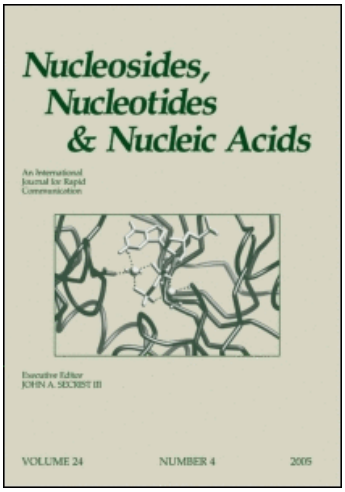

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Transglycosylation Reactions of 6-Thioguanine Acyclonucleosides

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TRANSGLYCOSYLATION REACTIONS OF 6-THIOGUANINE ACYCLONUCLEOSIDES [+]

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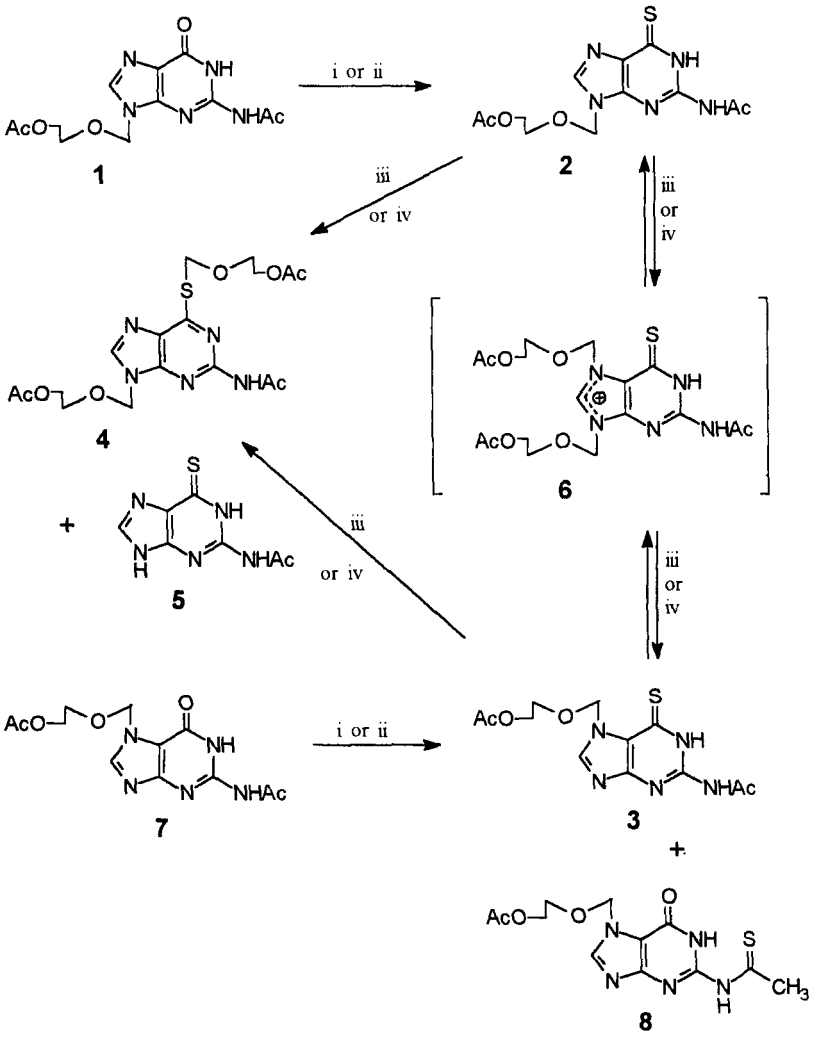
ABSTRACT: 9-(2-Acetoxyethoxy)methyl-N^2-acetyl-6-thioguanine (**2**) undergoes two different transglycosylation reactions: i) the 7 $\rightleftarrows$ 9 isomerization, which gives the respective 7-regioisomer (**3**) as the major product; ii) the 9 $\rightleftarrows$ S^6 glycosyl migration, which leads to a 9,S^6-disubstituted product (**4**). S^6-Methylation completely stopped the reversibility of transglycosylation.

Introduction

The fully protected derivatives of 6-oxopurine nucleosides, *e.g.* inosine, guanosine and their acyclic analogs, have so far been the only known series of compounds which readily undergo a fully reversible 7 $\rightleftarrows$ 9 isomerization.[1] The acid-catalyzed glycosyl migration process represents an intermolecular reaction,[2] and therefore, has found some significant application in the synthesis of biologically active nucleoside analogs *via* exchange methods.[3-5] It has been shown recently, however, that a close congener of guanosine, 6-thioguanosine, undergoes transglycosylation in a different way, when refluxed in chlorobenzene in the presence of acidic catalysts, or subjected to elevated temperatures exceeding 200°C.[6] Thus, two molecules of tetraacetyl-6-thioguanosine are converted to one molecule of 9,S^6-bis(ribofuranosyl) derivative and N^2-acetyl-6-thioguanine. The formation of a possible 7-riboisomer, which could be anticipated *per*

[+] This paper is dedicated to the memory of Professor Alexander Krayevski



SCHEME 1. *Reagents and conditions:* **i**, P_2S_5 in pyridine/H_2O, reflux, 5 h; **ii**, $[p\text{-}CH_3OC_6H_4P(S)S]_2$ in pyridine, reflux, 7 h; **iii**, 220°C, 10 min; **iv**, $p\text{-}CH_3C_6H_4SO_3H$ in chlorobenzene, reflux, 2 h.

analogiam to the reaction of tetraacetylguanosine,[1] has not been observed in that case. The irreversible N9 → S6 glycosyl migration can be rationalized due to a stronger nucleophilicity of sulfur, in comparison to oxygen in the 6-oxopurine series.

In continuation of our study on transglycosylation in the 6-thioguanine series, we have decided to replace the 2,3,5-tri-O-acetyl-β-D-ribofuranosyl group by an acyclic

substituent, which would be less conformationally restricted and less bulky than ribose. The (2-acetoxyethoxy)methyl group, which closely resembles the "upper" part of ribose, seems to perfectly meet those requirements. An unprotected compound of this structure, 9-[(2-hydroxyethoxy)methyl]-6-thioguanine, has already been synthesized.[7] However, unlike its 6-oxo precursor, acyclovir, it has been of no significant biological activity. A derivative of 6-thioacyclovir, substituted with the N^2-(*p*-butylanilinyl) group, reportedly shows some effect on DNA synthesis by HeLa cells *in vitro* (inhibition of thymidine incorporation).[8] On the other hand, the 7-regioisomer of 6-thioacyclovir, which might result from our study, would be a useful synthon for the synthesis of 2-aminopurine 7-acyclonucleosides, a class of compounds of already proved antiviral activity.[9]

Results and Discussion

9-[(2-Acetoxyethoxy)methyl]-N^2-acetyl-6-thioguanine (**2**), a model compound for the study of transglycosylation, was obtained by direct thiation of diacetylacyclovir (**1**)[3] with phosphorus pentasulfide[10] (27% of yield), or with Lawesson's reagent[11] (74%) (Scheme 1). The product was purified by short-column chromatography and crystallized from methanol, and its ^1H and ^{13}C NMR chemical shifts are given in Table 1 and 2. Quite unexpectedly, an attempted synthesis of the corresponding 7-regioisomer (**3**) from 7-[(2-acetoxyethoxy)-methyl]-N^2-acetyl-6-thioguanine (**7**)[3] appeared to be far more difficult. The substrate **7** underwent the thiation reactions very slowly, producing, as judged from the NMR spectra, not only the desired 6-thioguanine compound (**3**), but its N^2-thioacetyl-6-oxo isomer (**8**) as well. Separation of the resulting isomeric mixture by chromatography and crystallization (co-crystallizing compounds) was unsuccessful.

The acyclonucleoside **2** was then subjected to transglycosylation experiments. Under thermal conditions, *i.e.* heating without solvents and catalysts at 220°C for 10 min, the reaction afforded three products. Two of them, 9,S^6-di[(2-acetoxyethoxy)-methyl] derivative (**4**) and N^2-acetyl-6-thioguanine (**5**) could have been expected after a similar experiment of tetraacetyl-6-thioguanosine.[6] Surprisingly, the 7-regioisomer (**3**) was the third and the main product of that glycosyl migration reaction. The reaction was then repeated in chlorobenzene, in the presence of 0.1 equivalent of *p*-toluenesulfonic acid, affording the same products as above: **3** (51% of yield), **4** (7.5%), and **5** (8.5%). Thus, the

isomerization reaction of the 6-thio-9-regioisomer (**2**) appeared to be the superior synthetic pathway towards compound **3**, in comparison with direct thiation of the 6-oxo-7-regiosiomer (**7**).

Product **3** was crystallized from toluene and its structure was confirmed by the NMR analysis. Its ^{1}H and ^{13}C NMR spectra corresponded to one set of signals obtained for the mixture of **3** and **8**. In the ^{1}H NMR spectrum (Table 1), the signals of diagnostic protons 8H and OCH_2N (corresponding to 1'H of ribose) were shifted toward higher frequencies in comparison to those of 9-isomer **2** ($\Delta\delta$ 0.30 ppm and 0.60 ppm, respectively). These differences of chemical shifts between 9- and 7-isomers were larger than those in the 6-oxo series (compounds **1** and **7**; ($\Delta\delta$ 0.24 ppm and 0.21 ppm).[2] The ^{13}C $\Delta\delta$ value for C5 was 9.6 ppm (Table 2), being almost identical to that of the 6-oxo-9- and 7-isomers (9.0 ppm).[2] In turn, the NMR and UV spectra of the disubstituted compound **4** corresponded to those of 9,S^6-bis(ribofuranosyl) derivative.[6]

The progress of the transglycosylation reactions for 9- (**2**) and 7-substituted (**3**) acyclonucleosides was monitored by the HPLC analysis (Fig. 1 and 2). Interestingly, after a prolonged reaction time (120 min) both experiments gave an almost identical distribution of products. However, when the 9-isomer (**2**) was used as a substrate (Fig. 1), the formation of the 9,S^6-disubstituted compound **4** was faster than in the case of the 7-isomer (**3**; Fig. 2). Any compound of a putative structure of 7,S^6-disubstituted derivative was not detected in this study. It could also be deduced that the 7-isomer (**3**) is the most stable product under transglycosylation conditions, and this fact is in apparent contradiction to the results obtained for tetraacetyl-6-thioguanosine, which does not undergo a conversion to the respective 7-isomer.[6]

Taking into account all the results presented above, it is evident that 6-thio-acyclovir undergoes two different transglycosylation reactions: i) the reversible N $\rightleftarrows$ N glycosyl migration, which corresponds to the 7 $\rightleftarrows$ 9 isomerization of 6-oxopurine nucleosides[1] and probably proceeds *via* an unstable 7,9-diglycosylguanine intermediate (**6**), as it has been shown for acyclovir;[12] ii) the N9 $\rightleftarrows$ S6 transglycosylation, characteristic for 6-thioguanosine.[6] Therefore, the difference in transglycosylation reactions between 6-thioguanosine and 6-thioacyclovir must be related to the nature of glycosyl substituents. In the former compound, a 7-substituted product evidently cannot be formed due to steric

TABLE 1. 300 MHz ^{1}H NMR Chemical shifts (ref. TMS, δ, ppm) in $(CD_3)_2SO$.[a]

Compd	1-H	N^2H	8-H	1'H[b]	4'H[b]	5'H[b]	CH_3S	$NCOCH_3$[d]	$OCOCH_3$
2	13.38 s,1	12.05 s,1	8.33 s,1	5.50 s,2	4.07 m,2	3.70 m,2	-	2.22 s,3	1.94 s,3
3	13.43 s,1	11.91 s,1	8.63 s,1	6.10 s,2	4.07 m,2	3.77 m,2	-	2.21 s,3	1.96 s,3
4[c]	-	10.63 s,1	8.49 s,1	5.59 *5.74* s,2 *s,2*	3.75 m,4	4.09 m,4	-	2.21 s,3	1.92 *1.98* s,3 *s,3*
8	13.71 s,1	12.94 s,1	8.46 s,1	5.72 s,2	4.08 t,2	3.73 t,2	-	2.68 s,3	1.95 s,3
9	-	10.51 s,1	8.44 s,1	5.58 s,2	4.07 m,2	3.75 m,2	2.68 s,3	2.25 s,3	1.93 s,3
10	-	10.39 s,1	8.64 s,1	5.72 s,1	4.08 m,2	3.67 m,2	2.70 s,3	2.23 s,3	1.90 s,3

TABLE 2. 75.43 MHz ^{13}C NMR Chemical shifts (ref. TMS, ppm) in $(CD_3)_2SO$.

Compd	C-6	NC=O[d]	OC=O	C-2	C-4	C-8	C-5	C-1'[b]	C-4'[b]	C-5'[b]	N-Ac[d]	O-Ac	CH_3S
2	174.1	173.8	170.1	147.5	145.3	142.6	131.7	72.5	66.7	62.6	23.8	20.4	-
3	167.9	173.8	170.1	147.5	154.3	149.3	122.1	74.4	65.9	62.7	23.7	20.5	-
4[c]	158.3	168.9	170.1 *170.2*	152.4	150.3	144.3	127.1	72.3 *69.0*	66.7 *67.1*	62.6 *62.7*	24.6	20.5 *20.4*	-
8	156.9	200.6	170.1	146.9	152.3	145.4	112.2	74.9	66.4	62.6	35.5	20.5	-
9	160.6	169.0	170.1	152.4	149.5	143.7	127.1	72.2	67.1	62.7	24.7	20.4	11.2
10	159.9	168.9	170.1	152.4	157.2	148.9	118.8	75.6	65.7	62.5	24.5	20.4	11.8

[a] Figures following the observed multiplicities are numbers of protons estimated by integration; [b] the respective methylene groups of side chain are numbered as for ribose; [c] data for S^6-substituent in italics; [d] or thioacetyl group for **8**.

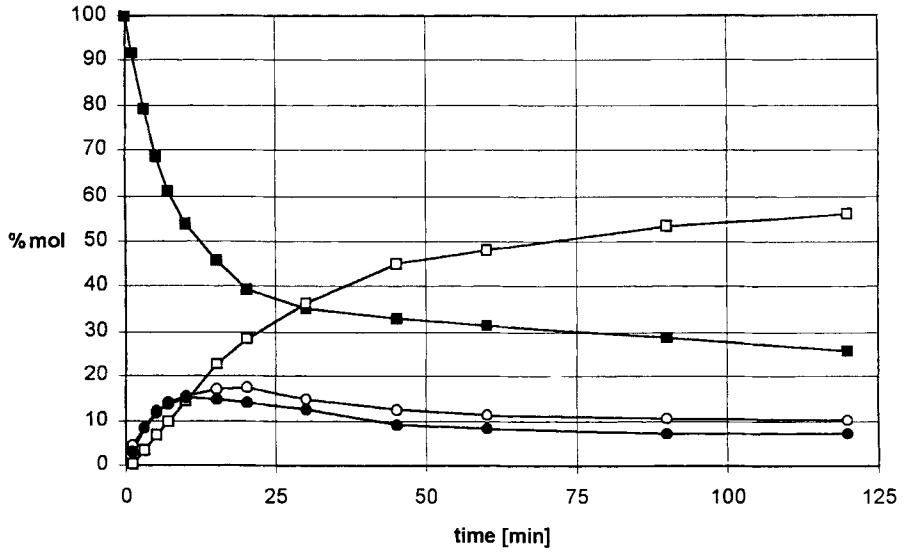


FIG. 1. Time-dependent product distribution for transglycosylation of diaacetylthioacyclovir (**2**) in the presence of *p*-toluenesulfonic acid (see Experimental): **2** ■; **3** □; **4** ●; **5** ○. The mole fractions are based on HPLC data.

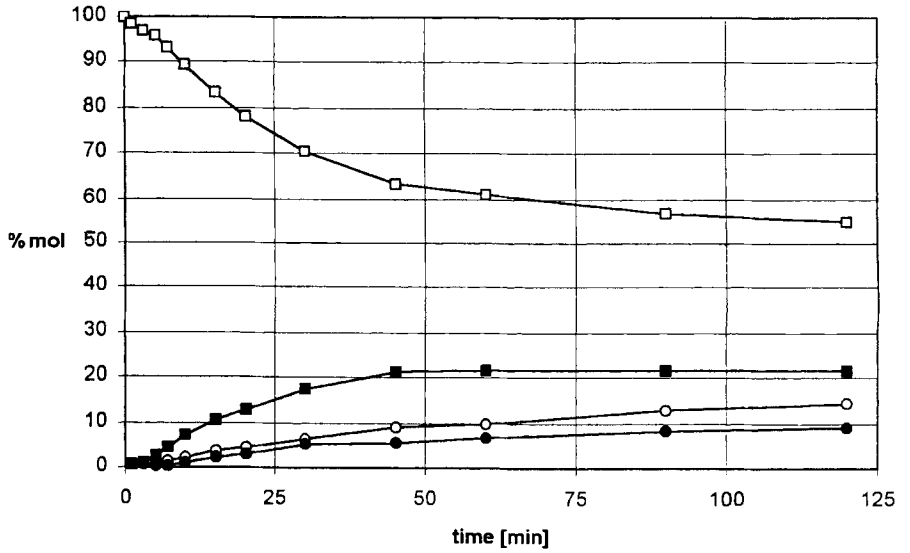
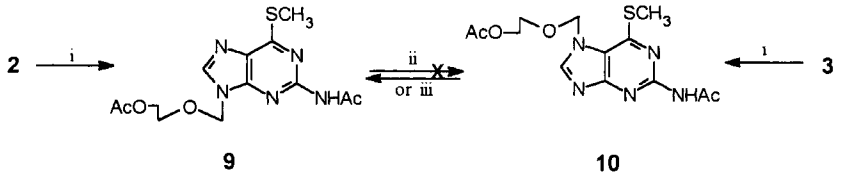


FIG. 2. Time-dependent product distribution for transglycosylation of the 7-regioisomer (**3**) in the presence of *p*-toluenesulfonic acid (see Experimental): **2** ■; **3** □; **4** ●; **5** ○.



SCHEME 2. *Reagents and conditions:* **i**, CH_3I/K_2CO_3, r.t., 1-2 h; **ii**, 200-220°C, 5-25 min; **iii**, *p*-$CH_3C_6H_4SO_3H$ in chlorobenzene, reflux, 30 min.

repulsion between the bulky 2,3,5-tri-O-acetyl-β-D-ribofuranosyl group and S6 atom, larger than O6 of the 6-oxopurine nucleosides. However, this is possible for a smaller and less rigid pseudosugar, the (2-acetoxyethoxy)methyl chain. It is worthy to note that this is the first case, in which the transglycosylation pathway depends on glycosyl substituents. In all transglycosylation reactions known so far no differences in reaction mechanisms between the 2,3,5-tri-O-acetyl-β-D-ribofuranosyl and (2-acetoxyethoxy)methyl series have been reported.[1]

Compounds **2** and **3** were methylated with methyl iodide in the presence of potassium carbonate to give the respective 6-methylthio derivatives **9** and **10** in a quantitative yield (Scheme 2). Transglycosylation experiments showed, that S^6-methylation of 6-thioacyclovir completely stopped the reversibility of isomerization. Thus, the respective 7-regioisomer of 6-thiomethyl derivative (**10**) underwent a quantitative transglycosylation to the thermodynamically more stable 9-regioisomer (**9**), whereas compound **9** remained unchanged under transglycosylation conditions. This can be explained as follows: methylation of S6 atom results in a fully aromatic character of the pyrimidine ring. Therefore, **9** and **10** belong rather to the "adenine class",[1] in which 9-glycosylated compounds are the most stable isomers. Quite similar effect of an increased stability of 9-regioisomers has already been reported for O^6-substituted derivatives of guanosine.[14,15]

Experimental

Melting points were determined on a Laboratory Devices Mel-Temp II micromelting points apparatus and are uncorrected. UV spectra were measured in methanol on a Beckman DU-65 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 300 FT

NMR spectrometer with tetramethylsilane as an internal standard. Elemental analyses were performed on a Perkin-Elmer 240 Elemental Analyzer. TLC was conducted on Merck silica gel F_{254} 60 plates using the following solvent systems (measured by volume): A, chloroform – methanol (9:1); B, toluene – ethanol (4:1); C, dichloromethane – ethanol (95:5). For preparative short-column chromatography Merck TLC gel H 60 was used.

Analytical high performance liquid chromatography (HPLC) was performed using the following components from Waters Division of Millipore: Nova Pak C_{18} column (8 x 100 mm Radial-Pak Cartridge), 600E Multisolvent Delivery System with U6K Universal Liquid Chromatography Injector, 486 Tunable Absorbance Detector and 746 Data Module.

Diacetylacyclovir (**1**) and its 7-isomer (**7**) were prepared as described previously,[2,3] and N^2-acetyl-6-thioguanine (**5**) was synthesized by direct thiation of N^2-acetylguanine with Lawesson's reagent in pyridine.[6]

9-[(2-Acetoxyethoxy)methyl]-N^2-acetyl-6-thioguanine (2). *Method A.* P_2S_5 (2.65 g, 11.94 mmol) was added to a solution of diacetylacyclovir (**1**; 1.0 g, 3.23 mmol) in pyridine (50 mL). The reaction mixture was treated with water (portions of 40 μL) in 30-min intervals, while refluxing with vigorous stirring for 5 h. Pyridine was then evaporated and a resulting solid foam was treated with chloroform (100 mL). The organic layer was washed with water (3 x 100 mL), dried over Na_2SO_4, evaporated to dryness and chromatographed on a silica gel short column in solvent C. Fractions containing the main product **2** were evaporated to a solid foam. Yield 296 mg (27%). An analytical sample was crystallized from methanol, mp 199-201°C. R_F 0.42(A); 0.28(B), 0.31(C) (substrate **1**: 0.34, 0.16, 0.14, respectively). λ_{max} 333 nm (ε 21,700). Anal. Calcd. for $C_{12}H_{15}N_5O_4S$ (325.34) C, 44.30; H, 4.65; N, 21.53, S, 9.85. Found: C, 44.44; H, 4.63; N, 21.64; S, 9.87.

Method B. Lawesson's reagent (2.0 g, 6.47 mmol) was added to a solution of **1** (2.0 g, 6.47 mmol) in freshly distilled pyridine (150 mL). The mixture was gently refluxed (oil bath temp. 130°C) with stirring for 7 h. The solvent was then evaporated and the resulting solid foam was chromatographed on a silica gel column in a chloroform – methanol gradient (from 98:2 to 9:1). Evaporation of appropriate fractions gave 1.546 g (74%) of **2** as a solid foam. The product was identical in all respects (TLC, NMR) to that obtained in Method A.

7-[(2-Acetoxyethoxy)methyl]-N^2-acetyl-6-thioguanine (3) and 7-[(2-acetoxyethoxy)methyl]-N^2-thioacetyl-6-thioguanine (8). A sample of **7** (1.0 g, 3.23 mmol) was subjected to thiation with P_2S_5 as it has been described for synthesis of **2**, Method A. After 5.5 h of heating at 120°C the reaction mixture was worked up as previously, and chromatographed on a silica gel short column in a chloroform – methanol gradient (98:2 →95:5, respectively). Fractions containing the main product were evaporated to yield a solid foam (335 mg, 31%); R_F 0.49(A); 0.48(B), 0.38(C), which was crystallized from ethanol. However, the crystalline material contained a 1:1 mixture of isomeric acyclonucleosides, as judged from the NMR spectra (Table 1 and 2). An attempted separation by crystallization or chromatography failed. Quite similar results were observed with Lawesson's reagent in pyridine or toluene. A pure sample of **3** was obtained in transglycosylation of **2** (see below).

Transglycosylation reactions of 2. 9,S^6-bis-[(2-Acetoxyethoxy)methyl]-N^2-acetyl-6-thioguanine (4) and 7-[(2-acetoxyethoxy)methyl]-N^2-acetyl-6-thioguanine (3). *Thermal conditions.* A sample of **2** (70 mg, 0.22 mmol) was heated without solvents in an open flask at 220°C for 10 min. The resulting melt was dissolved in chloroform and products were separated by short-column chromatography in a chloroform - methanol gradient (98:2→9:1). Evaporation of appropriate fractions gave (in order of elution): the 9,S^6-disubstituted derivative (**4**; 4.3 mg, 4.4%), 7-isomer (**3**; 21.0 mg, 31%), and 9-isomer (**2**; 29.3 mg, 41%). The products were identical (TLC, UV) to those obtained in the acid-catalyzed reaction in solution (see below).

In the presence of p-toluenesulfonic acid. A suspension of acyclonucleoside **2** (500 mg, 1.54 mmol) and *p*-toluenesulfonic acid monohydrate (30 mg, 0.154 mmol) was refluxed in chlorobenzene (80 mL; oil bath temp. 150°C) with stirring for 1 h. The solvent was then removed by evaporation. Short-column separation as described above afforded 50.2 mg (7.5%) of **4** as an oil, which was crystallized from toluene – chloroform, mp 120.5-122°C. R_F 0.53(A); 0.45(B), 0.45(C). λ_{max} 244 nm (ε 30,700), 292 (15,700), 298 (sh; 14,800). Anal. Calcd. for $C_{17}H_{23}N_5O_7S$ (441.46) C, 46.25; H, 5.25; N, 15.86, S, 7.26. Found: C, 46.06; H, 5.32; N, 15.91; S, 7.41. Evaporation of further fractions gave the

158-159°C. R_F 0.49(A); 0.48(B), 0.38(C). λ_{max} 292 nm (ε 6,700), 346 (18,100), 359 (sh; 14,500). Anal. Calcd. for $C_{12}H_{15}N_5O_4S$ (325.34) C, 44.30; H, 4.65; N, 21.53, S, 9.85. Found: C, 44.44; H, 4.65; N, 21.72; S, 9.66. Elution with chloroform – methanol 9:1 allowed to recover the unreacted substrate (**2**; 149 mg, 30%), and the last product, N^2-acetyl-6-thioguanine (**5**; 29.7mg, 8.5%), identical with the authentic sample (R_F 0.32 in solvent A) obtained by direct thiation of N^2-acetylguanine[6].

HPLC Analysis. The progress of reaction was monitored by the HPLC. Elution with a methanol – water reversed gradient (from 30% to 55% of methanol; flow rate 1 mL/min) gave a good separation of products. Retention times: 4.4 min (**5**), 7.0 (**2**), 12.3 (**3**), and 14.9 (**4**). The assignment of the peaks was performed by comparing the retention times and UV spectra with those of the original samples. UV-Absorption was measured at 299 nm, and the following ε_{299} values [L mol^{-1} cm^{-1}] were taken for the calculations of molar ratios: 10,130 for **2** and **8**; 6,220 for **3**; and 14,470 for **4**. The results are presented in Fig. 1

Transglycosylation of 3. A sample of the 7-regioisomer (**3**; 5.0 mg, 0.015 mmol) was refluxed in chlorobenzene (6 mL). When the substrate dissolved completely, *p*-TsOH (0.3 mg, 0.0015 mmol) was added in 0.1 ml of dry acetonitrile. The time-dependent distribution of products was analyzed by the HPLC method as described for compound **2**, and the results are presented in Fig. 2.

9-[(2-Acetoxyethoxy)methyl]-N^2-acetyl-S^6-methyl-6-thioguanine (9). Well-powdered potassium carbonate (81 mg, 0.58 mmol) was added to a solution of **2** (380 mg, 1.17 mmol) in dry methanol (25 mL). After 5 min of stirring the suspension was treated with methyl iodide (0.83 g, 5.85 mmol), and the reaction mixture was stirred at room temperature for 2 h. Methanol was then evaporated and the resulting foam was chromatographed on a silica gel column in a chloroform – methanol gradient (98:2→95:5). Evaporation of the UV-absorbing fractions gave compound **9** as a white solid foam (381mg, 96%). The product was crystallized from ethanol with an addition of small amounts of chloroform, mp 150.5-151.5°C. R_F 0.55(A); 0.47(B), 0.48(C). λ_{max} 248 nm (ε 34,400), 292 (21,600), 298 (sh; 19,100). Anal. Calcd. for $C_{13}H_{17}N_5O_4S$ (339.37) C, 46.01; H, 5.05; N, 20.64, S, 9.45. Found: C, 46.28; H, 5.09; N, 20.64; S, 9.44.

7-[(2-Acetoxyethoxy)methyl]-N^2-acetyl-S^6-methyl-6-thioguanine (10). The 7-isomer of diacetylthioacyclovir (**3**; 300 mg, 0.92 mmol) was methylated as described for synthesis of compound **9**, using 64 mg (0.46 mmol) of potassium carbonate, and 1.31 g (9.22 mmol) of methyl iodide, for 1 h. The product **10** was purified by chromatography in chloroform – methanol (98:2→95:5) to yield 301 mg (96%) of a solid foam, and crystallized from ethanol, mp 166-166.5°C. R_F 0.43(A); 0.23(B), 0.22(C). λ_{max} 240 nm (ε 27,600), 303 (13,600), 310 (sh; 12,000). Anal. Calcd. for $C_{13}H_{17}N_5O_4S$ (339.37) C, 46.01; H, 5.05; N, 20.64, S, 9.45. Found: C, 46.03; H, 5.04; N, 20.65; S, 9.39.

Transglycosylation reactions of 9 and 10. *Thermal conditions.* A sample of crystalline **10** (5 mg, 0.015 mmol) was heated in an open flask at 200°C for 20 min. The resulting melt was dissolved in methanol and analyzed by the HPLC, which showed the presence of **10** (37%) and its 9-isomer **9** (63%). A similar reaction of compound **9** did not result in the formation of **10**, even at 230°C for 10 min (TLC, HPLC).

In the presence of p-toluenesulfonic acid. A sample of crystalline **10** (5 mg, 0.015 mmol) was refluxed in chlorobenzene (3 mL) in the presence of *p*-TsOH (0.3 mg, 0.0015 mmol; added in 100 μL of acetonitrile) for 30 min. After this time TLC in solvent A and HPLC showed a quantitative conversion into the 9-isomer (**9**).

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