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A synthetic route to 9-(polyhydroxyalkyl)purines

Derek Horton,[a,*] Sheela Thomas[b] and Judith Gallucci[b]

[a]*Department of Chemistry, American University, 4400 Massachusetts Avenue, NW, Washington, DC 20016, USA*
[b]*Department of Chemistry, The Ohio State University, Columbus, OH 43210, USA*

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Abstract—Mercuric-ion promoted condensation of 6-chloropurine with acetylated dimethyl dithioacetals of D-ribose and D-arabinose in nitromethane afforded a separable mixture of 1′(*S*)-2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-*S*-methyl-1-thio-D-ribitol (**4**) and its 1′(*R*) diastereomer, and the corresponding 1′(*R*)-arabinitol analogue (**5**); the structure of **4** was confirmed by X-ray crystallography. Desulfurization of **4** and **5** by tributylstannane in toluene gave 2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-D-ribitol (**7**) and the arabinitol analogue **8**, convertible by the action of thiourea into the 1,6-dihydro-6-thioxopurin-9-yl analogues **9** and **10**, which on deacetylation furnished the corresponding acyclic-sugar nucleosides **11** and **12**.

Keywords: Nucleoside coupling; Acyclic sugar; Polyhydroxyalkylpurine; Stereochemistry; Desulfurization

1. Introduction

Nucleoside analogues in which the sugar component is in the acyclic-chain form are of interest as potential antitumor and antiviral agents. Earlier work from this laboratory has demonstrated a convenient synthetic approach to such structures, based on the coupling of a protected sugar dithioacetal to a suitable purine or pyrimidine base. Such coupling may be effected by activation of the dithioacetal by the action of halogen and reaction of the resultant 1-alkylthio-1-halo sugar derivative with the nucleoside base,[1] or under suitable conditions, by direct condensation of the dithioacetal with the nucleoside base.[2] The products obtained have the structure of a protected alditol chain substituted at C-1 by both the nucleoside base and an alkylthio group, and consequently a new center of asymmetry is generated at C-1.[3]

Full structural characterization of such products thus would require identification of stereochemical configuration at the new asymmetric center and also positive attribution of the point of attachment of the sugar chain on the nucleoside base. Polarimetric studies can provide indication for the former, and ultraviolet spectroscopy gives evidence for the latter, although neither technique is fully definitive. In this report, an X-ray single-crystal study is used to provide positive confirmation of both points in structures involving a purine and a pentose precursor.

In previous studies, attempts to remove the alkylthio group from the coupled acyclic nucleoside products by a variety of reagents have led invariably to detachment of the sugar chain from the nucleoside base. In this report, it is demonstrated that a free-radical procedure employing tributylstannane is an effective procedure for desulfurization with retention of the sugar chain–nucleoside base linkage, to afford the title products.

2. Results and discussion

The dimethyl dithioacetals of D-ribose and D-arabinose were selected for use as starting materials instead of the more commonly employed diethyl analogues, to facilitate the interpretation of NMR spectra of the transformation products. This necessitated the condensation of gaseous methanethiol in a cold trap, addition of the pentose dissolved in concentrated hydrochloric

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* Corresponding author. Tel.: +1 202 885 1767; fax: +1 202 885 1095; e-mail: carbchm@american.edu

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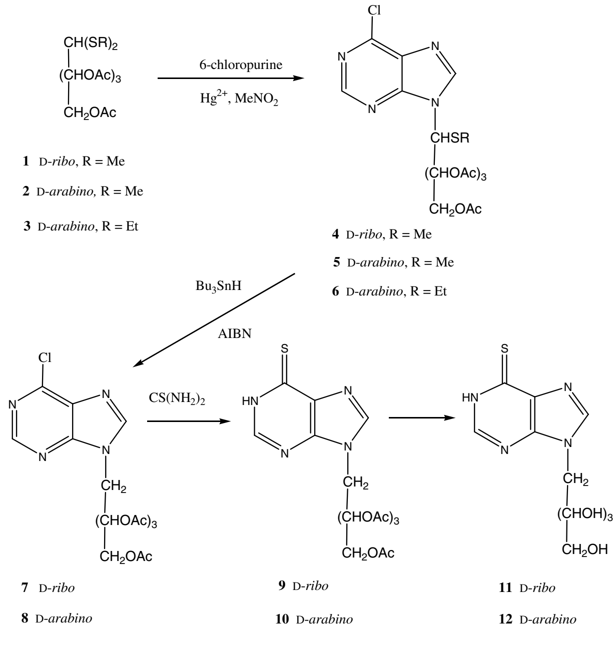
acid, and processing essentially according to Zinner et al.[4,5] to afford the crystalline products in 70% yield without need for chromatography. Conventional acetylation afforded syrupy D-ribose dimethyl dithioacetal tetraacetate **1** and the crystalline D-arabinose analogue **2**, which were used, along with the diethyl analogue **3** of **2**, in subsequent transformations.

The direct coupling procedure of Horton and Liu[2] was employed for linking the acetylated pentose dialkyl dithioacetals to 6-chloropurine. The acetylated dialkyl dithioacetals were condensed with 6-chloropurine in the presence of mercuric cyanide and yellow mercuric oxide in boiling nitromethane to yield the nucleoside coupling products. The acetylated D-ribose dimethyl dithioacetal **1** afforded, after chromatographic purification, a syrupy 3.7:1 mixture of 1′(*R*) and 1′(*S*)-2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-*S*-methyl-1-thio-D-ribitol, from which there crystallized the pure, levorotatory 1′(*S*) epimer (**4**). The ratio of the two epimers was determined by comparison of the H-1′ signals in the NMR spectra of the initial mixture and the spectrum of the crystalline 1′(*S*) product.

The same procedure with the acetylated D-arabinose dimethyl dithioacetal **2** afforded a single, crystalline, dextrorotatory product assigned (see later) as 1′(*R*)-2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-*S*-methyl-1-thio-D-arabinitol (**5**). Repetition of this procedure, but with the diethyl analogue **3** of **2**, led to 1′(*R*)-2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-*S*-ethyl-1-thio-D-arabinitol (**6**) as an analytically pure, dextrorotatory syrup. This compound was earlier reported[1] as a solvated syrup, prepared via a highly reactive 1-bromo derivative prepared from the dithioacetal **3**.



The coupled products **4**, **5**, and **6** gave satisfactory elemental analyses, but direct evidence for the N-9 linkage position between the sugar chain and the purine base, and the assigned chirality at C-1′ required additional evidence from NMR and UV spectral, along with chiroptical data (discussed later) and in particular a single-crystal X-ray structure on compound **4**.

Reductive removal of the alkylthio group from compounds **4**, **5**, and **6** in toluene solution was successfully achieved under free-radical conditions by the use of tributylstannane, with 1,1′-azobis(isobutanonitrile) (AIBN) as intiator and an inert atmosphere. Thus, 2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-D-ribitol (**7**) was obtained in 87% yield from compound **4** as an analytically pure levorotatory syrup. The 1-methylthio *arabino* analogue **5** under similar conditions gave a 78% yield of crystalline, dextrorotatory 2,3,4,6-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-D-arabinitol (**8**); the 1-ethylthio precursor **6** likewise afforded compound **8**. Elemental analyses confirmed that the desulfurized products **7** and **8** had not concurrently undergone dehalogenation.

It is noteworthy that the foregoing reaction did not proceed at all when commercial tributylstannane was used, but when the reagent was freshly prepared[6,7] and redistilled directly before use,[7] the reaction progressed satisfactorily. The AIBN initiator was essential; no reaction occurred in its absence. Benzoyl peroxide was also an effective initiator, but much larger quantities were required. Yields were not increased with prolonged heating of the reaction mixture, and a small amount of starting material remained at the end of the reaction period.

The 6-chloropurine derivatives **7** and **8** were allowed to react with thiourea in hot ethanol solution to afford 2,3,4,5-tetra-*O*-acetyl-1-deoxy-1-(1,6-dihydro-6-thioxopurin-9-yl)-D-ribitol (**9**) and the D-*arabino* analogue (**10**) as crystalline, analytically pure products, respectively. Compound **9** was soluble in hot ethanol and separated out on cooling, while compound **10** separated out from the hot mixture and was found to be of very low solubility in a variety of solvents. O-Deacetylation of **9** in methanol solution by the action of diethylamine for 48 h at room temperature led to crystalline 1-deoxy-1-(1,6-dihydro-6-thioxopurin-9-yl)-D-ribitol (**11**), and similar treatment of **10**, but with ammonia at 0 °C gave the D-arabinitol analogue **12**, which was likewise crystalline. Efforts to O-deacetylate **9** and **10** with methanolic sodium methoxide led to further decomposition.

Ultraviolet spectroscopy provided initial evidence for the position of attachment of the sugar chain to N-9 of the purine ring. Compounds **4**, **5**, **6**, **7**, and **8** exhibited absorption maxima at 264, 265, 266, 264, and 265 nm, respectively, in accord with literature values[8–11] of ~265 nm for 9-alkylpurines and different from the

Table 1. ^{1}H NMR chemical shifts[a] for compounds **4–10**

Compound	Chemical shifts (δ)											
	H-1′	H-1″	H-2′	H-3′	H-4′	H-5′	H-5″	H-2	H-8	OAc, SMe	SEt	NH
4	5.89 d		5.55 dd	5.43 dd	5.3 m	4.31 dd	4.09 dd	8.74 s	8.52 s	2.18 s, 2.12 s, 2.09 s, 2.0 s, 1.98 s		
5	5.90 d		5.75 dd	5.25 dd	5.14 m	4.26 dd	4.01 dd	8.74 s	8.42 s	2.12 s, 2.09 s, 2.05 s, 2.01 s, 2.0 s		
6	6.01 d		5.7 dd	5.29 dd	5.16 m	4.28 dd	4.03 dd	8.74 s	8.45 s	2.12 s, 2.10 s, 2.05 s, 2.02 s	2.44 q, 1.17 t	
7	4.65 dd	4.44 dd		—5.39 m—		4.32 dd	4.14 dd	8.71 s	8.08 s	2.18 s, 2.08 s, 2.03 s, 1.95 s		
8	4.59 dd		5.63 dt	5.46 dd	5.17 ddd	4.3–4.14 m		8.77 s	8.08 s	2.21 s, 2.08 s, 2.01 s, 1.94 s		
9	4.65–4.32 m			—5.42 m—		4.65–4.32 m		8.54 s	8.28 s	2.2 s, 2.13 s, 2.06 s, 2.03 s		8.54
10	4.34–4.30 m		5.34 d	5.38 dd	5.07 d	4.16 m		8.2 s	8.18 s	2.11 s, 1.97 s, 1.92 s, 1.81 s		8.18

[a] Measured at 200 MHz for solutions in $CDCl_3$ with Me_4Si as the internal standard.

Table 2. ^{1}H NMR coupling constants (Hz)[a] for compounds **4–8**

Compound	Coupling constants (Hz)								
	$J_{1',1''}$	$J_{1'',2'}$	$J_{1',2'}$	$J_{1',2''}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{4',5''}$	$J_{5',5''}$
4			3.9		7.2	4.4	6.6	3.7	12.1
5			6.5		3.0	7.8	2.8	5.3	12.5
6			6.1		3.2	8.9	2.9	5.4	12.5
7	14.8		2.9	7.9			2.7	5.5	12.3
8	14.6	9.3	3.3		2.6	8.9	2.8	4.1	

[a] Measured at 200 MHz for solutions in $CDCl_3$ with Me_4Si as the internal standard.

values (~270 nm) for 7-alkylpurines. Additional supporting evidence (see later) came from ^{13}C NMR data.

Compounds **4**, **5**, and **6** have a chiral center at C-1′. The D-*arabino* compounds **5** and **6** were obtained as single C-1′ epimers, whereas the D-*ribo* compound **4** was an epimeric mixture from which the major epimer was isolated crystalline. The highly polarizable heterocyclic substituent at C-1′ was expected to dominate and determine the net optical rotation for each compound, with only a minor contribution from the other asymmetric centers, allowing application of the Generalized Heterocycle Rule.[12] This rule states that, for a molecule containing an aromatic group attached to a carbon chain having a chalcogen substituent at the same position, when viewed in the Fischer projection, the epimer having the chalcogen on the right will be dextrorotatory and that with the chalcogen on the left will be levorotatory. On this basis,[13] the single epimers **5** and **6** having specific rotations of +97° and +107°, respectively, are assigned the 1′(*R*) configuration, whereas the crystalline major epimer of **4** having $[\alpha]_D$ −31 is assigned the 1′(*S*) configuration; the syrupy minor epimer presumably having the 1′(*R*) configuration. Unequivocal confirmation of these assignments was provided by a single-crystal X-ray structure[†] of the methylthio D-*ribo* derivative **4**, which proved the N-9 attachment to the purine ring and the 1(*S*) configuration at C-1′.

The 200-MHz ^{1}H NMR spectrum of the syrupy initial product of condensation of the D-*ribo* dithioacetal derivative **1** with 6-chloropurine showed narrow ($J_{1',2'} \sim 4$ Hz) doublet signals at δ 5.89 and 6.01 in 1:3.7 ratio, assigned to the H-1′ signals of the 1′(*R*) and 1′(*S*) diastereoisomeric coupling products. Crystallization from ether afforded the pure 1′(*S*) epimer **4**. The spectra of the corresponding D-*arabino* coupling products **5** and **6** indicated that they were single epimers. The spectra of all three compounds **4–6** in chloroform-*d* solution were of first order, and Tables 1 and 2 record chemical shifts and proton–proton coupling constants, respectively. Singlet signals near δ 8.74 and 8.45 were assigned to H-2 and H-8, respectively, of the purine ring, and the protons of the sugar chain showed the anticipated doublet of doublets for H-2′ and H-3′, and the expected ABXY system for H-4′ and H-5′, H-5″. The D-*arabino* compounds **5** and **6** showed large values for $J'_{1',2}$ and $J_{3',4'}$ and small values for $J_{2',3'}$, consistent with the expected[13–15] planar zigzag conformation of the carbon backbone chain, as depicted in **5a**, whereas for the D-*ribo* derivative **4** the respective values were $J'_{1',2}$ small, $J_{2',3'}$ large, and $J_{3',4'}$ small, indicative of a nonplanar carbon chain with C-5′ rotated out of the plane of

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[†] Full details are recorded in the Supplementary data.

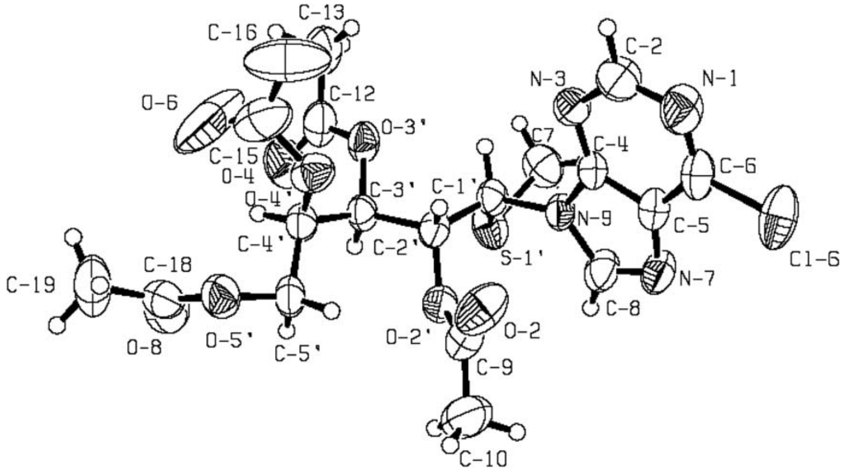
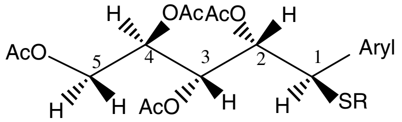


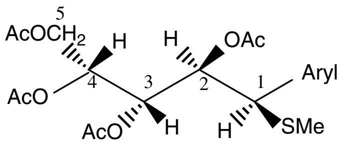
Figure 1. ORTEP diagram for the X-ray crystal structure of 1′(*S*)-2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-y1)-1-*S*-methyl-l-thio-D-ribitol (**4**).

C-1′–C-4′ to the $_3G^-$ orientation, as depicted in **4a**, alleviating the unfavorable 1,3-parallel relation between O-2′ and O-4′ that would have resulted in the fully extended planar, zigzag conformation of the sugar chain.

The single-crystal X-ray structure for **4** (Fig. 1) provides definitive evidence for the attachment of the sugar chain to N-9 of the purine as well as for the (*S*) configuration at C-1′, and also shows that the sugar chain adopts in the solid state a nonextended conformation; in this instance, the $_3G^+$ sickle arrangement with C-5′ out of the plane of the C-1′–C-4′ chain.



5a



4a

The ^{1}H NMR spectra of the 2,3,4,5-tetra-*O*-acety1-1-(6-chloropurin-9-y1)-1-deoxy-D-alditols (compounds **7** and **8**) showed the expected 2-proton pattern for the methylene group at C-1′, upfield by ~1.5 ppm from that for H-1′ in the 1′-thio precursors. The presence of only two 1-proton singlets for H-2 and H-8 of the purine ring and comparable to those observed for the 1′-thio precursors confirmed that the chlorine atom at C-6 had not been removed during the free-radical reaction. The spin-coupling data for the D-*arabino* derivative **8** were consistent with the planar, zigzag conformation of the sugar chain, as observed with the 1′-thio precursors, but for the D-*ribo* compound **7**, overlap of the H-2′, H-3′, and H-4′ signals precluded reliable conformational assignment.

The ^{1}H NMR spectrum of 2,3,4,5-tetra-*O*-acetyl-1-deoxy-1-(1,6-dihydro-6-thioxopurin-9-y1)-D-ribitol (**9**) was determined in chloroform-*d*, whereas the sparingly soluble D-*arabino* derivative (**10**) required dimethyl sulfoxide-d_6 to achieve adequate solubility. The anticipated singlets for H-2 and H-8 of the purine ring were observed, along with a D_2O-exchangeable signal almost overlapping the H-8 signal but clearly observable in an expanded spectrum. Close overlap of many of the resonances for protons of the sugar backbone chain in **9** precluded extraction of spin-coupling data and conformational assignments. There was better separation of the H-2′, H-3′, and H-4′ signals in the spectrum of **10**, but the low solubility of this compound precluded reliable assignments by proton–carbon-13 correlation methods.

Tables 3 and 4 list ^{13}C NMR data for the compounds in this study. Carbon resonances for the heterocyclic base in compounds **4**–**8** appear between 152 and 130 ppm, and the C-6 resonance is shifted much further downfield (to ~175 ppm) when a sulfur atom is attached, indicating that compounds **10**–**12** are the thione tautomers. The C-2 and C-8 resonances were readily recognized by their larger signal intensities and their doublet splitting in off-resonance spectra, and the more downfield resonance was assigned to C-2 by analogy with published[17] ^{13}C data on purine nucleosides. Assignments for C-4 and C-5, with C-5 at higher field than C-4, were made in comparison with earlier work.[16–19] The acetylated derivatives show the anticipated carbonyl resonances around 170 ppm, and acetate methyl resonances and *S*-alkyl peaks between 14 and 21 ppm. Carbon resonances of the sugar chain fell in the region 44–72 ppm, with the C-1′ methylene group of compounds **7**–**12** at distinctly higher field (~44–47 ppm) than the C-1′ resonance in the 1′-thio derivatives **4**–**6**.

Table 3. ^{13}C NMR spectral data[a] for compounds **4**–**8** and **10**–**12**

Compound	Chemical shifts, δ							
	C-1′	C-2′	C-3′	C-4′	C-5′	*C*OCH$_3$	CO*C*H$_3$	S*C*H$_3$
4	71.36	62.01	69.50	69.61	61.46	170.37, 169.77, 169.55, 169.17	20.73, 20.51	14.83
5	61.76	68.46	68.51	69.96	61.60	170.46, 169.71, 169.54, 169.47	20.78, 20.70, 20.55, 20.39	14.59
6	61.75	68.61	68.61	70.47	59.93	170.50, 169.74, 169.61	20.90, 20.77, 20.64, 20.45	26.0[b]
7	43.38	69.30	69.50	69.59	61.64	170.32, 169.85, 169.25	20.79, 20.48	—
8	44.29	67.67	67.92	68.24	60.93	169.61, 169.17, 168.90, 168.78	19.83, 19.97, 19.45	—
10	44.03	67.88	68.70	68.58	61.34	169.91, 169.60, 169.20	30.52, 20.4, 20.36, 20.11	—
11	46.20	69.98	72.44	73.28	62.94	—	—	—
12	47.22	67.99	70.93	71.0	63.38	—	—	—

[a] Measured at 50 MHz for solutions in CDCl$_3$.

[b] S*C*H$_2$ signal.

Table 4. ^{13}C NMR spectral data[a] for purine resonances in the acylic-sugar nucleosides and the 6-chloropurine anion

Compound	Chemical shifts, δ									
	C-2(γ)[b]	δ[c]	C-4(α)	Δ	C-5(β)	δ	C-6(γ)	δ	C-8(α)	δ
6-Chloropurine[d] anion	149.03		159.82		131.35		145.87		152.67	
4	152.22	−3.19	152.22	+7.6	132.55	−1.2	151.74	−5.87	144.13	+8.54
5	152.21	−3.18	151.88	+7.94	131.68	−0.33	151.69	−5.82	143.58	+9.09
6	152.23	−3.20	152.23	+7.59	131.98	−0.63	151.79	−5.92	143.86	+8.81
7	152.10	−3.07	152.10	+7.72	132.33	−0.98	151.98	−6.11	145.34	+7.33
8	151.26	−2.23	151.55	+8.27	130.81	−0.54	150.15	−4.28	144.84	+7.83
10	144.25		144.94		143.06		175.81		134.68	
11	144.39		144.77		134.79		175.64		143.68	
12	144.57		144.24		134.88		175.55		143.68	

[a] Measured at 50 MHz, in CDCl$_3$, except for compounds **10**–**12**, which were measured at 125 MHz for solutions in Me$_2$SO-*d*$_6$.

[b] Positions in parentheses are with respect to N-9 of the purine base.

[c] δ denotes chemical shifts with respect to 6-chloropurine anion, positive values denoting an upfield shift and negative values a downfield shift.

[d] From Ref. 2.

Chemical-shift data for the purine carbon atoms provide further information on the point of attachment of the sugar to the purine ring.[16] Reported data for 2,6-dichloro-9-methylpurine and 2,6-dichloro-7-methylpurine[18] show distinctly different shift-patterns for the 7- and 9-substituted derivatives. Pugmire et al., in their studies on *N*-methylpurines,[18] evaluated the effect of *N*-methyl substitution as opposed to nitrogen protonation. They observed that methyl substitution in the purine ring results in a large upfield shift of the α carbons and a small downfield shift of the β and γ carbons as compared with the purine anion.[2] Similar trends were observed in the present work, with large upfield α shifts and small downfield β and γ shifts (see Table 4). The shifts of the α carbons were about +8 ppm, whereas the β carbons were seen to move slightly downfield from the 6-chloropurine anion. Larger downfield shifts, around −3 and −5 ppm, respectively, were observed for the γ carbon atoms C-2 and C-6. These correlations provide additional strong support for assignment of these nucleosides as the 9-substituted products.

The electron-impact mass spectra of the nucleoside derivatives **4**–**10** showed[20] molecular-ion peaks at $[M]^+$, $[M+1]^+$, or $[M+2]^+$, and the alkylthio derivatives **4**–**6** showed characteristic $[M-SR]^+$ peaks. Spectra of the 1-(6-chloropurin-9-yl) derivatives **7** and **8** showed close similarities with that of the 6-thioxo compound **9**, indicating little influence by the substitution mode on the heterocyclic ring. In all of the acetylated compounds, elimination of the acetoxyl group occurred by the loss of CH_3CO_2H, CH_3CO, or $CH_2{=}C{=}O$, and the most intense peak was that of the acetyl ion CH_3CO^+ (*m*/*z* 43). Fission of the base could be observed in all of the spectra by the presence of [B+1] and [B+2] peaks.

3. Experimental

3.1. General methods

Melting points are uncorrected values taken on a Thomas–Hoover Unimelt apparatus. Optical rotations were determined on a Perkin–Elmer Model 141 polarimeter and 1-dm tubes were used. ^{1}H NMR spectra were recorded on a 200-MHz, Bruker WP-200 spectrometer operating on the Fourier-transform mode at 25 °C. ^{13}C NMR spectra were recorded at 50.3 MHz with a Bruker WP-200 spectrometer operating in the Fourier-transform mode at 35 °C or at 125 MHz. UV spectra were recorded with a Hitachi Perkin–Elmer 200 spectrometer. TLC was performed on precoated plastic plates (0.2 mm) of Silica Gel 60E-254, and the zones were detected either by spraying the plates with 10% H_2SO_4 followed by heating, or by UV light. Column chromatography was performed with Silica Gel 60 (particle size 0.040–0.063 mm). Mass spectra were recorded by C. R. Weisenberger with a Kratos MS-30 mass spectrometer. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Georgia. All reactions with tributylstannane were performed in dry glassware under an atmosphere of argon. Tributylstannane was distilled under diminished pressure. Toluene was dried by fractional distillation. MeOH was dried by distillation over CaH_2.

3.2. Preparation of D-ribose dimethyl dithioacetal

To MeSH (12 g, 0.25 mol) condensed in a reaction bottle over an acetone–dry ice bath was added D-ribose (15.0 g, 0.1 mol) that had been dissolved in concd HCl (20 mL) just prior to the addition. The mixture was stirred with cooling by an acetone–dry ice bath for 15 min and then at room temperature for 2 h, after which time TLC (4:1 $CHCl_3$–MeOH) indicated complete conversion into the product. The mixture was then poured into ice-water (500 mL), made neutral with $PbCO_3$, and filtered. The filtrate was evaporated under diminished pressure, the residue obtained was leached with MeOH, and the mixture was filtered to remove the remaining lead salts. Evaporation of the MeOH yielded the product as a white solid, which on recrystallization from EtOAc gave 16.02 g (70%), of dithioacetal, mp 73.5–74 °C, $[\alpha]_D^{25}$ −9° (MeOH). Lit.[4] mp 76–76.5 °C; $[\alpha]_D$ −9.6 (MeOH).

3.3. Preparation of D-arabinose dimethyl dithioacetal

Following the procedure just described for the D-ribose analogue, D-arabinose (25 g, 0.17 mol) dissolved in cold concd HCl (25 mL) was added to MeSH (23 g, 0.5 mol), and the product was isolated by the same procedure. The crude product was acetylated without further purification.

3.4. 2,3,4,5-Tetra-*O*-acetyl-D-ribose dimethyl dithioacetal (1)

To a solution of D-ribose dimethyl dithioacetal (15 g, 65.8 mmol) was added Ac_2O (120 mL), and the mixture, after being stirred for 48 h at room temperature, was poured into ice-water (250 mL) to give an insoluble syrup. This was extracted with $CHCl_3$, washed with $NaHCO_3$ until neutral, water and then dried (Na_2SO_4). Evaporation of the solvent yielded a syrup. This was divided into two parts, and each was applied to a silica gel column (3.5 × 45 cm) and eluted with 2:1 hexane–EtOAc to yield **1** (21.1 g, 81%) as a clear syrup: $[\alpha]_D^{25}$ +34° (MeOH).

3.5. Preparation of 2,3,4,5-tetra-*O*-acetyl-D-arabinose dimethyl dithioacetal (2)

To D-arabinose dimethyl dithioacetal (**2**, 2 g, 8.8 mmol), dissolved in pyridine (25 mL), was added Ac_2O (15 mL). The mixture was stirred at room temperature for 24 h and then poured over ice-water (300 mL), whereby product **2** separated out as a white solid. This was filtered and dried; yield 3.33 g (96%). Recrystallization from Et_2O gave pure **2**: mp 82 °C, $[\alpha]_D^{25}$ +30° (MeOH). Lit.[5] mp 84 °C; $[\alpha]_D$ +34.1 (MeOH).

3.6. 2,3,4,5-Tetra-*O*-acetyl-D-arabinose diethyl dithioacetal (3)

Conventional acetylation[21] of D-arabinose diethyl dithioacetal[22] and recrystallization from MeOH gave pure **3**: mp 80.5–81.5 °C, $[\alpha]_D^{25}$ +32 (MeOH). Lit.[5] mp 80 °C, $[\alpha]_D$ +34.9 (MeOH).

3.7. 1′(*S*)-2,3,4,5-Tetra-*O*-acetyl-1-(6-chloropurin-9-y1)-1-*S*-methyl-l-thio-D-ribitol (4) and its 1′(*R*) diastereomer

A mixture of 2,3,4,5-tetra-*O*-acetyl-D-ribose dimethyl dithioacetal (**1**, 2.62 g, 6.62 mmol), 6-chloropurine (1.58 g, 10.2 mmol), $Hg(CN)_2$ (2.58 g, 10.2 mmol), HgO (0.9 g, 4.16 mmol), anhyd $CaSO_4$ (0.53 g), and $MeNO_2$ (65 mL) was boiled under reflux for 22 h. The mixture was filtered hot, and the filtrate on evaporation under diminished pressure yielded a yellow powder and a syrup. These were extracted with hot $CHCl_3$, and the mixture was filtered. The filtrate was washed with 30% aq KI (3 × 50 mL), water (3 × 75 mL) and dried (Na_2SO_4). Evaporation of the solvent yielded a syrup that was eluted with 1:1 hexane–EtOAc from a column (2.5 × 30 cm) of silica gel to yield **4** (2.1 g, 63%) as a 3.7:1 mixture of the 1-epimers. Some starting dithioacetal (**1**, 0.28 g) could be recovered from the column.

Upon crystallization from Et_2O, the major epimer [1′(*S*)] was isolated from the mixture as a white solid: mp 102–103 °C, $[\alpha]_D$ −31° (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}C1N_4O_8S$: C, 45.37; H, 4.57; Cl, 7.06; N, 11.14; S, 6.37. Found: C, 45.46; H, 4.59; Cl, 7.16; N, 11.08; S, 6.30.

3.8. 1′(*R*)-2,3,4,5-Tetra-*O*-acetyl-1-(6-chloropurin-9-y1)-1-deoxy-l-*S*-methyl-1-thio-D-arabinitol (5)

A mixture of 2,3,4,5-tetra-*O*-acetyl-D-arabinose dimethyl dithioacetal (**2**, 10 g, 25.3 mmol), 6-chloropurine (3.91 g, 25.3 mmol), $Hg(CN)_2$ (9.83 g, 38.9 mmol), HgO (3.44 g, 15.9 mmol), $CaSO_4$ (2 g), and $MeNO_2$ (400 mL) was boiled under reflux for 23 h. It was then filtered hot, and the filtrate was evaporated under diminished pressure. The residue obtained was extracted with hot $CHCl_3$, and the mixture was filtered. The filtrate was washed with aq KI (4 × 50 mL), water (3 × 50 mL) and dried (Na_2SO_4). The solvent was evaporated to yield a yellow solid that was dissolved in 1:1 hexane–EtOAc, applied to a column (3.3 × 40 cm) of silica gel and eluted with 1:1 hexane–EtOAc. The first fraction to be eluted was the starting material **2** (1.7 g) followed by product **5** (4.55 g, 43%): mp 113–114.5 °C; $[\alpha]_D$ +97° (*c*, 0.2, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}ClN_4O_8S$: C, 45.37; H, 4.57; Cl, 7.06; N, 11.14; S, 6.37. Found: C, 45.44; H, 4.63; Cl, 7.01; N, 11.11; S, 6.45.

3.9. 1′(*R*)-2,3,4,5-Tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-*S*-ethyl-1-thio-D-arabinitol (6)

A mixture of **3** (9 g, 21 mmol), 6-chloropurine (3.3 g, 21 mmol), $Hg(CN)_2$ (8.2 g, 33 mmol), HgO (2.9 g, 13 mmol), $CaSO_4$ (2.8 g), and $MeNO_2$ (150 mL) was boiled under reflux for 21 h, and then processed as in the preceding procedure. Removal of the solvent yielded a syrup that was applied to a column (3.3 × 40 cm) of silica gel and eluted with 1:1 hexane–EtOAc to yield compound **6** (5.1 g, 47%) as a syrup; $[\alpha]_D$ +107° (*c*, 0.4, $CHCl_3$) Anal. Calcd for $C_{20}H_{25}ClN_4O_8S$: C, 46.47; H, 4.84; Cl, 6.87; N, 10.84; S, 6.19. Found: C, 46.23; H, 4.9; Cl, 6.93; N, 10.69; S, 6.24.

The starting material **3** (1 g) was recovered from the column as the first fraction.

This compound was earlier reported[1] as a syrupy single epimer, still containing some solvent, and without analytical data: $[\alpha]_D$ +81° ($CHCl_3$).

3.10. 2,3,4,5-Tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-D-ribitol (7)

To toluene (10 mL) refluxing under argon was added freshly distilled tributylstannane (0.6 mL, 0.66 g, 2.23 mmol), prepared as in Ref. 7. The mixture was boiled under reflux for 10 min, and to it was added compound **4** (0.65 g, 1.29 mmol) and 1,1′-azobis(isobutanonitrile) (17 mg) dissolved in toluene (10 mL). The mixture was boiled for 23 h and then cooled, and evaporated to a syrup. This was dissolved in MeCN (25 mL) and extracted with hexane (3 × 25 mL), to remove the tin residues. The MeCN was then removed under diminished pressure to yield a thick syrup that was applied to a column (1 × 50 cm) of silica gel and eluted with 1:1 hexane–EtOAc to yield **7** as a syrup (0.47 g, 80%): $[\alpha]_D$ −12° (*c* 0.067, $CHCl_3$). Unreacted starting material (60 mg) was recovered as the first fraction, resulting in a corrected yield of 87% of product **7**. Anal. Calcd for $C_{18}H_{21}ClN_4O_8$: C, 47.32; H, 4.6; Cl, 7.78; N, 12.27. Found: C, 47.12; H, 4.69; Cl, 7.87; N, 12.02.

3.11. 2,3,4,5-Tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-D-arabinitol (8)

3.11.1. (a) From 1′(*R*)-2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-l-*S*-methyl-1-thio-D-arabinitol (5). To 10 mL of toluene refluxing under argon were added Bu_3SnH (0.6 mL, 0.66 g, 2.23 mmol) and **14** (0.65 g, 1.29 mmol) dissolved in 25 mL of toluene and 1,1′-azobis(isobutanonitrile) (17 mg). The clear yellow solution was boiled under reflux for 25 h and then cooled, and toluene was evaporated off to yield a syrup. This was dissolved in MeCN (50 mL) and extracted with hexane (3 × 30 mL). The MeCN was then removed under diminished pressure, and the syrup obtained was applied to a column (1 × 50 cm) of silica gel that was eluted with 1:2 hexane–EtOAc. Compound **8** (0.46 g, 78%) was obtained as a clear syrup that solidified to a white product; mp 87–88.5 °C; $[\alpha]_D$ +74° (*c* 0.19, $CHCl_3$). The starting material (33 mg) was also recovered as the first fraction from the column. Anal. Calcd for $C_{18}H_{21}ClN_4O_8$: C, 47.32; H, 4.6; Cl, 7.78; N, 12.27. Found: C, 47.26; H, 4.67; Cl, 7.73; N, 12.20.

3.11.2. (b) From 1′(*R*)-2,3,4,5-tetra-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-*S*-ethyl-1-thio-D-arabinitol (6). To 10 mL of toluene refluxing under argon were added Bu_3SnH (0.6 mL, 0.66 g, 2.2 mmol) and compound **3** (0.67 g, 1.3 mmol) dissolved in toluene (10 mL), and 1,1′-azobis(isobutanonitrile) (7 mg). The mixture was boiled under reflux for 25 h, cooled and evaporated to a syrup. This was dissolved in MeCN (20 mL) and extracted with hexane (3 × 25 mL). Processing as in the preceding experiment afforded compound **8** as a syrup; yield 0.38 g (63%). The starting material (0.05 g) could be recovered as an earlier fraction from the column. The product was seen by NMR to be identical with **8** prepared by procedure (a).

3.12. 2,3,4,5-Tetra-*O*-acetyl-1-deoxy-1-(1,6-dihydro-6-thioxopurin-9-yl)-D-ribitol (9)

To thiourea (0.116 g, 1.53 mmol) was added compound **7** (0.6 g, 1.34 mmol) dissolved in EtOH (20 mL), and the mixture was boiled under reflux for 4 h. It was then cooled, filtered, and evaporated to yield crude **9** as a white solid. Recrystallization from EtOH afforded pure **9**; yield 0.31 g (52%): mp 184–185 °C; $[\alpha]_D$ −6° (*c* 0.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}N_4O_8S$: C, 47.58; H, 4.85; N, 12.33; S, 7.05. Found: C, 47.42; H, 4.89; N, 12.29; S, 7.12.

3.13. 2,3,4,5-Tetra-*O*-acetyl-1-deoxy-1-(1,6-dihydro-6-thioxopurin-9-yl)-D-arabinitol (10)

To thiourea (0.058 g, 0.76 mmol) dissolved in EtOH (5 mL) was added compound **8** (0.3 g, 0.66 mmol) dissolved in EtOH (10 mL). The mixture was refluxed for

4 h and then cooled, and the white solid that separated out was filtered off to give **10** (0.24 g, 80%): mp 215–216 °C; $[\alpha]_D$ +85° (*c* 0.2 in Me_2SO). Anal. Calcd for $C_{18}H_{22}N_4O_8S$: C, 47.88; H, 4.85; N, 12.33; S, 7.05. Found: C, 45.57; H, 4.9; N, 12.33; S, 7.10.

3.14. 1-Deoxy-1-(1,6-dihydro-6-thioxopurin-9-y1)-D-ribitol (11)

2,3,4,5-Tetra-*O*-acety1-1-deoxy-1-(1,6-dihydro-6-thioxopurin-9-y1)-D-ribitol (**9**, 0.25 g, 0.55 mmol) was dissolved in MeOH (50 mL), and to it was added Et_2NH (0.5 mL, 0.35 g, 4.8 mmol). The mixture was stirred at room temperature, and TLC monitoring (MeOH) indicated the reaction to be complete after 45 h. Evaporation of the solvent yielded a solid that was recrystallized from EtOH to give pure **11** (100 mg, 62%): mp (dec) 250 °C; $[\alpha]_D$ +1° (*c* 0.01, EtOH). Anal. Calcd for $C_{10}H_{14}N_4O_4S$: C, 41.96; H, 4.9; N, 19.58; S, 11.19. Found: C, 41.84; H, 4.95; N, 19.55; S, 11.11.

3.15. 1-Deoxy-1-(1,6-dihydro-6-thioxopurin-9-yl)-D-arabinitol (12)

A stream of NH_3 gas was bubbled for 30 min through a suspension of 2,3,4,5-tetra-*O*-acety1-1-(1,6-dihydro-6-thioxopurin-9-y1)-1-deoxy-D-arabinitol (**10**, 100 mg, 0.22 mmol) in MeOH (10 mL) cooled in an ice-water bath. The mixture was kept at 0 °C for 24 h, after which time TLC (MeOH) indicated complete conversion into the product. The solvent was then removed under diminished pressure, and the residue was dissolved in MeOH and allowed to crystallize, yielding 34 mg (57%) of pure **12**: mp (dec) 299 °C; $[\alpha]_D$ +40° (*c* 1.7, Me_2SO). Anal. Calcd for $C_{10}H_{14}N_4O_4S$: C, 41.96; H, 4.9; N, 19.58; S, 11.20. Found: C, 41.77; H, 4.95; N, 19.46; S, 11.07.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.05.019.

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