Tol); 132.64 (C-5); 143.72 (CH-8); 144.29 and 144.63 (C-*p*-Tol); 151.41 (C-4); 152.49 (CH-2); 152.77 (C-6); 165.93 and 166.11 (CO-Tol). IR ($CHCl_3$): ν = 1721, 1612, 1602, 1497, 1408, 1358, 1334, 1269, 1178, 1102, 1042, 1021, 966, 840, 644, 526, 508 cm^{-1}.

General procedure for preparation of 6-(iodomethyl)purines (6)

Finkelstein reaction of mesylates (5) with NaI (step D). A solution of NaI (300 mg, 2 mmol) in acetone (4 ml) was added to a solution of 6-(methanesulfonyloxymethyl)purine **5** (1 mmol) in dry acetone (6 ml) under Ar atmosphere. Reaction was quantitative and completed after 1.5 h. Reaction mixture was directly applied on a column of silica gel and chromatographed (hexanes–ethyl acetate 1 : 1–1 : 2).

Direct dehydroxy-iodination (step E). A solution of 6-(hydroxymethyl)purine **3** (1 mmol) in CH_2Cl_2 (2 ml) was added to a solution of Ph_3P (314 mg, 1.2 mmol), I_2 (305 mg, 1.2 mmol) and ^{i}Pr_2EtN (0.24 ml, 1.4 mmol) in CH_2Cl_2 (5 ml) under Ar atmosphere. After consumption of starting material (30 min.), the reaction mixture was directly applied on a column of silica gel and product was eluted with hexanes–ethyl acetate 3 : 1–1 : 1.

All 6-(iodomethyl)purines **6a**–**d** were very sensitive for moisture and light. They were used immediately in the next step.

9-Benzyl-6-(iodomethyl)purine (6a). Yield: 88% from 6-(hydroxymethyl)purine **3a** (steps B + D), 68% (step E). White solid which turned yellow after time (mp 130–131 °C). Exact mass (APCI HR MS) found: 351.0094 calcd for $C_{13}H_{12}N_4I$: 351.0107. FAB MS *m/z* (%): 351 (MH^+, 0.1); 225 (100); 135 (11); 91 (32). ^{1}H NMR (400 MHz, $CDCl_3$): 4.86 (s, 2H, CH_2-I); 5.44 (s, 2H, CH_2-N); 7.31–7.41 (m, 5H, Ph); 8.10 (s, 1H, H-8); 8.95 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): −2.06 (CH_2-I); 47.56 (CH_2-N); 128.04, 128.80 and 129.26 (CH-Ph); 130.91 (C-5); 134.85 (C-*i*-Ph); 144.38 (CH-8); 151.80 (C-4); 152.83 (CH-2); 157.82 (C-6). IR ($CHCl_3$): ν = 3092, 3069, 3037, 1595, 1500, 1457, 1403, 1332, 1072, 1030, 648, 576 cm^{-1}.

6-(Iodomethyl)-9-(tetrahydropyran-2-yl)purine (6b). Yield: 91% from 6-(hydroxymethyl)purine **3b** (steps B + D), 79% (step E). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 1.72–1.86 and 2.03–2.20 (m, 6H, CH_2-THP); 3.80 (td, 1H, J = 11.8 and 2.6, bCH_2-O-THP); 4.19 (ddt, 1H, J = 11.8, 4.3 and 1.8, aCH_2-O-THP); 4.84 and 4.88 (2 × d, 2 × 1H, J_{gem} = 9.2, CH_2-I); 5.80 (dd, 1H, J = 10.4 and 2.5, CH-O-THP); 8.35 (s, 1H, H-8); 8.91 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$): −2.11 (CH_2-I); 22.71, 24.81 and 31.80 (CH_2-THP); 68.87 (CH_2-O-THP); 82.12 (CH-O-THP); 131.03 (C-5); 142.39 (CH-8); 150.90 (C-4); 152.59 (CH-2); 157.78 (C-6). IR ($CHCl_3$): ν = 2952, 2862, 1597, 1495, 1403, 1334, 1087, 1046, 913, 876, 645, 589 cm^{-1}.

6-(Iodomethyl)-9-(2,3,5-tri-*O*-toluoyl-β-D-ribofuranosyl)purine (6c). Yield: 84% from 6-(hydroxymethyl)purine **3c** (steps B + D). Yellowish foam. FAB MS *m/z* (%): 747 (MH^+, 0.5); 621 (8); 487 (10); 119 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 2.38 and 2.42 (2 × s, 9H,CH_3-Tol); 4.66 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.1, H-5′b); 4.82 (s, 2H, CH_2-I); 4.83 (td, 1H, $J_{4',3'}$ = 4.7, $J_{4',5'}$ = 4.1, 3.1, H-4′); 4.90 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.1, H-5′a); 6.21 (dd, 1H, $J_{3',2'}$ = 5.8, $J_{3',4'}$ = 4.7, H-3′); 6.38 (t, 1H, $J_{2',3'}$ = 5.8, $J_{2',1'}$ = 5.4, H-2′); 6.47 (d, 1H, $J_{1',2'}$ = 5.4, H-1′); 7.16, 7.22 and 7.26 (3 × m, 3 × 2H, H-*m*-Tol); 7.82, 7.91 and 7.99 (3 × m, 3 × 2H, H-*o*-Tol); 8.27 (s, 1H, H-8); 8.80 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): −2.40 (CH_2-I); 21.71 and 21.74 (CH_3-Tol); 63.37 (CH_2-5′); 71.34 (CH-3′); 73.68 (CH-2′); 81.07

(CH-4′); 86.96 (CH-1′); 125.59, 125.98 and 126.55 (C-*i*-Tol); 129.24, 129.27 and 129.35 (CH-*m*-Tol); 129.78, 129.87 and 129.89 (CH-*o*-Tol); 132.62 (C-5); 143.21 (CH-8); 144.26, 144.60 and 144.74 (C-*p*-Tol); 151.31 (C-4); 152.88 (CH-2); 158.23 (C-6); 165.18, 165.37 and 166.19 (CO-Tol). IR ($CHCl_3$): ν = 1727, 1612, 1595, 1497, 1408, 1334, 1268, 1180, 1154, 1126, 1114, 1093, 1020, 839, 643 cm^{-1}.

6-(Iodomethyl)-9-(2-deoxy-3,5-di-*O*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (6d). Yield: 89% from 6-(hydroxymethyl)purine **3d** (steps B + D). Yellowish solid. ^{1}H NMR (500 MHz, $CDCl_3$): 2.41 and 2.45 (2 × s, 2 × 3H, CH_3-Tol); 2.86 (ddd, 1H, J_{gem} = 14.2, $J_{2'b,1'}$ = 5.8, $J_{2'b,3'}$ = 2.1, H-2′b); 3.19 (ddd, 1H, J_{gem} = 14.2, $J_{2'a,1'}$ = 8.4, $J_{2'a,3'}$ = 6.4, H-2′a); 4.64–4.70 (m, 3H, H-4′ and H-5′b); 4.78 (dd, 1H, J_{gem} = 13.4, $J_{5'a,4'}$ = 5.3, H-5′a); 4.83 (s, 2H, CH_2-I); 5.84 (dt, 1H, $J_{3',2'}$ = 6.4, 2.1, $J_{3',4'}$ = 2.2, H-3′); 6.59 (dd, 1H, $J_{1'2'}$ = 8.4, 5.8, H-1′); 7.23 and 7.29 (2 × m, 2 × 2H, H-*m*-Tol); 7.90 and 7.98 (2 × m, 2 × 2H, H-*o*-Tol); 8.30 (s, 1H, H-8); 8.55 (s, 1H, H-2). ^{13}C NMR (128.5 MHz, $CDCl_3$): −2.27 (CH_2-I); 21.71 and 21.76 (CH_3-Tol); 37.83 (CH_2-2′); 63.91 (CH_2-5′); 75.03 (CH-3′); 83.21 (CH-4′); 85.00 (CH-1′); 126.33 and 126.60 (C-*i*-Tol); 129.32 (CH-*m*-Tol); 129.64 and 129.82 (CH-*o*-Tol); 131.61 (C-5); 142.81 (CH-8); 144.24 and 144.61 (C-*p*-Tol); 151.14 (C-4); 152.64 (CH-2); 158.09 (C-6); 165.94 and 166.14 (CO-Tol). IR ($CHCl_3$): ν = 1721, 1612, 1595, 1495, 1456, 1405, 1332, 1269, 1179, 1102, 1021, 841, 645, 584 cm^{-1}.

Acknowledgements

This work is a part of the research project Z4 055 0506. It was supported by the Grant Agency of the Czech Republic (grant No. 203/03/0035) by the "Centre for New Antivirals and Antineoplastics" (1M6138896301) and by Sumitomo Chemical, Inc. (Osaka, Japan).

References

1 (*a*) M. Hocek, A. Holý, I. Votruba and H. Dvořáková, *J. Med. Chem.*, 2000, **43**, 1817–1825; (*b*) M. Hocek, A. Holý, I. Votruba and H. Dvořáková, *Collect. Czech. Chem. Commun.*, 2001, **66**, 483–499.
2 D. Hocková, M. Hocek, H. Dvořáková and I. Votruba, *Tetrahedron*, 1999, **55**, 11109–11118.
3 P. Šilhár, R. Pohl, I. Votruba and M. Hocek, *Org. Lett.*, 2004, **6**, 3225–3228.
4 J. A. Montgomery and K. J. Hewson, *J. Med. Chem.*, 1968, **11**, 48–52.
5 W. B. Parker, S. A. King, P. W. Allan, L. L. Bennett Jr., J. A. Secrist, III, J. A. Montgomery, K. S. Gilbert, W. R. Waud, A. H. Wells, G. Y. Gillespie and E. J. Sorscher, *Hum. Gene Ther.*, 1997, **8**, 1637–1644.
6 (*a*) A. A. Henry, A. G. Olsen, S. Matsuda, C. Yu, B. H. Geierstanger and F. E. Romesberg, *J. Am. Chem. Soc.*, 2004, **126**, 6923–6931; (*b*) J. S. Lai and E. T. Kool, *Chem. Eur. J.*, 2005, **11**, 2966–2971; (*c*) A. Zahn, C. Brotschi and C. J. Leumann, *Chem. Eur. J.*, 2005, **11**, 2125–2129.
7 S. Cohen, E. Thom and A. Bendich, *J. Org. Chem.*, 1962, **27**, 3545–3549.
8 M. Shimazaki, H. Nakamura, Y. Iitaka and M. Ohno, *Chem. Pharm. Bull.*, 1983, **31**, 3104–3112.
9 (*a*) W. J. Middleton, *J. Org. Chem.*, 1975, **40**, 574–578; (*b*) L. N. Markovskii, V. E. Pashinnik and A. V. Kirsanov, *Synthesis*, 1973, 787–789.
10 (*a*) S. Takamatsu, S. Katayama, N. Hirose, E. D. Cock, G. Schelkens, M. Demillequand, J. Brepoels and K. Izawa, *Nucleosides, Nucleotides & Nucleic Acids*, 2002, **21**, 849–861; (*b*) B. Bennua-Skalmowski and H. Vorbrüggen, *Tetrahedron Lett.*, 1995, **36**, 2611–2614.
11 (*a*) G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic and H. J. Cheng, *J. Org. Chem.*, 1999, **64**, 7048–7054; (*b*) B. Dolensky and K. L. Kirk, *Collect. Czech. Chem. Commun.*, 2002, **67**, 1335–1344.
12 (*a*) F. L. M. Pattison and J. E. Millington, *Can. J. Chem.*, 1956, **34**, 757–760; (*b*) J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *J. Am. Chem. Soc.*, 1956, **78**, 4812–4814; (*c*) M. B. Giudicelli, D. Picq and B. Veyron, *Tetrahedron Lett.*, 1990, **31**, 6527–6530.
13 (*a*) D. D. Tanner, H. Yabuuchi and E. V. Blackburn, *J. Am. Chem. Soc.*, 1971, **93**, 4802–4808; (*b*) W. F. Edgell and L. Parts, *J. Am. Chem. Soc.*, 1955, **77**, 4899–4902.
14 (*a*) S. Levy, E. Livni, D. Elmaleh and W. Curatolo, *J. Chem. Soc., Chem. Commun.*, 1982, 972–973; (*b*) S. W. Landvatter and J. A. Katzenellenbogen, *J. Med. Chem.*, 1982, **25**, 1300–1307.
15 H. Finkelstein, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 1528–1532.
16 G. A. Wiley, R. L. Hershkowitz, B. M. Rein and B. C. Chung, *J. Am. Chem. Soc.*, 1964, **86**, 964–965.
17 (*a*) P. Tannhauser, R. J. Pratt and E. V. Jensen, *J. Am. Chem. Soc.*, 1956, **78**, 2658–2659; (*b*) B. Helferich and R. Gootz, *Ber. Dtsch. Chem. Ges.*, 1929, **62**, 2505–2507.
18 M. Hocek and A. Holý, *Collect. Czech. Chem. Commun.*, 1995, **60**, 1386–1389.
19 G. Zemplén and A. Kunz, *Ber. Dtsch. Chem. Ges.*, 1923, **56**, 1705–1710.
20 R. P. Agarwal and R. E. Parks, Jr., *Methods Enzymol.*, 1978, **51**, 502–507.
21 Z. Kazimierczuk, H. B. Cottam, G. R. Revankar and R. K. Robins, *J. Am. Chem. Soc.*, 1984, **106**, 6379–6382.
22 (*a*) J. F. Gerster, J. W. Jones and R. K. Robins, *J. Org. Chem.*, 1963, **28**, 945–948; (*b*) Z. Janeba, P. Francom and M. J. Robins, *J. Org. Chem.*, 2003, **68**, 989–992.
23 P. Bigler, H. Muhle and M. Neuenschwander, *Synthesis*, 1978, 593–594.