H, m, H3′,4′), 4.40–4.53 (3 H, m, H2′, CH_2Ph), 4.66, 4.67 (two 1 H s, CH_2Ph), 6.27 (1 H, d, H1′, $J_{1',2'}$ = 4.6 Hz), 7.31–7.35 (10 H, m, 2 × CH_2Ph), 7.27, 7.35 (two 1 H s, H2,8). Anal. Calcd for $C_{24}H_{25}N_5O_4$: C, 64.44; H, 5.63; N, 15.65. Found: C, 64.39; H, 5.71; N, 15.50.

2′-Deoxy-2′-fluoro-3′,5′-di-*O*-benzyladenosine (36). Compound **35** (447 mg, 1 mmol, dried by coevaporation with pyridine) was dissolved in CH_2Cl_2 (5 mL), and this solution was added into a solution of DAST (660 μL, 5 mmol) containing pyridine (880 μL). The mixture was stirred overnight then diluted with CH_2Cl_2 (100 mL), and the reaction was quenched by addition of 5% $NaHCO_3$ (10 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$–EtOH (95:5 v/v) to give **36** (362 mg, 82%) as a foam: ^{1}H NMR ($CDCl_3$) δ 3.62 (1 H, dd, H5′, $J_{4',5'}$ = 3.3 Hz, $J_{5',5''}$ = 11.0 Hz), 3.90 (1 H, dd, H5″, $J_{4',5''}$ = 2.2 Hz), 4.38–5.15 (7 H, m, H2′,3′,4′, 2 × CH_2Ph), 5.78 (2 H, s, NH_2), 6.28 (1 H, dd, H1′, $J_{1',2'}$ = 2.0 Hz, $J_{1',F}$ = 16.7 Hz), 7.25–7.39 (10 H, m, 2 × CH_2Ph), 8.11, 8.50 (two 1 H, s, H2,8). Anal. Calcd for $C_{24}H_{24}N_5O_3F$: C, 64.13; H, 5.38; N, 15.58. Found: C, 63.87; H, 5.22; N, 15.39.

2′-Deoxy-2′-fluoroadenosine (3). To a solution of **36** (450 mg, 1 mmol) in MeOH (20 mL) was added 10% Pd/C (200 mg), and the mixture was shaken in a Parr hydrogenation apparatus (50 psi) overnight. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give **3** (250 mg, 93%), mp 232–234 °C (lit.[32] mp 233 °C). ^{1}H NMR of this sample was identical with that of an authentic sample.[30,31]

Molecular Modeling. Structures of **21a** and **10** were generated on a Silicon Graphics Iris Personal Workstation using the QUANTA software (Polygen Corporation), and the CHARMm progress was used for energy calculation. Each molecule was sketched with the ChemNote software (Polygen) to create a 2D structure with light atoms and bonds. The corrected 3D structure was furnished using a molecular editor. The minimized-energy conformations were obtained in two stages: the structures were initially minimized for 300 iterations with the steepest descents algorithm, followed by a 300-step minimization using the Adopted-basis Newton Raphson algorithm. The dynamics data set was generated in 300 steps from 0 to 300 K, followed by equilibration and simulation (300 iterations each). The time step for this process was 0.001 ps each.

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A New One-Step Synthesis of 8-Aminopurine Nucleoside Analogues from 6-(Glycosylamino)-5-nitrosopyrimidines[1]

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The reaction of 6-[[β-D-(per-*O*-acetyl)glycopyranosyl]amino]-5-nitrosopyrimidines (**1**) with $POCl_3$/formamide furnished 8-amino-9-[(per-*O*-acetyl)glycopyranosyl]purines (**2**) in good yield. In this reaction formamide seems to play a double role, as the source of the C(8)-amino group of the purine and as the agent responsible for the reduction of the C(5)-nitroso group of the pyrimidine to a hydroxylamino group. A mechanism which reflects this belief is presented. Chemical evidence that supports the mechanism is provided.

Introduction

There has been long-standing interest in the development of methods for the synthesis of 8-aminopurine nucleosides[2] because such compounds often display antimicrobial and antitumor activity. For example, lethal effects on the growth of 435 cultured rat hepatoma cells have been observed on treatment of the cells with 8-aminoadenosine 3′,5′-cyclic monophosphate derivatives.[3] Furthermore, 8-aminopurine nucleoside analogues are potent inhibitors of purine nucleoside phosphorylase.[4]

One synthesis of 8-aminopurine nucleosides involves the replacement of the bromine atom of an 8-bromopurine nucleoside precursor. Because the C(8) bromine cannot be directly displaced by ammonia,[2a] in contrast to its easy displacement by primary or secondary amines,[2a,b,5] the amino group must be introduced by treating the bromide with aqueous hydrazine[2] or by hydrogenating the azido group formed on treating the bromide with sodium azide in DMSO.[2a] Furthermore, no methods for producing the title compounds directly from 6-(glycosylamino)pyrimidines are known. The classical route to 8-aminopurines from such precursors, i.e., treating 4,5-diaminopyrimidines with guanidine or cyanogen bromide,[6] fails when a glycosyl moiety is attached to the pyrimidine.

A study of the reaction of 6-(glycosylamino)-5-nitrosopyrimidines with Vilsmeier-type reagents[1] showed that treating such pyrimidines with $POCl_3$/formamide provided 8-amino-9-glycosylpurines. Here we report the results of an investigation of this reaction.

Results and Discussion

The work described here is based on the finding of Yoneda and co-workers[7] that 8-(*N*-alkylamino)purines or

(1) Presented in part at the 6th European Symposium on Organic Chemistry, Belgrade, Yugoslavia, Sept. 10–15, 1989; A-P121. Melguizo, M.; Nogueras, M.; Sánchez, A.; Quijano, M. L. *Tetrahedron Lett.* **1989**, *30*, 2669.

(2) (a) Holmes, R. E.; Robins, R. K. *J. Am. Chem. Soc.* **1965**, *87*, 1772. (b) Long, R. A.; Robins, R. K.; Townsend, L. B. *J. Org. Chem.* **1967**, *32*, 2751.

(3) See: Robins R. K. *Nucleosides Nucleotides* **1982**, *1*, 205 and references therein.

(4) (a) Sewach, D. S.; Chern, J.-W.; Pillote, K. E.; Townsend, L. B.; Daddona, P. E. *Cancer Res.* **1986**, *46*, 519. (b) Sanghvi, Y. S.; Hanna, N. B.; Larson, S. B.; Fujitaki, J. M.; Willis, R. C.; Smith, R. A.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1988**, *31*, 330.

(5) Minamoto, K.; Fujiki, Y.; Shiomi, N.; Uda, Y.; Sasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2337.

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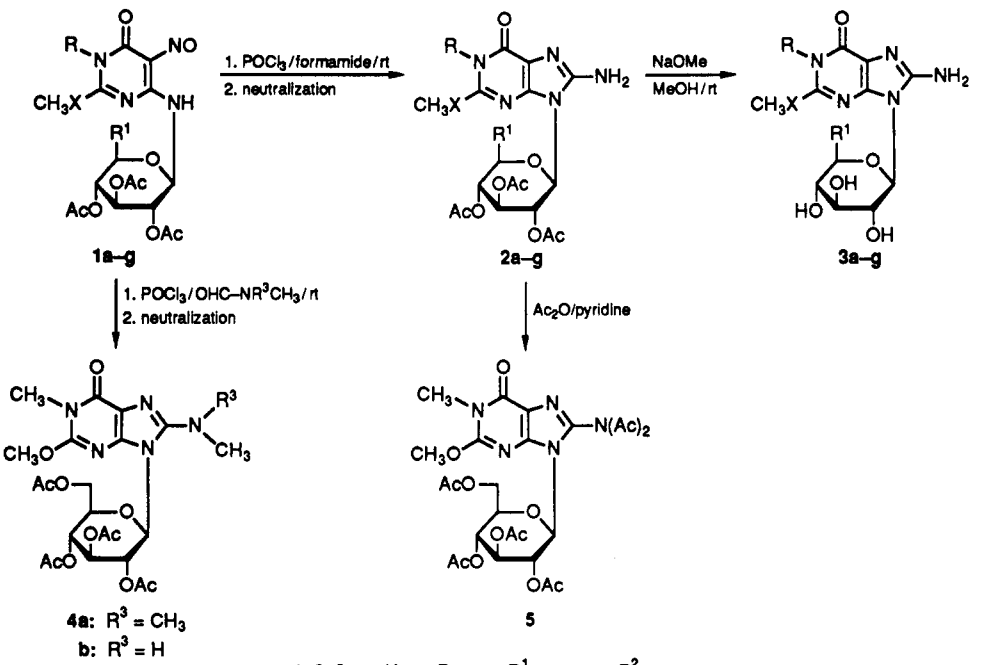
0022-3263/92/1957-0559$03.00/0

Scheme I



1, 2, 3	X	R	R^1	R^2
a	O	H	CH_2OAc	CH_2OH
b	O	CH_3	CH_2OAc	CH_2OH
c	O	CH_3	H	H
d	S	H	CH_2OAc	CH_2OH
e	S	H	H	H
f	S	CH_3	CH_2OAc	CH_2OH
g	S	CH_3	H	H

8-(*N,N*-dialkylamino)purines are formed on treatment of 6-amino-5-nitrosopyrimidines with mixtures of $POCl_3$ and an *N*-alkyl- or *N,N*-dialkylformamide. Low to moderate yields of the purines were obtained. A high reaction temperature (130 °C) was required because, at room temperature, dimeric products were obtained. Thus, further heating at 130 °C was necessary in order to obtain 8-(*N*-alkylamino)purines. The desired products were not formed when formamide was used in place of an *N*-alkyl- or *N,N*-dialkylformamide.

The use of a high reaction temperature, which was required for the reaction of simple 6-amino-5-nitrosopyrimidines, seemed inappropriate in the case of the more labile derivatives **1**.[8] In fact, 8-(*N*-alkylamino)-9-glycosylpurines **4** were obtained on treatment of **1b** with mixtures of $POCl_3$ and *N*-methylformamide or *N,N*-dimethylformamide (DMF) at room temperature[1] (Scheme I).

Reaction of **1b** with $POCl_3$/*N*-methylformamide afforded **4b** in a 36% yield, whereas reaction with $POCl_3$/DMF gave a mixture of **4a** (36%) and **4b** (43%). When $POCl_3$/formamide was used under similar conditions, i.e., with formamide in excess, the reaction failed, as it did in similar cases reported by Yoneda et al. However, the use of $POCl_3$ in excess allowed the 8-amino-9-glycosylpurine **2b** to be obtained. This is the first time that an 8-amino-9-glycosylpurine has been obtained directly from a 6-(glycosylamino)-5-nitrosopyrimidine. In this manner seven different 6-(glycosylamino)-5-nitrosopyrimidines, **1a–g**, were converted into the corresponding 8-amino-9-glycosylpurines (Scheme I).

The spectra of the cyclic products **2** and of the deprotected analogues **3** were consistent with their assigned structures[9] (see Tables I–V). Additional evidence for the presence of a primary amino group in **2** was that an *N,N*-diacetyl derivative (**5**) was formed on treatment of **2b** with acetic anhydride and pyridine (Scheme I). The ^1H NMR spectrum of **5** shows two broad singlets, at 2.5 and 2.2 ppm, due to the two 8-*N*-acetyl groups. The presence of two signals suggests the existence of a barrier to rotation about the C(8)–$N(Ac)_2$ bond axis, which is possibly a result of steric interaction between the *N*-acetyl groups and the glycosyl moiety.

Deamination of **2g** by treatment with, successively, HNO_2 at 0 °C and ethanol at 50 °C afforded the 8-glycosylpurine **6** (Scheme II). The spectra and other physical properties of **6** were identical to those of the compound obtained by O-acetylation of the purine **9**, which was obtained by treating with formamidine acetate the 5-aminopyrimidine **8**,[10] the product of the reduction of the 6-(xylosylamino)-5-nitrosopyrimidine **7**[10] by aqueous $(NH_4)_2S$ (Scheme II).

A mechanism of the formation of 8-aminopurines from 6-amino-5-nitrosopyrimidines must explain how the nitrogen atom of the nitroso group of the pyrimidine is reduced to the oxidation state of an amine nitrogen, and how the C(8) carbon atom of the product came to be in a higher oxidation state than was the formamide carbon atom from which it is derived.

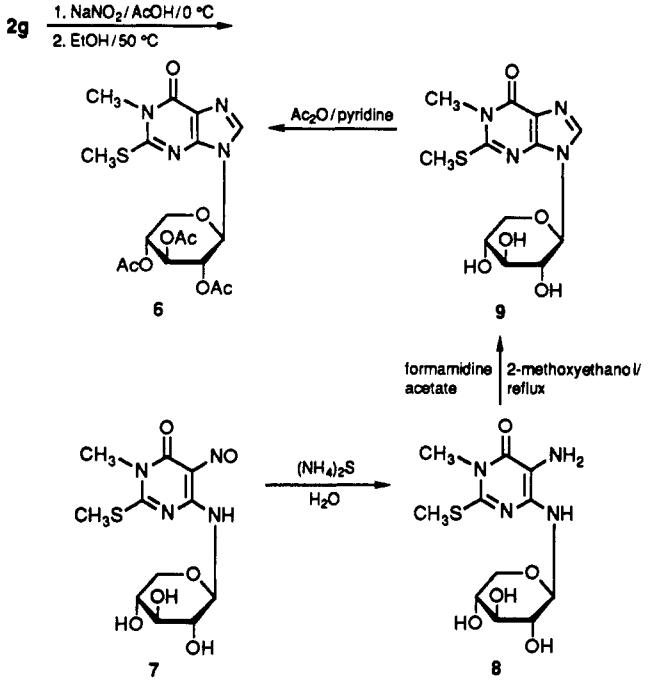
(7) Yoneda, F.; Higuchi, H.; Matsuda, T.; Senga, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1836.

(8) Nogueras, M.; López, R.; Gutierrez, M. D.; Sánchez, A. *J. Therm. Anal.* **1988**, *34*, 1335.

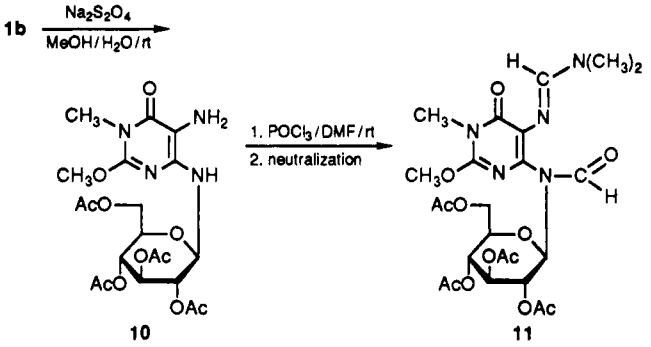
(9) No elemental analyses were obtained for the compounds of series 3 because nonstoichiometrical amounts of the crystallization solvent (alcohols, see the Experimental Section) were present in the crystalline solids, as the ^1H RMN spectra of compounds 3 showed. However, satisfactory analyses were obtained for the corresponding O-deacetylated derivatives (the series 4 compounds, see the Experimental Section).

(10) Nogueras, M.; Sánchez, A.; Asenjo, R.; Melgarejo, M.; Rodríguez, M.; Rodríguez, C. *An. Quim.* **1984**, *80C*, 234.

Scheme II



Scheme III

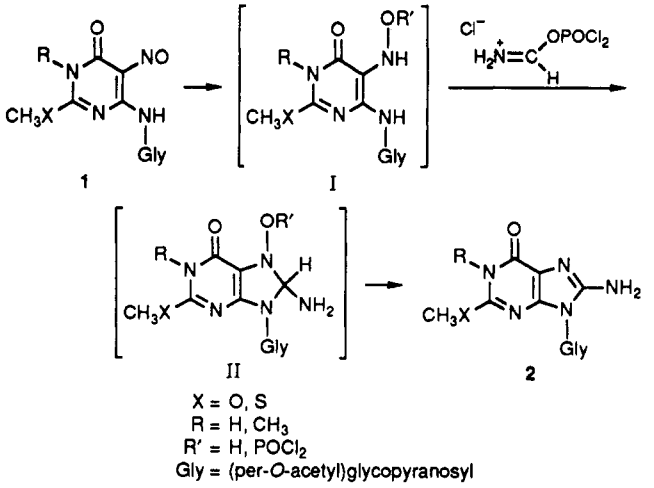


Because the reducing properties of formamide, and formic acid derivatives in general, are well-documented,[11] it is believed that, in these reactions, formamidine not only serves as the source of the C(8)-amino group of the purine but also reduces the nitroso group of the pyrimidine. This belief is consistent with the results obtained by others,[12] who recognized that, in reactions similar to that described here (e.g., the reaction of 6-amino-5-nitrosopyrimidines with aryl aldehydes to yield 8-arylpurines), a formic acid derivative could act as a reducing agent.

The reduction of the nitrogen of the nitroso group to the oxidation state of an amino nitrogen does not seem to be the first step in the cyclization. This statement is based on the results of the reactions outlined in Scheme III. Thus, the 5-amino-6-(glucosylamino)pyrimidine **10** (obtained by the dithionite reduction of the nitroso derivative **1b**) on reaction with $POCl_3$/DMF did not afford the corresponding 8-aminopurine (**4**), as did the related 6-(glycosylamino)-5-nitrosopyrimidines (Scheme I), but instead gave the formylated derivative **11**.

The transformation of the 6-(glycosylamino)-5-nitrosopyrimidines **1** into the 8-amino-9-glycosylpurines **2** on reaction with $POCl_3$/formamide most likely proceeds via the initial reduction of the nitroso group to a hydroxylamino group (Scheme IV) to afford either a 6-(glycosylamino)-5-(hydroxyamino)pyrimidine (I, R′ = H) or its *O*-phosphoryl derivative (I, R′ = $POCl_2$). The reaction of I with a Vilsmeier-type intermediate, formed by the reaction of $POCl_3$ and formamide, would afford a 7,8-dihydro-7-hydroxy-8-aminopurine like II, from which elimination of the elements of R′OH would give the 8-amino-9-glycosylpurine **2**. Thus, the transformation of II into **2** involves the concomitant oxidation of C(8) and reduction of N(7).

Scheme IV



Experimental Section

General Methods. ^1H NMR spectra were recorded with a Hitachi-Perkin-Elmer R-600 spectrometer (60 MHz). Chemical shifts (δ) are reported in ppm downfield from TMS. ^{13}C NMR spectra were recorded with a Bruker AM-300 spectrometer belonging to "Servicios Técnicos de la Universidad de Granada" (STUGRA), 18071 Granada, Spain. TMS served as the internal reference. The DEPT technique was used to assign the signals. The multiplicity of individual signals is designated as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, pst = pseudotriplet, q = quartet, m = multiplet. Mass spectra were recorded with a Hewlett-Packard HP-5988-A courtesy of STUGRA. Elemental analyses were performed with a Perkin-Elmer 240C, also courtesy of STUGRA. Specific rotations were measured with a Perkin-Elmer 141 polarimeter (c = 1 in all cases). UV spectra were recorded with a Bausch & Lomb Spectronic 2000 spectrophotometer. IR spectra were recorded with a Beckman 4250 spectrophotometer. Melting points are uncorrected and were determined with a Gallekamp melting point apparatus. Thin-layer chromatography (TLC) was performed with Merck 60 F_{254} silica gel precoated plates (0.2 mm). Visualization was effected by UV irradiation and by spraying with 4% H_2SO_4/MeOH and subsequent heating. Column chromatography was performed with Merck silica gel 60 (0.063–0.2 mm).

General Procedure for the Synthesis of 8-Amino-9-[β-D-(per-*O*-acetyl)glycopyranosyl]purines 2 from 1. The finely powdered 6-[[β-D-(per-*O*-acetyl)glycopyranosyl]amino]-5-nitrosopyrimidine **1** was added to an ice/water-cooled stirred mixture of freshly distilled $POCl_3$ (1.5 mL/mmol of **1**) and formamide (10 equiv/1 equiv of **1**). The viscous mixture that resulted was stirred at rt until no starting material was detected by TLC (CH_2Cl_2/MeOH, 9:1). The mixture was diluted with CH_2Cl_2 (30 mL/mmol of $POCl_3$) and was then neutralized by shaking it with saturated aqueous $NaHCO_3$. The organic layer was decanted, washed with water, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH). Appropriate fractions were pooled, and the solvent was evaporated in vacuo to afford compound **2**. Analytical data for **2a–g** are collected in Tables I and II.

8-Amino-9-[β-D-(tetra-*O*-acetyl)glucopyranosyl]-2-methoxypurin-6(1*H*)-one (2a). From 2.68 g (5.35 mmol) of 6-[[β-D-(tetra-*O*-acetyl)glucopyranosyl]amino]-2-methoxy-5-nitroso-

(11) Gibson, H. W. *Chem. Soc. Rev.* **1969**, 673.
(12) Taylor, E. C.; García, E. E. *J. Am. Chem. Soc.* **1964**, *86*, 4721.

Table I. Data for 8-Amino-9-[(per-*O*-acetyl)glycopyranosyl]purines 2

compd	reaction time (h)	mp (°C) (solvent)	UV (MeOH) λ_{max} (nm) (log ϵ)	IR (KBr) ν (cm^{-1})
2a	1	165 dec (MeOH)	251 (4.13), 283 (3.86)	3425, 3405, 3290, 1750, 1700, 1630, 1595, 1580, 1570, 1250, 1225, 1100, 1090, 1050
2b	2.25	218 dec (EtOH)	250 (4.06), 282 (3.75)	3180, 1760, 1700, 1650, 1600, 1560, 1495, 1225, 1090, 1060, 1035
2c	2.5	166 dec (EtOH)	252 (4.08), 284 (3.79)	3420, 3345, 3190, 1765, 1700, 1640, 1600, 1550, 1490, 1250, 1220, 1080, 1070, 1035
2d	2.25	180 dec (MeOH)	215 (4.03), 269 (4.16), 303 (4.00)	3450, 3290, 3230, 1750, 1690, 1625, 1570, 1555, 1530, 1250, 1220, 1100, 1090, 1045, 1035
2e	1.5	190 dec (MeOH)	215 (4.02), 269 (4.13), 302 (3.96)	3490, 3395, 3280, 1755, 1735, 1700, 1610, 1560, 1525, 1250, 1220, 1085, 1075, 1055, 1035
2f	2	149 dec (CCl_4/EtOH)	216 (4.18), 269 (4.09), 306 (3.97)	3425, 3340, 1760, 1685, 1635, 1580, 1560, 1510, 1225, 1090, 1055, 1035
2g	4	170 dec (MeOH/Et_2O)	216 (4.22), 2.69 (4.13), 306 (4.13)	3410, 3335, 1760, 1685, 1635, 1575, 1560, 1505, 1245, 1220, 1100, 1075, 1030

Table II. ^1H NMR Spectral Data of Compounds 2[a]

							glycosyl moiety	
compd	solvent	H-1[b]	1-CH_3	*O*-CH_3	*S*-CH_3	8-NH_2[b]	acetates	rest
2a	$CDCl_3$	*c*	–	4.0	–	5.5	2.0–2.1 (3 s, 9 H), 1.8 (s, 3 H)	5.0–6.0 (m, 4 H), 3.7–4.7 (m, 3 H)
2a	DMSO-d_6	12.0 (br s)	–	4.0	–	6.2 (br s)	2.0–2.1 (3 s, 9 H), 1.8 (s, 3 H)	5.0–6.7 (m, 4 H), 3.7–4.7 (m, 3 H)
2b	$CDCl_3$	–	3.3	4.1	–	8.8[d] (br s)	1.9–2.0 (3 s, 9 H), 1.75 (s, 3 H)	5.9–6.6 (m, 2 H), 4.8–5.8 (m, 3 H), 3.8–4.4 (m, 2 H)
2b	DMSO-d_6	–	3.3	4.1	–	7.7[d] (br s)	2.0–2.1 (3 s, 9 H), 1.8 (s, 3 H)	5.1–6.4 (m, 5 H), 3.5–4.5 (m, 2 H)
2c	DMSO-d_6	–	3.3	4.0	–	6.25	1.9–2.0 (2 s, 6 H), 1.75 (s, 3 H)	5.0–6.7 (m, 4 H), 3.5–4.5 (m, 2 H)
2d	$CDCl_3$	*c*	–	–	2.6	5.9 (br s)	1.9–2.0 (3 s, 9 H), 1.7 (s, 3 H)	5.0–6.4 (m, 4 H), 3.8–4.7 (m, 3 H)
2d	DMSO-d_6	12.0 (br s)	–	–	2.6	6.3 (br s)	1.9–2.0 (3 s, 9 H), 1.7 (s, 3 H)	4.9–6.8 (m, 4 H), 3.8–4.8 (m, 3 H)
2e	DMSO-d_6	*c*	–	–	2.5	6.4 (br s)	1.9–2.0 (2 s, 6 H), 1.7 (s, 3 H)	5.8 (m, 2 H), 5.3 (m, 2 H), 3.4–4.7 (m, 2 H)
2f	$CDCl_3$	–	3.6	–	2.6	5.3 (br s)	2.0–2.1 (3 s, 9 H), 1.7 (s, 3 H)	5.6–6.0 (m, 2 H), 5.0–5.6 (m, 2 H), 3.8–4.4 (m, 3 H)
2f	DMSO-d_6	–	3.5	–	2.6	6.6 (br s)	2.0–2.1 (3 s, 9 H), 1.7 (s, 3 H)	6.0 (m, 2 H), 5.2–5.7 (m, 2 H), 3.7–4.6 (m, 3 H)
2g	DMSO-d_6	–	3.5	–	2.7	6.5 (br s)	2.0–2.1 (2 s, 6 H), 1.8 (s, 3 H)	5.7–6.2 (m, 2 H), 5.0–5.7 (m, 2 H), 3.6–4.4 (m, 2 H)

[a] Chemical shifts in δ (ppm) downfield from internal Me_4Si. Spectra recorded at 60 MHz. Peaks are singlets unless indicated otherwise. The multiplicity of individual signals is designated as follows: br s = broad singlet, m = multiplet. [b] D_2O-exchangeable. [c] Not observed due to the great broadness of the signal. [d] Probably strongly shifted downfield as a result of hydrogen bonding with the ethanol present. Signals due to ethanol are present in the spectra.

pyrimidin-4(3*H*)-one (**1a**) was obtained 1.15 g (2.25 mmol, 42%) of **2a**.

8-Amino-9-[β-D-(tetra-*O*-acetyl)glucopyranosyl]-1-methyl-2-methoxypurin-6(1*H*)-one (2b). From 1.50 g (2.92 mmol) of 6-[[β-D-(tetra-*O*-acetyl)glucopyranosyl]amino]-3-methyl-2-methoxy-5-nitrosopyrimidin-4(3*H*)-one (**1b**) was obtained 1.34 g (2.55 mmol, 87%) of **2b**.

8-Amino-9-[β-D-(tri-*O*-acetyl)xylopyranosyl]-1-methyl-2-methoxypurin-6(1*H*)-one (2c). From 4.50 g (10.17 mmol) of 6-[[β-D-(tri-*O*-acetyl)xylopyranosyl]amino]-3-methyl-2-methoxy-5-nitrosopyrimidin-4(3*H*)-one (**1c**) was obtained 3.47 g (7.66 mmol, 75%) of **2c**.

8-Amino-9-[β-D-(tetra-*O*-acetyl)glucopyranosyl]-2-(methylthio)purin-6(1*H*)-one (2d). From 4.06 g (7.86 mmol) of 6-[[β-D-(tetra-*O*-acetyl)glucopyranosyl]amino]-2-(methylthio)-5-nitrosopyrimidin-4(3*H*)-one (**1d**) was obtained 3.40 g (6.45 mmol, 82%) of **2d**.

8-Amino-9-[β-D-(tri-*O*-acetyl)xylopyranosyl]-2-(methylthio)purin-6(1*H*)-one (2e). From 6.04 g (13.60 mmol) of 6-[[β-D-(tri-*O*-acetyl)xylopyranosyl]amino]-2-(methylthio)-5-nitrosopyrimidin-4(3*H*)-one (**1e**) was obtained 1.70 g (3.72 mmol, 27%) of **2e**.

8-Amino-9-[β-D-(tetra-*O*-acetyl)glucopyranosyl]-1-methyl-2-(methylthio)-purin-6(1*H*)-one (2f). From 4.63 g (8.73 mmol) of 6-[[β-D-(tetra-*O*-acetyl)glucopyranosyl]amino]-3-methyl-2-(methylthio)-5-nitrosopyrimidin-4(3*H*)-one (**1f**) was obtained 4.05 g (7.49 mmol, 86%) of **2f**.

8-Amino-9-[β-D-(tri-*O*-acetyl)xylopyranosyl]-1-methyl-2-(methylthio)-purin-6(1*H*)-one (2g). From 4.14 g (9.03 mmol) of 6-[[β-D-(tri-*O*-acetyl)xylopyranosyl]amino]-3-methyl-2-(methylthio)-5-nitrosopyrimidin-4(3*H*)-one (**1g**) was obtained 3.17 g (6.75 mmol, 42%) of **2g**.

General Procedure for the Synthesis of 3 by the Deacetylation of 2. To a suspension of **2** in MeOH (4 mL/mmol of **2**) was added a 1 M methanolic NaOMe (1 equiv of NaOMe). The mixture was stirred at rt for the appropriate amount of time. The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 9:1). The starting compound **2** dissolved rapidly, and a solid precipitated. The solid was collected by filtration and was then dissolved in water. The solution was neutralized with 1 N aqueous HCl and was then boiled with activated charcoal. The mixture was filtered, and the filtrate was allowed to stand at rt. A crystalline precipitate of **3** formed and was collected by filtration. The solid was washed with water and dried in vacuo in a desiccator. Analytical data for **3a–g** are collected in Tables III, IV, and V.

8-Amino-9-β-D-glucopyranosyl-2-methoxypurin-6(1*H*)-one (3a). From 0.53 g (1.04 mmol) of **2a** was obtained 0.28 g (0.82 mmol, 78%) of **3a**.

1,6-Dihydro-8-amino-9-β-D-glucopyranosyl-1-methyl-2-methoxypurin-6(1*H*)-one (3b). In the reaction of **2b** (1.88 g, 3.57 mmol), after treatment with NaOMe for 5 min as described in the general procedure, no precipitate appeared. The solvent was evaporated under reduced pressure, and the residue was dissolved in water. The solution was neutralized with 1 N aqueous HCl and was then boiled with charcoal. The mixture was filtered, and the filtrate was allowed to stand at rt. A solid precipitated. This was collected by filtration, washed with water, and dried in vacuo to yield 0.54 g (1.51 mmol, 42%) of **3b**.

8-Amino-9-β-D-xylopyranosyl-1-methyl-2-methoxypurin-6(1*H*)-one (3c). From 1.00 g (2.20 mmol) of **2c** was obtained 0.64 g (1.96 mmol, 89%) of **3c**.

8-Amino-9-β-D-glucopyranosyl-2-(methylthio)purin-6-(1*H*)-one (3d). From 1.20 g (2.28 mmol) of **2d** was obtained 0.73 g (2.02 mmol, 89%) of **3d**.

8-Amino-9-β-D-xylopyranosyl-2-(methylthio)purin-6-(1*H*)-one (3e). From 1.36 g (2.99 mmol) of **2e** was obtained 0.86 g (2.61 mmol, 88%) of **3e**.

Table III. Data for 8-Amino-9-glycopyranosylpurines 3

compd	reaction time (min)	mp (°C)	molecular formula	elemental analysis, C, H, N	$[\alpha]^{19}_D$, deg (DMSO, c = 1)	UV (H_2O, pH 7) λ_{max} (nm) (log ϵ)	IR (KBr) ν (cm^{-1})	MS[a] m/z (rel int)
3a	10	221 dec	$C_{12}H_{17}N_5O_7$ (343.30)	calcd: 41.98, 4.99, 20.40 found: 41.88, 4.99, 19.97	+23.8	251 (4.08), 281 (3.88)	3600–3000, 1690, 1590, 1090, 1075, 1050, 1030	181 (51, aglycon$^+$)
3b	5	208–210 dec	$C_{13}H_{19}N_5O_7$ (357.32)	calcd: 43.70, 5.36, 19.60 found: 43.64, 5.21, 19.71	+18.1	252 (4.07), 280 (3.86)	3600–3000, 1710, 1640, 1570, 1550, 1495, 1090, 1075, 1055, 1020	357 (<1, M$^+$), 195 (100, aglycon$^+$)
3c	5	228 dec	$C_{12}H_{17}N_5O_6$ (327.30)	calcd: 44.04, 5.24, 21.40 found: 43.62, 5.03, 21.80	−20.0	252 (4.07), 279 (3.88)	3600–3000, 1695, 1630, 1555, 1495, 1090, 1070, 1010	195 (53, aglycon$^+$)
3d	5	230 dec	$C_{12}H_{17}N_5O_6S$ (359.36)	calcd: 40.11, 4.77, 19.49 found: 39.90, 4.76, 19.97	+19.5	270 (4.18), 297 (4.01)	3600–3000, 1695, 1655, 1570, 1080, 1055, 1040, 1020	359 (<1, M$^+$), 197 (100, aglycon$^+$)
3e	15	232 dec	$C_{11}H_{15}N_5O_5S$ (329.33)	calcd: 40.12, 4.59, 21.26 found: 39.82, 5.26, 21.37	−29.3	270 (4.19), 297 (4.02)	3600–3000, 1685, 1645, 1575, 1100, 1075, 1050, 1010	329 (1, M$^+$), 197 (46, aglycon$^+$)
3f	5	198 dec	$C_{13}H_{19}N_5O_6S$ (373.38)	calcd: 41.82, 5.13, 18.76 found: 41.50, 5.26, 18.59	+19.7	205 (4.33), 271 (4.13), 299 (3.98)	3600–3000, 1685, 1635, 1575, 1560, 1505, 1090, 1070, 1055, 1040	272 (4, M$^+$), 211 (100, aglycon$^+$)
3g	5	250 dec	$C_{12}H_{17}N_5O_5S$ (343.36)	calcd: 41.98, 4.99, 20.40 found: 41.73, 4.77, 19.94	−32.0	205 (4.32), 271 (4.13), 300 (3.98)	3600–2800, 1675, 1640, 1580, 1560, 1500, 1090, 1070, 1055, 1015	343 (5, M$^+$), 211 (100, aglycon$^+$)

[a] EI, 70 eV.

8-Amino-9-β-D-glucopyranosyl-1-methyl-2-(methylthio)-purin-6(1*H*)-one (3f). From 1.13 g (2.09 mmol) of **2f** was obtained 0.68 g (1.83 mmol, 88%) of **3f**.

8-Amino-9-β-D-xylopyranosyl-1-methyl-2-(methylthio)-purin-6(1*H*)-one (3g). From 0.84 g (1.79 mmol) of **2g** was obtained 0.56 g (1.64 mmol, 91%) of **3g**.

9-[β-D-(Tetra-*O*-acetyl)glucopyranosyl]-8-(dimethylamino)-1-methyl-2-methoxypurin-6(1*H*)-one (4a) and 9-[β-D-(Tetra-*O*-acetyl)glucopyranosyl]-1-methyl-2-methoxy-8-(methylamino)purin-6(1*H*)-one (4b). Freshly distilled $POCl_3$ (2.30 g, 15 mmol) was added drop-by-drop with stirring to ice/water-cooled DMF (2 mL). Then finely powdered 6-[[β-D-(tetra-*O*-acetyl)glucopyranosyl]amino]-3-methyl-2-methoxy-5-nitrosopyrimidine-4(3*H*)-one (**1b**,[8] 0.514 g, 1 mmol) was added. The cooled mixture was stirred for 5 min, was then allowed to warm to rt, and was kept there for 1.5 h. The mixture was diluted with $CHCl_3$ (40 mL) and then was neutralized by shaking it with saturated aqueous $HNaCO_3$. The organic layer was decanted and dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH). Appropriate homogeneous fractions were pooled, and the solvent was evaporated in vacuo to afford, in order of elution, compounds **4a** (0.200 g, 36%) and **4b** (0.232 g, 43%). Compound **4a** was recrystallized from Et_2O/MeOH/hexane: mp 125 °C; $[\alpha]^{19}_D$ = −46.9° ($CHCl_3$); UV λ_{max} (nm) (log ϵ) (MeOH) 259 (4.10); IR (KBr) 1760, 1700, 1595, 1560, 1495, 1230, 1090, 1060, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.5 (m, 1 H, H-2′), 5.55 (d, J = 9.0 Hz, 1 H, H-1′), 5.3 (m, 2 H, H-3′ and H-4′), 4.2 (m, 2 H, C(6′)H_2), 4.1 (s, 3 H, OCH_3), 3.9 (m, 1 H, H-5′), 3.5 (s, 3 H, N(1)CH_3), 2.9 (s, 6 H, 8-N(CH_3)$_2$), 2.0–2.1 (2 s, 9 H, acetates), 1.8 (s, 3 H, acetate); ^1H NMR (DMSO-d_6) δ 6.5 (m, 1 H, H-2′), 6.0 (d, J = 8.2 Hz, 1 H, H-1′), 5.7 (pst, 1 H, H-4′), 5.2 (pst, 1 H, H-2′), 4.6–4.1 (m, 3 H, H-5′ and C(6′)H_2), 4.1 (s, 3 H, OCH_3), 3.4 (s, 3 H, N(1)CH_3), 2.9 (s, 6 H, 8-N(CH_3)$_2$), 2.0–2.1 (2 s, 9 H, acetates), 1.8 (s, 3 H, acetate); MS m/z (rel int, assignment) 553 (6, M$^+$), 223 (100, aglycon$^+$).

Anal. Calcd for $C_{23}H_{31}N_5O_{10}$ (553.52): C, 49.91; H, 5.64; N, 12.65. Found: C, 49.62; H, 5.82; N, 12.51.

Compound **4b** was recrystallized from Et_2O/EtOH/hexane: mp 149 °C; $[\alpha]^{19}_D$ = +16.9° ($CHCl_3$); UV λ_{max} (nm) (log ϵ) (MeOH) 267 (3.74), 256 (4.02); IR (KBr) 1760, 1690, 1615, 1580, 1550, 1490, 1225, 1090, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.9 (m, 2 H, sugar), 5.7–5.1 (m, 3 H, one D_2O-exchangeable proton, 8-NH and two sugar protons), 4.5–4.0 (m, 3 H, sugar), 4.1 (s, 3 H, OCH_3), 3.5 (s, 3 H, N(1)CH_3), 3.0 (d, J = 4.6 Hz, became singlet after D_2O exchange, 8-NHCH_3), 2.0–2.1 (3 s, 9 H, acetates), 1.75 (s, 3 H, acetate); ^{13}C NMR ($CDCl_3$) δ 168.62, 168.19, 167.64, 166.84 (acetates); 154.12, 152.25, 149.00, 143.90, 112.94 (purine carbons); 78.70, 72.68, 71.39, 66.48, 65.86 (glucose CH groups); 59.86 (C-6′); 54.30 (O-CH_3); 28.02 (8-N-CH_3); 26.37 (N(1)-CH_3); 18.70, 18.32 (acetate CH_3); MS m/z (rel int, assignment) 539 (4, M$^+$), 209 (100, aglycon$^+$).

Anal. Calcd for $C_{22}H_{29}N_5O_{11}$ (539.50): C, 48.98; H, 5.42; N, 12.98. Found: C, 49.23; H, 5.51; N, 13.05.

Synthesis of 4b. Procedure B. Freshly distilled $POCl_3$ (0.620 g, 4.04 mmol) was added drop-by-drop to a stirred, ice/water-cooled solution of *N*-methylformamide (0.048 g, 0.81 mmol) in CH_2Cl_2 (4 mL). Then **1b** (0.208 g, 0.40 mmol) was added. The solution was stirred at 35 °C for 3.5 h. The mixture was neutralized and was worked up in a manner similar to that described above. TLC (CH_2Cl_2/MeOH, 9:1) showed that the product was a complex mixture that contained one major component. This was isolated by column chromatography on silica gel (CH_2Cl_2/MeOH). The appropriate homogeneous fractions were pooled, and the solvent was evaporated in vacuo to yield 0.079 g (36%) of **4b**.

9-[β-D-(Tetra-*O*-acetyl)glucopyranosyl]-1-methyl-2-methoxy-8-(*N*,*N*-diacetylamino)purin-6(1*H*)-one (5). Dry pyridine was added to a solution of **2b** (0.363 g, 0.69 mmol) in Ac_2O (10 mL). The mixture was stirred at rt for 24 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel ($CHCl_3$/EtOH). Appropriate fractions were collected and pooled, and the solvent was evaporated in vacuo to afford 0.290 g (0.48 mmol, 69%) of **5**. Compound **5** was recrystallized from $CHCl_3$/EtOH/hexane: mp 120 °C; UV λ_{max} (nm) (log ϵ) (MeOH) 252 (4.03); IR (KBr) 1760, 1740, 1705,

Table IV. ^{1}H NMR Data for Compounds 3[a]

compd	H-1[b]	1-CH_3	O-CH_3	S-CH_3	8-NH_2[b]	glycosyl moiety H-1′	glycosyl moiety rest
3a	c	-	3.8	-	5.8 (br s)	5.1 (d, J = 8.9 Hz)	3.2–6.4 (m)
3b	-	3.3	4.0	-	5.9 (br s)	5.25 (d, J = 8.9 Hz)	3.2–6.4 (m)
3c	-	3.3	4.0	-	6.0 (br s)	5.1 (d, J = 8.9 Hz)	3.0–6.4 (m)
3d	c	-	-	2.5	6.2 (br s)	5.3 (d, J = 8.9 Hz)	3.0–6.6 (m)
3e	c	-	-	2.5	6.3 (br s)	5.2 (d, J = 8.9 Hz)	3.0–7.0 (m)
3f	-	3.4	-	2.5	6.1 (br s)	d	3.0–6.6 (m)
3g	-	3.3	-	2.5	6.1 (br s)	5.1 (d, J = 9.6 Hz)	2.9–6.8 (m)

[a] Chemical shifts in δ (ppm) from internal Me_4Si. Spectra of DMSO-d_6 solutions recorded at 60 MHz. Peaks are singlets unless indicated otherwise. The multiplicity of individual signals is designated as follows: br s = broad singlet, m = multiplet. [b] D_2O-exchangeable. [c] Not observed due to the great broadness of the signal. [d] Not discernible.

Table V. ^{13}C NMR Data for Compounds 3[a]

compd	purine moiety 1-CH_3	O-CH_3	S-CH_3	C(5)	rest	glycosyl moiety C(1′)	CH_2[b]	rest
3a	-	54.41	-	115.45	155.86, 153.50, 149.78, 147.41	82.78	60.63	79.61, 77.17, 69.21, 69.09
3b	27.41	55.49	-	114.74	155.11, 152.66, 149.94, 145.49	82.70	60.63	79.58, 77.17, 69.23, 69.03
3c	27.40	55.46	-	114.98	155.12, 152.53, 150.17, 145.42	83.52	68.17	77.56, 69.06, 68.86
3d	-	-	13.04	117.74	155.97, 152.36, 150.42, 147.75	82.87	60.75	79.56, 77.16, 69.36, 69.14
3e	-	-	13.04	117.68	155.36, 152.68, 150.50, 147.73	83.58	68.11	77.50, 69.07, 68.95
3f	29.70	-	14.83	116.91	155.47, 153.76, 150.71, 146.08	82.87	60.78	79.49, 77.15, 69.44, 69.27
3g	29.67	-	14.79	117.09	155.44, 153.62, 150.87, 145.99	83.59	68.09	77.50, 69.13, 69.03

[a] Chemical shifts in δ (ppm) downfield from internal Me_4Si. Spectra are of DMSO-d_6 solutions. Peaks were assigned by using the DEPT technique. [b] C(5′)H_2 for the xylopyranosides or C(6′)H_2 for the glucopyranosides.

1560, 1530, 1495, 1210, 1090, 1050, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.5 (m, 1 H, H-2′), 4.9–5.6 (m, 3 H, H-1′, H-2′, and H-3′), 3.8–4.3 (m, 3 H, H-5′ and (6′)H_2), 4.2 (s, 3 H, OCH_3), 3.5 (s, 3 H, 1-CH_3), 2.5 (br s, 3 H, 8-*N*-acetyl), 2.2 (br s, 3 H, 8-*N*-acetyl), 2.0–3.1 (3 s, 9 H, acetates), 1.9 (s, 3 H, acetate).

Anal. Calcd for $C_{25}H_{31}N_5O_{13}$ (609.52): C, 49.26; H, 5.13; N, 11.49. Found: C, 49.20; H, 5.50; N, 11.32.

9-[β-D-(Tri-*O*-acetyl)xylopyranosyl]-1-methyl-2-(methylthio)purin-6(1*H*)-one (6). Procedure A. Formamidine acetate (0.711 g, 7.41 mmol) was added to a suspension of 5-amino-6-(β-D-xylopyranosylamino)-3-methyl-2-(methylthio)pyrimidin-4(3*H*)-one (8, 1.66 g, 4.94 mmol) in 2-methoxyethanol (25 mL). The mixture was refluxed, with stirring, under N_2 for 2.5 h. Then the solvent was distilled until the mixture was half its original volume. The clear solution that resulted was kept at 0–5 °C for 12 h. A crystalline solid precipitated. This was collected by filtration, washed with EtOH, and dried in a desiccator in vacuo to afford 1.00 g (2.89 mmol, 58%) of **9**. An analytical sample of **9** was obtained by recrystallization from EtOH/H_2O: mp 225 °C; $[\alpha]^{18}_D$ = −23.2° ($CHCl_3$); UV λ_{max} (nm) (log ε) (H_2O, pH 7) 262 (4.07), 280 (4.00); IR (KBr) 3600–3000, 1700, 1575, 1535, 1495, 1120, 1090, 1060, 1015 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.2 (s, 1 H, 8-H), 5.3 (d, J = 9.2 Hz, 1 H, H-1′), 5.0–5.6 (m, 2 H, D_2O-exchangeable, OH), 3.0–4.4 (m, 1 H, D_2O-exchangeable, OH), 2.4–4.2 (m, 5 H, sugar), 3.5 (s, 3 H, 1-CH_3), 2.6 (s, 3 H, SCH_3); ^{13}C NMR (DMSO-d_6) δ 158.88, 156.30, 146.95 (C-2, C-4, C-6); 138.78 (C-8); 119.67 (C-5); 83.88 (C-1′); 77.15, 70.19, 69.16 (C-2′, C-3′, C-4′); 68.31 (C-5′); 29.82 (1-CH_3), 14.90 (SCH_3); MS *m/z* (rel int, assignment) 328 (12, M^+), 196 (87, aglycon$^+$).

Anal. Calcd for $C_{12}H_{16}N_4O_5S\cdot 2H_2O$ (346.36): C, 39.55; H, 5.53; N, 15.38. Found: C, 39.47; H, 5.43; N, 15.23.

A suspension of **9** (0.83 g, 2.39 mmol), Ac_2O (12 mL), and pyridine (12 mL) was stirred at rt for 12 h. The solution that resulted was poured on crushed ice (200 g). The mixture was allowed to stand at rt for 12 h. The aqueous solution that resulted was extracted with $CHCl_3$. The extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was mixed with EtOH. Then the EtOH was evaporated. This was repeated until a solid foam was obtained. This was recrystallized from EtOH to afford 0.47 g (1.03 mmol, 43%) of **6**: mp 187 °C dec; $[\alpha]^{18}_D$ = 0.0° (DMSO); UV λ_{max} (nm) (log ε) (MeOH) 260 (4.06), 283 (4.00); IR (KBr) 3080, 1760, 1695, 1560, 1530, 1495, 1240, 1210, 1085, 1065, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.8 (s, 1 H, H-8), 4.9–5.9 (m, 4 H, sugar), 4.3 (m, 1 H, sugar), 3.6 (m, 1 H, sugar), 3.6 (s, 3 H, 1-CH_3), 2.65 (s, 3 H, SCH_3), 2.0–2.1 (2 s, 6 H, acetates), 1.8 (s, 3 H, acetate).

Anal. Calcd for $C_{18}H_{22}H_4O_8S$ (454.45): C, 47.57; H, 4.88; N, 12.33. Found: C, 47.48; H, 4.77; N, 12.07.

Synthesis of Compound 6. Procedure B. $NaNO_2$ (0.170 g, 2.40 mmol) was added to a solution of **2g** (0.380 g, 0.80 mmol) in glacial HOAc (1.5 mL). The stirred mixture was cooled in an ice/water bath for 1 h. Then, EtOH (50 mL) was added, and the mixture was warmed to 50 °C and was kept there for 1.5 h. The mixture was diluted with CH_2Cl_2 (200 mL) and neutralized by shaking it with saturated aqueous $NaHCO_3$. The organic layer was decanted, washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a solid foam. The major component of the foam was isolated by column chromatography on silica gel (CH_2Cl_2/EtOH). Appropriate fractions were pooled, and the solvent was evaporated in vacuo. The residue was crystallized from EtOH to afford 0.057 g (0.12 mmol, 17%) of **6**. The physical properties of the compounds synthesized by procedures A and B were identical.

5-[[(Dimethylamino)methylene]amino]-3-methyl-2-methoxy-6-[*N*-formyl-*N*-[β-D-(tetra-*O*-acetyl)glucopyranosyl]-amino]pyrimidin-4(3*H*)-one (11). A solution of sodium dithionite (6.00 g) in H_2O (60 mL) was added to a suspension of **1b** (3.09 g, 6.00 mmol) in MeOH (60 mL). The mixture was stirred at rt until the initial deep blue color became pale-yellow (15 min). Water was added, and the mixture was extracted with $CHCl_3$. The extract was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford compound **10** as a solid foam (2.10 g, 70%), which was shown to be homogeneous by TLC; mp 162 °C; UV λ_{max} (nm) (log ε) (MeOH) 255 (3.62) shoulder, 293 (4.00); IR (KBr) 3390, 1755, 1655, 1635, 1535, 1230, 1090, 1055, 1030 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.6 (d, J = 9.0 Hz, 1 H, D_2O-exchangeable, 6-NH), 4.8–6.0 (m, 6 H, two D_2O-exchangeable protons, 5-NH_2 and four sugar protons), 3.8–4.4 (m, 3 H, sugar), 4.0 (s, 3 H, OCH_3), 3.3 (s, 3 H, 3-CH_3), 2.0 (s, 12 H, acetates). Immediately after its isolation, compound **10** (0.770 g, 1.54 mmol) was dissolved in ice/water-cooled DMF (3 mL). Freshly distilled $POCl_3$ (0.282 mL, 3.08 mmol) was then added drop-by-drop with stirring. The stirred mixture was then warmed to rt and was kept there for 5 h. It was diluted with $CHCl_3$ (40 mL) and neutralized by shaking it with saturated aqueous $NaHCO_3$. The organic layer was decanted, washed with water, and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOH). Appropriate fractions were pooled and concentrated in vacuo to furnish a solid foam. This was recrystallized from EtOH/Et_2O/hexane to afford 0.304 g (0.52 mmol, 34%) of **11**: mp 128 °C; UV λ_{max} (nm) (log ε) (MeOH) 221 (4.04), 274 (3.86), 316 (3.80); IR (KBr) 1775, 1700, 1660, 1605, 1590,

1560, 1225, 1090, 1050, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.85 (s, 1 H, 4-NCHO), 8.5 (s, 1 H, 5-N=CH), 5.0–6.1 (m, 4 H, sugar), 3.8–4.4 (m, 3 H, sugar), 4.1 (s, 3 H, OCH_3), 3.45 (s, 3 H, 3-CH_3), 2.95 (br s, 6 H, $N(CH_3)_2$), 1.8–2.1 (4 s, 12 H, acetates).

Anal. Calcd for $C_{22}H_{33}N_5O_{12}$ (583.55): C, 49.40; H, 5.70; N, 12.00. Found: C, 49.39; H, 5.85; N, 11.75.

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Registry No. **1a**, 125162-88-1; **1b**, 124516-16-1; **1c**, 125172-02-3; **1d**, 125162-90-5; **1f**, 125162-92-7; **1g**, 125162-91-6; **2a**, 137363-03-2; **2b**, 137363-04-3; **2d**, 137363-05-4; **2e**, 137363-06-5; **2f**, 137363-07-6; **2g**, 137363-08-7; **3a**, 137393-24-9; **3b**, 137393-25-0; **3c**, 137363-09-8; **3d**, 137433-68-2; **3e**, 137363-10-1; **3f**, 137393-26-1; **3g**, 137363-11-2; **4a**, 124516-17-2; **4b**, 124516-18-3; **5**, 124516-20-7; **6**, 137363-12-3; **7**, 97442-99-4; **8**, 95965-90-5; **9**, 137363-13-4; **10**, 137393-27-2; **11**, 137363-14-5.

A New Convergent Route to 1-Substituted Ellipticines

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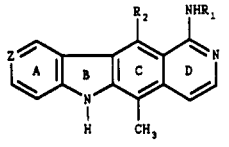
1-(2-Fluoro-4-pyridyl)ethanone was synthesized from 2-fluoropyridine and was ortho-lithiated after activation as the propylene glycol ketal. The resulting 3-lithio derivative was trapped by various electrophiles but reacted in low yield with N-protected 3-indolecarbaldehyde. Model compounds 1-[[[2-(diethylamino)ethyl]amino]-3-pyridyl]ethanol and -ethanone were prepared and selectively condensed with indole. 1-[[[2-(Diethylamino)-ethyl]amino]-3-pyridyl]ethanol and -ethanone bearing a ketal-protected acetyl moiety at the C-4 position have been obtained in high yields starting from the propylene glycol ketal of 1-(2-fluoro-4-pyridyl)ethanone. These reagents could not be condensed with indole either due to side reactions between the C-3 and C-4 functions or to steric hindrance. 1-(2-Substituted-4-bromo-3-pyridyl)ethanols were synthesized via a metalation/halogen-dance strategy starting from 2-fluoropyridine. 1-(2,4-Dihalo-3-pyridyl)-1-chloroethane could be prepared and condensed with 1-indolylmagnesium iodide, which allowed the construction of the expected 3-[1-(3-pyridyl)ethyl]indole skeleton. Functionalization of the pyridine C-4 bromo position was achieved by a vinylstannane cross-coupling reaction using a palladium(0) catalyst. Acidic treatment of the resulting 4-(1-ethoxyethenyl)pyridine led to 1-fluoroellipticine. The whole sequence requires six steps from indole and 2-fluoropyridine and allows an attractive overall yield.

Introduction

In the field of antitumor compounds, much interest has been focused by chemists on the ellipticine series.[1] Some ellipticine derivatives, such as 9-hydroxyellipticine[2] and the derived acetate of 9-hydroxy-2-methylellipticium (Celiptium),[3] have proved to be powerful anticancer agents but exhibit a high toxicity. 9-Aza and 9-methoxy derivatives of 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole bearing a [(dialkylamino)propyl]amino moiety at the C-1 position show a high anticancer activity against myeloblastic leukemias as well as solid tumors[4-6] with lower cardiovascular effects compared with the parent ellipticines.



Z = CH, C-OCH_3, N ; R_2 = H, CH_3 ; R_1 = $(CH_2)_nNEt_2$

General and convenient procedures for the synthesis of such 1,9-difunctionalized ellipticines were not available and tedious multistep strategies were required.[7,8] A general pathway to 1,9-disubstituted ellipticines soon appeared as an attractive challenge for our laboratory. The chosen synthetic strategy was the construction of the C-ring of the ellipticine skeleton by means of indole and polyfunctionalized pyridine building blocks, which could be prepared by such selective reactions as directed ortho metalation,[10] halogen-dance,[18] Cross-Coupling reaction...[12]

Among the numerous syntheses of ellipticines or analogues based on the construction of the C-ring,[13] some involve reaction between a 4-substituted 3-lithiopyridine and an indole derivative bearing a 3-carbonyl function. At the beginning of the 1980s, the only reported results in this field were those of Snieckus who prepared ellipticine by a tandem lithiation strategy of both pyridine and indole.[14]

Bisagni was later interested in such a route to ellipticine analogues and for this purpose he succeeded in lithiating 2-(2-methoxy-4-pyridyl)-4,4-dimethyl-2-oxazoline[15] and

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