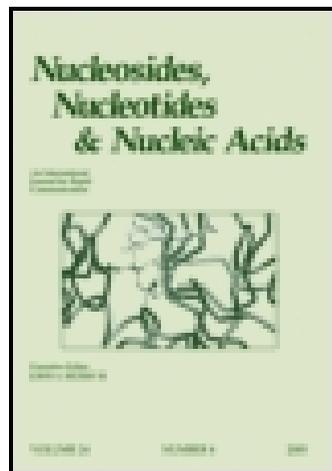


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A Novel Palladium-Catalyzed Deoxygenation of Guanine O⁶-Arenesulfonates. A Practicable Synthesis of 2-Aminopurine Nucleosides and Related Analogs

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**A NOVEL PALLADIUM-CATALYZED DEOXYGENATION OF GUANINE
*O*⁶-ARENESULFONATES. A PRACTICABLE SYNTHESIS OF 2-AMINOPURINE
NUCLEOSIDES AND RELATED ANALOGS.**

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Abstract: A simple synthesis of 2-aminopurine nucleosides and related derivatives has been accomplished from the corresponding guanine *O*⁶-arenesulfonates. Studies towards the determination of optimum conditions for reduction and regioselectivity control are also reported.

The ability to chemically synthesize DNA and RNA oligomers has made it possible to incorporate modified or unnatural base components into short DNA and RNA chains. MacMillan and Verdine¹ recently defined two main strategies: 1. the dedicated monomer strategy using a monomer building block at an early stage in the synthesis, which is generally used, and 2. the convertible nucleoside strategy involving a flexible unit with the appropriate leaving group, which could be displaced at the end of the DNA or RNA synthesis. The 2-aminopurine moiety (AP) is of particular interest because of the existence of an altered *Tetrahymena* group I enzyme (ribozyme), which binds to the base of 2-aminopurine ribonucleoside with greater affinity than to its usual substrate, guanosine.² Besides, effective antiviral prodrugs such as 6-deoxyacyclovir³ and famciclovir⁴ belong to this class of compounds as well as *N*²-substituted-AP nucleosides, which were shown to inhibit mammalian DNA polymerase α .⁵

Our engagement in the synthesis of AP-acyclic guanosine analogs as prodrugs⁶ indicated a need for a simpler modification of the position 6 of guanine which might be further used with a post-synthetic strategy for purines. Since the *O*⁶-

This paper is dedicated to the memory of Professor Roland K. Robins.

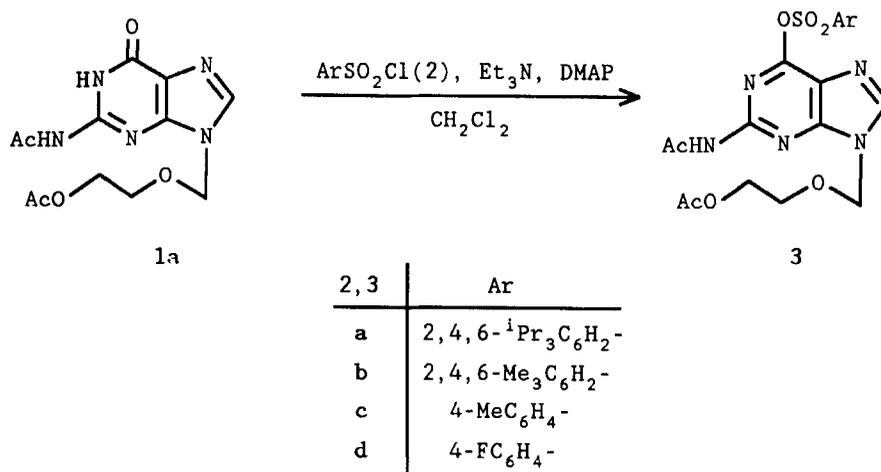
sulfonylated derivatives of guanosine^{7,8} were particularly susceptible to nucleophilic substitution at C⁶, we and others⁹⁻¹² found them to be potentially useful synthetic intermediates for carrying out transformations such as substitutions or hydrogenations in order to overcome largely restricted modifications of guanosine (or other related acyclic analogs) to the corresponding 6-thio-¹³⁻¹⁵ or 6-chloropurines.⁶

To the best of our knowledge, hydrogenation procedures were only conducted *via* a Raney-Ni reduction of thioguanine derivatives^{14,15} or alternatively from 2-amino-6-chloropurine derivatives which can be reduced chemically (H₂/Pd/C,^{16,17} or R₃NH⁺HCO₂⁻/Pd/C^{4,6}) and photochemically (Et₃N, hv)¹⁸ or electrochemically¹⁹ to give AP-nucleosides. Additionally, a two-step route involving NaSH displacement of 6-pyridyl species obtained *via* conversion of guanine nucleosides using trifluoroacetic anhydride in pyridine,¹⁵ as well as the silver oxide mediated oxidation of 2-amino-6-hydrazinopurine nucleoside derivative obtained by displacement of the protected O⁶-(triisopropylbenzenesulfonyl)guanosine,²⁰ were reported.

It is obvious that compounds **3a-d** could serve as synthons at the monomer level, affording by their substitution stable intermediates like O⁶-(2-nitrophenyl), or chlorophenyl and provides a general route for the synthesis of 6-alkoxy- and 6-amino- or 6-thioguanosine and 2'-deoxyguanosine derivatives.^{9-13,20-23} Since O⁶-(mesitylenesulfonyl)deoxyguanosine was easily prepared from commercial guanine phosphoramidite monomer and incorporated into oligomers with satisfactory coupling yield, it would fulfill our stratagem, if it shows an ability of possible C-O *versus* S-O cleavage under appropriate conditions. Thus a competitive desulfonyloxylation strategy *versus* desulfonylation of **3a-d** was thought of, aimed at dedicated monomer or convertible nucleoside strategy.

There have been no attempts of direct conversions of guanine O⁶-sulfonates into 6-deoxygenated state (2-aminopurine) *via* catalytic reduction. A need for a practical synthesis of 6-deoxyacyclovir from readily available acyclovir allows it to be used in turn for its conversion to adequate O⁶-arenesulfonates (Scheme 1). A subsequent transformation to 2-aminopurine derivatives **4** was then thoroughly investigated and is disclosed in this report.

Based on the work of Reese⁷ and Hata,⁸ who have introduced O⁶-arenesulfonyl guanosine derivatives, we have reacted N²,O-diacetylacyclovir **1a** with several arenesulfonyl chlorides in dichloromethane and triethylamine along with a catalytic amount of 4-dimethylaminopyridine (DMAP). The reaction was carried out at room temperature with a molar ratio of the reactants⁹ **1a** : **2** : Et₃N : DMAP equals 1 : 2 : 4 : 0.05. Sulfonylation was performed with 2,4,6-triisopropylbenzene-



Scheme 1

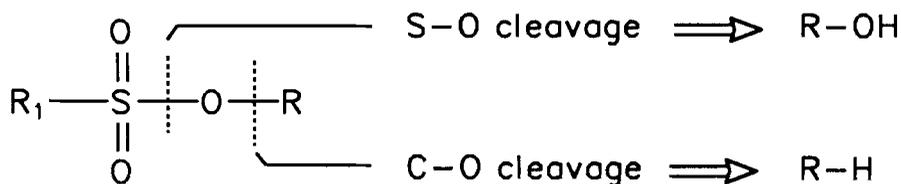
Table 1. Reaction of compound 1a with arenesulfonyl chlorides 2a-d

Product	t[h]	yield ^a [%]	m.p. [°C]
3a	1.5-2.5	95	foam
3b	1	81	138.5-141 and 175-179
3c	10	74	143-145
3d	24	70	132.5-133

^aisolated yields.

sulfonyl (**2a**), 2,4,6-trimethylbenzenesulfonyl (**2b**), p-toluenesulfonyl (**2c**) and p-fluorobenzenesulfonyl (**2d**) chlorides. All sulfonates but **3a** were isolated as crystalline solids after purification by column chromatography and crystallization in very good yields (Table 1).

The initial idea of making a stable and more accessible protected guanine derivative was accomplished by the synthesis of arenesulfonates **3a-d**. However, the most selective cleavage of the C-O bond (palladium-catalyzed deoxygenation) could be expected with perfluoroalkanesulfonates²⁴ possessing electron attracting group R₁. It has been already mentioned that any synthetic attempts failed due to the extreme reactivity of anticipated intermediates.^{21,26}

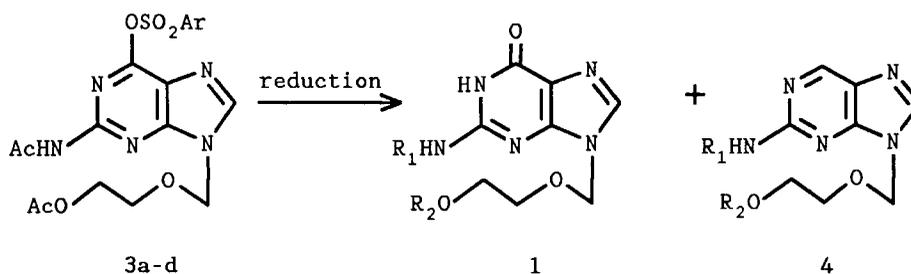


Fortunately, the recent study of Cabri *et al.*²⁷ has revealed that with an appropriate choice of reaction conditions, substrate, reducing agent, catalyst, ligands and solvents, desulfonation could be prevented, resulting in completely selective C-O bond hydrogenolyses. In this paper we have focused on the choice of an adequate reducing agent in order to minimize competitive S-O bond cleavage of the parent guanine *O*⁶-sulfonate during reduction.

There have been only two reports on deoxygenation of heterocycles^{24,25} (quinolyne-2-ylperfluoroalkanesulfonates), all other work was concentrated on phenyl ethers or sulfonates.^{24,25,27-34} Reduction of phenyl tosylate with a Raney-Ni catalyst³³ afforded exclusively benzene, while LiAlH₄ reduction yielded phenol.³⁴ Extension of these reactions to the stable arenesulfonyl derivatives **3a-d** would predict concomitant C-O and S-O cleavage to afford purine derivatives **1a-d** and/or **4a-d**. Therefore, it was decided to compare two methods: 1. Palladium or platinum-catalyzed hydrogenation and/or catalytic transfer hydrogenation (CTH) and 2. tetrahydroborate reductions of the available arenesulfonates (Scheme 2, Table 2).

Compounds **3a-d** were hydrogenated in absolute ethanol using palladium or platinum catalysts (10% Pd/C,³⁰ 10% Pd/CaCO₃, or PtO₂²⁴) in the presence of Et₃N (2 eq) at 60-70°C. Favourable C-O/S-O cleavage ratios and reaction rates were obtained with 10% Pd/C and Pd/CaCO₃, while the latter required longer reaction times for a similar distribution of products, respectively. Reactions catalyzed by PtO₂ were extremely slow, leading to guanines **1** only (not included in Table 2). During the course of reactions, partial deprotection of acetyl groups of both major products was detected. This was not unusual due to the presence of Et₃N. Similar selective deblocking (Et₃N, EtOH, reflux) was reported before.⁶

It was expected that the nature of substituents on the arenesulfonate moiety might affect the reduction and the most reactive among sulfonates **3a-d** provided promising results. Nevertheless, the most crucial factor in reducing S-O scission is by steric hindrance.³¹ This finding corroborates our results since considerable enhancement of C-O *versus* S-O cleavage was obtained with more sterically crowded sulfonate esters. A typical example using Pd/C shows a change in the ratio from 60/40 to 80/20 to 99/1 (**3c** to **3b** to **3a**).



1, 4	R ₁	R ₂
a	Ac	Ac
b	Ac	H
c	H	Ac
d	H	H

Scheme 2

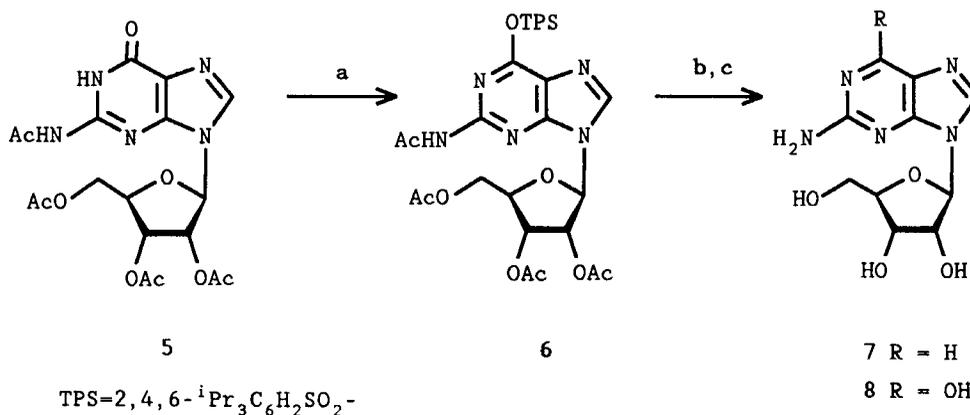
Thus, a direct and short-cut method for the preparation of 2-aminopurine nucleoside monomers is now available. However, the use of molecular hydrogen is not a practical method for large scale reactions. Therefore, other approaches using CTH were tried.^{6,28} Unfortunately, when triethylammonium formate was used as the hydrogen donor in the presence of 10% Pd/C catalyst on **3a**, only 20% conversion to **4a** was achieved, the rest were the products **1a-d**. Similar results were obtained with sodium hypophosphite³⁵, while reaction with cyclohexene showed no tendency for C-O bond scission. There was no satisfactory reaction with hydrazine^{32,36} as well. More promising results were obtained with a homogenous palladium catalyst generated *in situ*, from Pd(OAc)₂ (0.05 eq) and the appropriate ligand (0.055 eq) in dioxane at 90°C with triethylammonium formate as a hydrogen source.²⁷ Much better selectivity was obtained with 1,3-bis(diphenylphosphino)propane (DPPP) instead of the generally used triphenylphosphine (PPh₃) as ligand (Table 2). The choice of the bulky substituent in **3a**, and more effective ligand DPPP affected considerably the competitive C-O *versus* S-O cleavage in a favorable direction and shortened the reaction time. Additional improvement was finally made (80/20 ratio) with **3d** and DPPP according to the enhanced reactivity of 4-fluorobenzenesulfonyl moiety.²⁷ NaBH₄ reduction attempt in polyethyleneglycol (PEG-400)³⁷ at 70°C resulted in preferential S-O bond cleavage.

Finally, this new approach has been successfully applied to N²-acetyl-2',3',5'-tri-O-acetyl-O⁶-(triisopropylbenzenesulfonyl)guanosine **6** [yield 90%, yellow

Table 2. Reduction of guanine O⁶-arenesulfonates 3a-d

substr.	reducing system	conditions	time (h)	yield ^a (%)				ratio 1/4			
				1a	1b	1c	1d		4a	4b	4c
3a	H ₂ , 10% Pd/C	EtOH, 70°C	3	1.0				99.0			1/99
3b			3	14.0	1.0	5.0	0.2	78.6	1.2		20/80
3c			3	32.2	4.7	2.5		60.6			39/61
3d			1	12.3	0.8	1.2	0.3	74.7	4.7	6.0	15/85
3a	H ₂ , 10% Pd/CaCO ₃	EtOH, 70°C	24	2.0				98.0			2/98
3b			24	1.1		2.2	0.4	91.8	4.5		4/96
3c			24	1.0		6.6	0.4	87.3	4.7		8/92
3a	Et ₃ NH ⁺ HCOO ⁻ , 10% Pd/C	EtOH, reflux	7	53.6	1.7	23.4	0.7	20.2	0.4		79/21
3b			6.5	76.6	3.0	12.1	0.7	7.6			92/8
3c			5	85.4	1.5	11.8		1.3			99/1
3d			3	68.2	0.7	30.2		0.9			99/1
3a	Et ₃ NH ⁺ HCOO ⁻ ,	dioxane,	6	81.6	1.6	0.7	1.1	15.0			85/15
3b	Pd(OAc) ₂ , PPh ₃	90°C	12	72.9	2.9	3.4	0.6	19.1	1.1		80/20
3d			1	18.2	3.0	0.4		57.6	20.8		22/78
3a	Et ₃ NH ⁺ HCOO ⁻ ,	dioxane,	2.5	36.1				63.9			36/64
3b	Pd(OAc) ₂ , DPPP	90°C	2	65.6				34.4			66/34
3d			0.5	19.3		0.3		80.4			20/80
3a	NaBH ₄ , PEG 400	70°C	6	2.5	0.9	28.9	57.6	2.9	7.2		90/10
3b			4	1.3		40.6	52.8	1.7	3.6		95/5
3c			2	1.2		35.6	53.9	2.7	6.6		91/9

^a Determined by HPLC under conditions given in the Experimental section.



(a) 2, 4, 6- $^i\text{Pr}_3\text{C}_6\text{H}_2\text{SO}_2\text{Cl}$ (TPSCl), Et_3N , DMAP, CH_2Cl_2

(b) Method A: H_2 , 10% Pd/C, EtOH, 70°C

Method B: $\text{Et}_3\text{NH}^+\text{HCO}_2^-$, Pd(OAc) $_2$, DPPP, dioxane, 90°C

(c) aq. MeNH $_2$

method	7/8
A	80/20
B	90/10

Scheme 3

foam; MS (FAB) $m/z = 718$ ($\text{M} + \text{H}$) $^+$. The AP derivative **7**¹⁶ and guanosine **8** were obtained in favourable ratios under either heterogeneous (method A: 80/20) or homogeneous reduction conditions (method B: 90/10) (Scheme 3).

The reduction of the protected guanine derivatives using either Pd/C/H $_2$ or Pd/C/triethylammonium formate system has proved to be an effective route for the synthesis of 2-aminopurines. With an appropriate choice of sterically hindered arenesulfonates, catalysts and ligands, the competitive S-O bond reduction could be practically eliminated.

Experimental part

Materials and methods. Dichloromethane and 1,4-dioxane were distilled over P $_4\text{O}_{10}$ and LiAlH $_4$, respectively. Compound **1a** was obtained from Krka, Pharmaceuticals, Novo mesto, Slovenia. Other reagents and solvents were of commercial purity. Evaporations were conducted in *vacuo* with a rotary evaporator. Flash chromatography was carried out on Silica gel 60 (40-63 μm , Merck) and analytical TLC on precoated plates Silica gel F $_{254}$ (Merck). The spots were visualized with UV light (254 nm). Reverse-phase HPLC was performed on a

Knauer apparatus using a Lichrospher C18 (250 x 4.0 mm; 5 μ m) column. A 93/7 (v/v) mixture of glycine buffer/MeCN was applied within the first 20 min of analysis, followed by an 85/15 mixture for 10 min at a flow rate of 1.0 ml/min. Samples were detected with an UV monitor (Knauer) at 254 nm. Glycine buffer (pH 5.5) was prepared from an aqueous solution consisting of 7.507 g of glycine and 5.840 g of sodium chloride in 1000 ml of water, followed by pH adjustment with 0.1 M HCl. Retention times were: **1d** (4.03 min); **4d** (6.15 min); **4b** (7.23 min); **1b** (11.45 min); **1c** (13.38 min); **4c** (24.24 min); **4a** (26.42 min); **1a** (28.37 min).

Melting points were determined on a Kofler apparatus and are uncorrected. Mass spectra were recorded on a VG Autospec Q spectrometer at the Jožef Stefan Institute, Ljubljana. Microanalyses were performed at the Department of Chemistry, University of Ljubljana. ^1H - (299.94 MHz), and ^{13}C -NMR (75.43 MHz) spectra were recorded with a Varian VXR-300 instrument. Me_4Si was used as an internal reference for solutions in CDCl_3 (δ_{C} 77.00 ppm) or $\text{Me}_2\text{SO}-d_6$ (δ_{C} 39.50 ppm). IR spectra were recorded on Bio-Rad FTS 15/80 spectrophotometer.

General procedure for *O*⁶-sulfonylation of 9-[(2-acetoxyethoxy)methyl]-2-acetylamino-1,9-dihydro-6H-purin-6-one (1a**).** (Scheme 1, Table 1). Sulfonyl chloride **2** (20.0 mmol) was added to a stirred suspension of **1a** (3.09 g, 10 mmol), DMAP (61 mg, 0.5 mmol) and Et_3N (5.6 ml, 40 mmol) in anhydrous CH_2Cl_2 (100 ml). Stirring was continued at room temperature until **1a** had disappeared on TLC and a clear solution came to notice. Reaction with **2d** did not proceed with complete conversion and was simply filtered after 24 h. The mixture was washed twice with 100 ml water, and the resulting aqueous phase back extracted with CH_2Cl_2 (50 ml). The organic phase was collected, treated with brine (75 ml), dried over Na_2SO_4 , and evaporated. The residue was chromatographed on a silica gel column (125 g) with Et_2O (400 ml), followed by EtOAc (400 ml) to give the product **3a**. Compounds **3b-d** were isolated in the same manner with CH_2Cl_2 and EtOAc as eluents, followed by crystallization.

9-[(2-Acetoxyethoxy)methyl]-2-acetylamino-6-(2,4,6-triisopropylbenzenesulfonyloxy)-9H-purine (3a**).** Yield 95%, yellow foam; IR (film) 2963, 1740, 1694, 1623, 1584, 1520, 1378, 1294, 1231, 1173, 1049, 1026, 770, 718, 666 cm^{-1} ; ^1H -NMR (CDCl_3) δ 1.28 (d, 18H, $\text{CH}(\text{CH}_3)_2$; J 6.8 Hz), 2.02 (s, 3H, OCOCH_3), 2.39 (s, 3H, NHCOCH_3), 2.95 (heptet, 1H, $\text{CH}(\text{CH}_3)_2$; J 6.8 Hz), 3.81 (m, 2H, $\text{CH}_2\text{CH}_2\text{OAc}$), 4.04-4.28 (m, 4H, $\text{CH}_2\text{CH}_2\text{OAc}$ and $\text{CH}(\text{CH}_3)_2$), 5.64 (s, 2H, H-1'), 7.25 (s, 2H, ArH-3',5'), 8.13 (s, 1H, H-8), 8.20 (br s, 1H, NH) ppm; ^{13}C -NMR (CDCl_3) δ 20.66, 23.44, 24.48, 24.92, 29.82, 34.26, 62.68, 68.02, 72.93,

118.86, 123.96, 130.85, 144.01, 150.81, 151.93, 154.66, 154.74, 155.55, 170.64, 170.82 ppm; MS(FAB): m/z 576 (M+H)⁺.

Anal. Calcd for C₂₇H₃₇N₅O₇S (575.69): C, 56.33; H, 6.48; N, 12.17. Found: C, 56.62; H, 6.21; N, 11.76.

9-[(2-Acetoxyethoxy)methyl]-2-acetylamino-6-(2,4,6-trimethylbenzenesulfonyloxy)-9H-purine (3b). Yield 81%, from EtOAc: yellow crystals; mp 138.5-141°C (dec.); IR (film) 3268, 2983, 2945, 1739, 1694, 1624, 1583, 1520, 1372, 1292, 1232, 1201, 1172, 1049, 1025, 771, 719, 663 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.02 (s, 3H, OCOCH₃), 2.34 (s, 3H, 4'-ArCH₃), 2.47 (s, 3H, NHCOCH₃), 2.71 (s, 6H, 2',6'-ArCH₃), 3.79 (m, 2H, CH₂CH₂OAc), 4.19 (m, 2H, CH₂CH₂OAc), 5.63 (s, 2H, H-1'), 7.02 (s, 2H, ArH-3',5'), 8.15 (s, 1H, H-8), 8.28 (br s, 1H, NH) ppm; ¹³C-NMR (CDCl₃) δ 20.67, 21.04, 22.61, 25.02, 62.67, 67.99, 72.95, 118.69, 131.73, 131.83, 140.18, 144.09, 144.42, 151.95, 154.55, 155.44, 170.66, 170.91 ppm; MS(FAB): m/z 492 (M+H)⁺.

Anal. Calcd for C₂₁H₂₅N₅O₇S (491.53): C, 51.32; H, 5.13; N, 14.25. Found: C, 51.45; H, 4.84; N, 14.31.

9-[(2-Acetoxyethoxy)methyl]-2-acetylamino-6-(p-toluenesulfonyloxy)-9H-purine (3c). Yield 74%, from EtOAc: white crystals; mp 143-145°C; IR (film) 3266, 3101, 2955, 1737, 1696, 1624, 1585, 1520, 1376, 1292, 1232, 1177, 1049, 1024, 719, 666 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.02 (s, 3H, OCOCH₃), 2.47 (s, 3H, ArCH₃), 2.50 (s, 3H, NHCOCH₃), 3.79 (m, 2H, CH₂CH₂OAc), 4.19 (m, 2H, CH₂CH₂OAc), 5.64 (s, 2H, H-1'), 7.39 and 8.01 (2 m, 4H, ArH), 8.16 (s, 1H, H-8), 8.67 (br s, 1H, NH) ppm; ¹³C-NMR (CDCl₃) δ 20.74, 21.74, 25.17, 62.69, 67.97, 72.96, 118.57, 128.56, 129.71, 133.04, 144.15, 145.96, 151.82, 154.00, 155.35, 170.51, 170.62 ppm. MS(FAB): m/z 464 (M+H)⁺.

Anal. Calcd for C₁₉H₂₁N₅O₇S (463.47): C, 49.24; H, 4.57; N, 15.11. Found: C, 49.09; H, 4.27; N, 15.05.

9-[(2-Acetoxyethoxy)methyl]-2-acetylamino-6-(p-fluorobenzenesulfonyloxy)-9H-purine (3d). Yield 70%, from EtOAc/diisopropylether (1/1): white crystals; mp 132.5-133°C; IR (film) 3107, 1736, 1697, 1625, 1587, 1520, 1379, 1294, 1234, 1203, 1178, 1049, 1022, 780, 720 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.03 (s, 3H, OCOCH₃), 2.53 (s, 3H, NHCOCH₃), 3.78 (m, 2H, CH₂CH₂OAc), 4.20 (m, 2H, CH₂CH₂OAc), 5.63 (s, 2H, H-1'), 7.29 and 8.21 (2 m, 4H, ArH), 8.11 (s, 1H, H-8), 8.39 (br s, 1H, NH) ppm; ¹³C-NMR (CDCl₃) δ 20.74, 25.22, 62.67, 68.07, 73.03, 116.72 (d, *J*_{CF} 23 Hz), 118.75, 131.85 (d, *J*_{CF} 10 Hz), 144.23, 151.99, 154.09, 155.64, 164.65, 168.07, 170.52, 170.72 ppm. MS(FAB): m/z 468 (M+H)⁺.

Anal. Calcd for $C_{18}H_{18}FN_5O_7S$ (467.44): C, 46.25; H, 3.88; N, 14.98. Found: C, 46.53; H, 3.74; N, 15.51.

General Procedure for Palladium-Catalyzed Reduction with Molecular Hydrogen (Table 2). Sulfonate **3** (0.5 mmol) was dissolved in abs. ethanol (15 ml) and Et_3N (0.7 ml, 5 mmol) and 10% Pd/C or 10% Pd/CaCO₃ (100 mg; Fluka) was added. The reaction was carried out in a Parr hydrogenator at 3.1 bar (3.1×10^5 Pa) at 65–75°C. The resulting mixture was filtered hot after the completion of the reaction. The filtrate was evaporated and analyzed by HPLC.

9-[(2-Acetoxyethoxy)methyl]-2-acetylamino-9H-purine (4a). Et_3N (24 ml, 173 mmol) and 10% Pd/C (1.8 g) was added to the solution of **3a** (9.94 g, 17.3 mmol) in abs. ethanol (250 ml) and the reaction mixture hydrogenated in a Parr hydrogenator at 3.1 bar (3.1×10^5 Pa) at 65–75°C. After 3.5 h the mixture was filtered hot, the filtrate evaporated, and the residue crystallized from abs. ethanol (40 ml) to yield 3.5 g (69%) of a white crystalline product, mp 133–136°C, identical to the reported sample.⁶

2-Acetylamino-9-[(2-hydroxyethoxy)methyl]-9H-purine (4b). A mixture of **4a** (1.453 g, 4.95 mmol) in MeOH (30 ml), pre-saturated with NH_3 at 0°C, was stirred at room temperature for 12 h. Volatile materials were evaporated at 50°C and the residue crystallized from acetonitrile (160 ml) to give colorless needles; yield 1.04 g (84%); mp 180.5–181.5°C; IR (KBr) 3479, 3011, 1712, 1605, 1540, 1511, 1413, 1372, 1234, 1126, 1050 cm^{-1} . ¹H-NMR (Me_2SO-d_6) δ 2.23 (s, 3H, CH₃CO), 3.49 (m, 2H, CH₂CH₂OH), 3.57 (m, 2H, CH₂CH₂OH), 4.68 (t, 1H, OH; *J* 5.5 Hz), 5.64 (s, 2H, H-1'), 8.60 (s, 1H, H-8), 9.01 (s, 1H, H-6), 10.62 (br s, 1H, NH) ppm; ¹³C-NMR (Me_2SO-d_6) δ 24.59 (CH₃; *J* 128.5 Hz), 59.96 (CH₂CH₂OH, *J* 140 Hz), 71.09 (CH₂CH₂OH; *J* 141 Hz), 72.31 (C-1'; *J* 161 Hz), 130.10 (C-5; *J* 11.5, 6.5 Hz), 146.31 (C-8; *J* 213 Hz), 148.89 (C-6; *J* 184 Hz), 152.26 (C-4), 153.23 (C-2; *J* 12 Hz), 168.99 (CO) ppm. MS (EI): *m/z* 251 (M⁺).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.21; N, 27.87. Found: C, 47.96; H, 4.98; N, 27.84.

General Procedure for Palladium-Catalyzed Heterogenous CTH with Triethylammonium Formate (Table 2). Et_3N (1.75 ml, 12.5 mmol), HCOOH (0.25 ml, 6.6 mmol) and 10% Pd/C (20 mg) were sequentially added to a stirred solution of **3** (1.25 mmol) in abs. ethanol (5 ml). The resulting mixture was refluxed for an indicated period of time and hot-filtered afterwards. The filtrate was evaporated and analyzed by HPLC.

General Procedure for Palladium-Catalyzed Homogeneous CTH with Triethylammonium Formate (Table 2). Et_3N (287 μ l, 2 mmol), HCOOH (75 μ l,

2mmol), PPh₃ or DPPP (27.5 μmol), and Pd(OAc)₂ (6 mg, 25 μmol) were sequentially added to a stirred solution of **3** (0.5 mmol) in 1,4-dioxane (3.6 ml). The resulting mixture was heated with stirring at 90°C under N₂ atmosphere for an indicated period of time and hot-filtered afterwards. The filtrate was evaporated and analyzed by HPLC.

General Procedure for Sodium Borohydride Reduction (Table 2). NaBH₄ (29 mg, 0.75 mmol) was added to a mixture of **3** (0.5 mmol) in PEG-400 (3 ml). The reaction mixture was stirred at 70°C for an indicated period of time, then diluted with water (1 ml), neutralized and directly analyzed by HPLC.

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REFERENCES

1. MacMillan, A.M., Verdine, G.L., *Tetrahedron* **1991**, *47*, 2603.
2. Doudna, J.A., Szostak, J.W., Rich, A., Usman, N. *J. Org. Chem.* **1990**, *55*, 5547.
3. Krenitsky, T.A., Hall, W.W., deMiranda, P., Beauchamp, L.M., Schaeffer, H.J., Whiteman, P.D. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3209.
4. Harnden, M.R., Jarvest, R.L., Boyd, M.R., Sutton, D., Vere Hodge, R.A. *J. Med. Chem.* **1989**, *32*, 1738.
5. Wright, G.E., Dudycz, L.W., Kazimierczuk, Z., Brown, N.C., Khan, N.N. *ibid.* **1987**, *30*, 109.
6. Štimac, A., Kobe, J. *Synthesis* **1990**, 461.
7. Bridson, P.K, Markiewicz, W.T., Reese, C.B. *J. Chem. Soc. Chem. Comm.* **1977**, 791.
8. Daskalov, H.P., Sekine, M., Hata, T. *Tetrahedron Lett.* **1980**, *21*, 3899; *idem.*, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3076.
9. Gaffney, B.L., Jones, R.A. *Tetrahedron Lett.* **1982**, *23*, 2253.
10. Reese, C.B., Skone, P.A. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1263.
11. Gaffney, B.L., Marky, L.A., Jones, R.A. *Biochemistry* **1984**, *23*, 5686.
12. Gaffney, B.L., Marky, L.A., Jones, R.A. *Tetrahedron* **1984**, *40*, 3.
13. Xu, Y.Z., Zheng, Q., Swann, P.F. *Tetrahedron Lett.* **1991**, *32*, 2817.
14. Fox, J.J., Wempen, I., Hampton, A., Doerr, I.L. *J. Amer. Chem. Soc.* **1958**, *80*, 1669.

15. Kung, P.-P., Jones, R.A. *Tetrahedron Lett.* **1991**, 32, 3919.
16. Vickers, R.S., Gerster, J.F., Robins, R.K. *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W.W., Tipson, R.S., Eds., Interscience, New York, **1986**, Vol. 1, p 244.
17. Milne, G.H., Townsend, L.B. *J. Med. Chem.* **1974**, 17, 263.
18. Nair, V., Young, D.A., DeSilvia, R.Jr. *J. Org. Chem.* **1987**, 52, 1344.
19. Kusmierek, J.T., Czocharlska, B., Johansson, N.G., Shugar, D. *Acta Chem. Scand.* **1987**, B41, 701.
20. McLaughlin, L.W., Leong, T., Benseler, F., Piel, N. *Nucl. Acids Res.* **1988**, 16, 5631.
21. Herdewijn, P., Van Aerschot, A. *Tetrahedron Lett.* **1989**, 30, 855.
22. Waters, T.R., Connolly, B.A. *Nucleosides & Nucleotides* **1992**, 11, 1561.
23. Rao, T.S., Jayaraman, K., Durland, R.H., Revankar, G.R. *Tetrahedron Lett.* **1992**, 33, 7651.
24. Subramanian, L.R., Martinez, A.G., Fernandez, A.H., Alvarez, R.M. *Synthesis* **1984**, 481.
25. Cacchi, S., Ciattini, P.G., Morera, E., Ortar, G. *Tetrahedron Lett.* **1986**, 27, 5541.
26. Robins, M.J., Hawrelak, S.D., Hernandez, A.E., Wnuk, S.F. *Nucleosides & Nucleotides* **1992**, 11, 821.
27. Cabri, W., De Bernardinis, S., Francalanci, F., Penco, S., Santi, R. *J. Org. Chem.* **1990**, 55, 350.
28. Entwistle, I.D., Hussey, B.J., Johnstone, R.A.W. *Tetrahedron Lett.* **1980**, 21, 4747.
29. Martinez, A.G., Alvarez, R.M., Aguirre, J.A., Subramanian, L.R. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1595.
30. Clauss, K., Jensen, H. *Angew. Chem.* **1973**, 85, 981.
31. Netscher, T., Schwesinger, R., Trupp, B., Prinzbach, H. *Tetrahedron Lett.* **1987**, 28, 2115.
32. Rottendorf, H., Sternhell, S. *Aust. J. Chem.* **1963**, 16, 647.
33. Kenner, G.W., Murray, M.A. *J. Chem. Soc.* **1949**, S178.
34. Schmid, H., Karrer, P. *Helv. Chim. Acta.* **1949**, 32, 1371.
35. Marques, C.A., Selva, M., Tundo, P. *J. Chem. Soc. Perkin Trans. 1* **1993**, 529.
36. Furst, A., Berlo, R.C., Hooton, S. *Chem. Rev.* **1965**, 65, 51.
37. Santaniello, E., Fiecchi, A., Manzocchi, A., Ferraboschi, P. *J. Org. Chem.* **1983**, 48, 3074.