Synthesis of 4- and 5-(*s*-Triazolo[4,3-*b*]pyridazinyl-3)-substituted Cyclic Polyols

Cvetka Turk, Jurij Svete, Amalija Golobič, Ljubo Golič, and Branko Stanovnik*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia

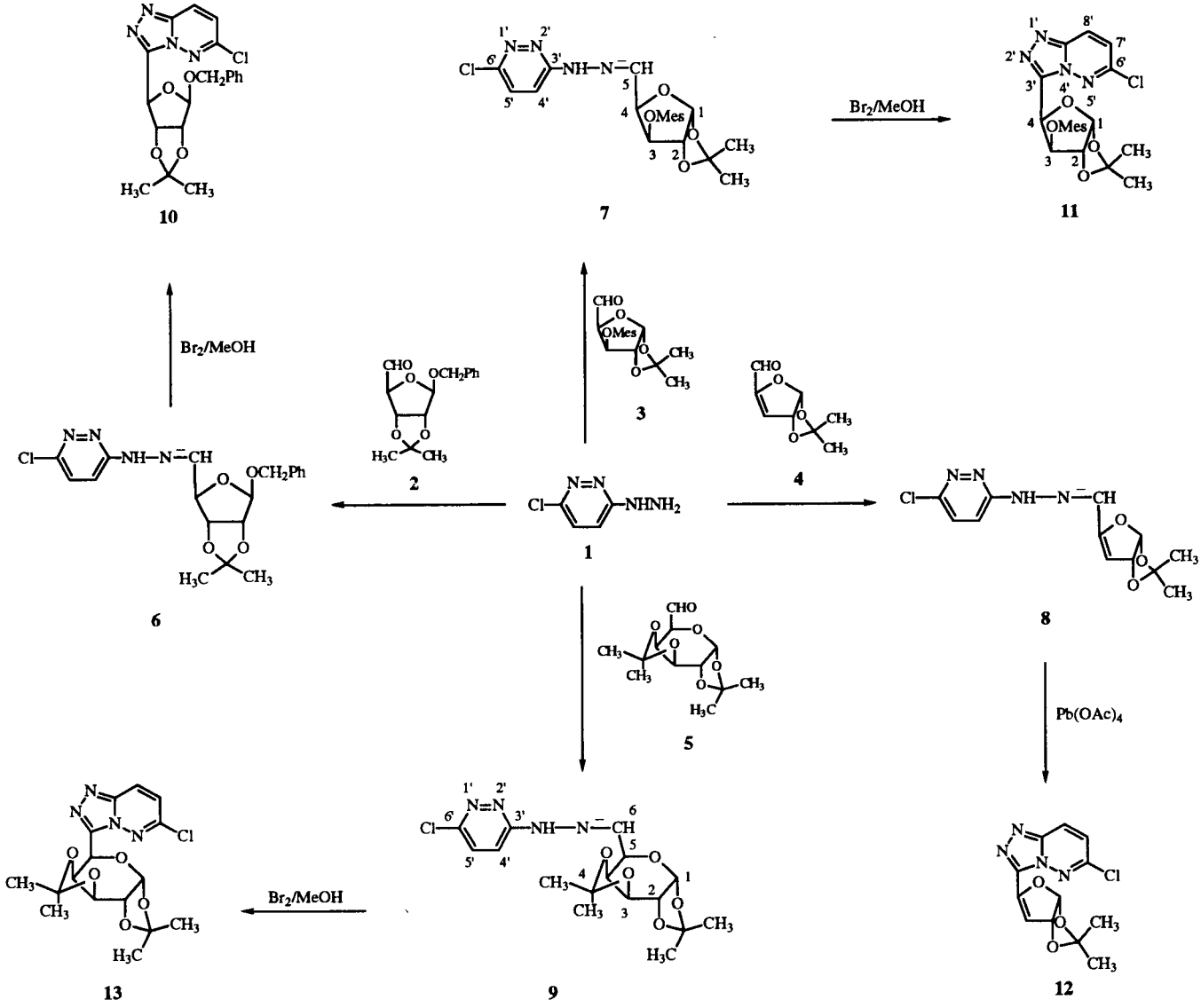
Received February 11, 1998

4(*R*)-(6-Chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,4-furanoses **10** and **11**, 5(*R*)-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,5-pyranose **13**, and 2(*S*),3(*R*)-dihydro-5-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidenefuran (**12**) were prepared by cyclization of hydrazones **6-9** obtained from 6-chloro-3-hydrazinopyridazine (**1**) and aldofuranoses **2**, **3** and **4**, and aldopyranose **5**.

J. Heterocyclic Chem., **35**, 513 (1998).

Carbon nucleosides and related compounds bearing carbon-linked nitrogen heterocycles have elicited numerous synthetic and biological studies [1-4] due to their activity or potential antiviral and antitumor activities [5-11].

Scheme 1



Recently, we have reported the synthesis of azolopyridazinyl substituted sugars by 1,3-dipolar cycloaddition of methyl acrylate to protected and unprotected aldose-azomethinimines [12-14] and by oxidative cyclization of aldose-hydrazones prepared from heterocyclic hydrazino compounds [15].

We report now the synthesis of (*s*-triazolo[4,3-*b*]pyridazinyl-3)-substituted cyclic sugars by cyclization of hydrazones prepared from 6-chloro-3-hydrazinopyridazine (**1**) [16] and cyclic sugars: benzyl 2,3-*O*-isopropylidene-β-*D*-*ribo*-pentodialdo-1,4-furanoside (**2**) [17], 1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-*D*-*xylo*-pentodialdo-1,4-furanose (**3**) [18], 1,2-*O*-isopropylidene-α-*D*-*glycero*-pent-3-enodialdo-1,4-furanose (**4**) [18], 1,2:3,4-di-*O*-isopropylidene-α-*D*-*galacto*-hexodialdo-1,5-pyranose (**5**) [19]. In the reaction between **1** and cyclic sugars **2-5** in ethanol at room temperature the corresponding hydrazones: 6-chloro-3-hydrazinopyridazine benzyl 2,3-*O*-isopropylidene-β-*D*-*ribo*-pentodialdo-1,4-furanoside hydrazone (**6**), 6-chloro-3-hydrazinopyridazine 1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-*D*-*xylo*-pentodialdo-1,4-furanose hydrazone (**7**), 6-chloro-3-hydrazinopyridazine 1,2-*O*-isopropylidene-α-*D*-*glycero*-pent-3-enodialdo-1,4-furanose hydrazone (**8**), and 6-chloro-3-hydrazinopyridazine 1,2:3,4-di-*O*-isopropylidene-α-*D*-*galacto*-hexodialdo-1,5-pyranose hydrazone (**9**) were formed, respectively.

The cyclization of hydrazones **6**, **7** and **9** was achieved with bromine in methanol in the presence of sodium acetate at room temperature to give benzyl 4(*R*)-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidene-β-*D*-*eritro*-1,4-furanoside (**10**), 4(*R*)-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-*L*-*threo*-1,4-furanose (**11**) and 5(*R*)-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,2:3,4-di-*O*-isopropylidene-α-*L*-*arabino*-1,5-pyranose (**13**), respectively in 77-82% yield, while hydrazone **8** was oxidised with lead tetraacetate in methylene chloride at room temperature to give 2(*S*),3(*R*)-dihydro-5-(6-chloro-*s*-triazolo-[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidenefuran (**12**) in 56% yield (Scheme 1, Tables 1 and 2).

When compound **11** was heated at reflux temperature for two hours with potassium hydroxide in a mixture of water and dioxane (1:3), elimination of methanesulfonic acid and hydrolysis of chlorine at position 6 of *s*-triazolo[4,3-*b*]pyridazine part of the molecule took place to give 2(*S*),3(*R*)-dihydro-5-(6-hydroxy-*s*-triazolo[4,3-*b*]-pyridazinyl-3)-2,3-*O*-isopropylidenefuran (**14**) in 91% yield. By monitoring the reaction by tlc we observed the presence of another compound, but it was not found in the

Table 1

Experimental and Analytical Data

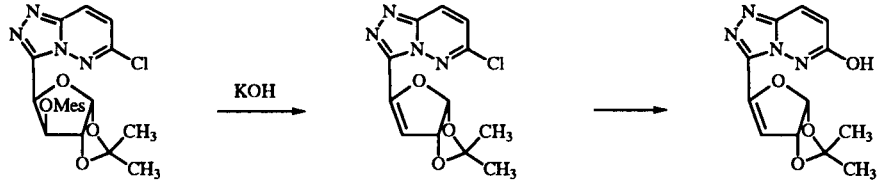
Compound	Yield (%)	mp °C Specific Rotation	Molecular Formula Analyses
6	77	169-171 (from absolute ethanol) $[\alpha]^{22}_D$ -83.2° (c = 0.38, $CHCl_3$)	$C_{19}H_{21}ClN_4O_4$ Calcd: C, 56.37; H, 5.23; N, 13.84 Found: C, 56.43; H, 5.08; N, 13.96
7	82	190-192 dec (from absolute ethanol) $[\alpha]^{22}_D$ -76.7° (c = 1.02, $CHCl_3$)	$C_{13}H_{17}ClN_4O_6S$ Calcd: C, 39.75; H, 4.36; N, 14.26 Found: C, 39.65; H, 4.27; N, 14.01
8	80	179-181 dec (from absolute ethanol)	$C_{12}H_{13}ClN_4O_3$ Calcd: C, 48.58; H, 4.42; N, 18.88 Found: C, 48.53; H, 4.33; N, 19.12
9	80	203-205 (from absolute ethanol)	$C_{16}H_{21}ClN_4O_5$ Calcd: C, 49.94; H, 5.50; N, 14.56 Found: C, 49.55; H, 5.39; N, 14.39
10	85	141-143 (from absolute ethanol) $[\alpha]^{22}_D$ -99.2° (c = 0.95, $CHCl_3$)	$C_{19}H_{19}ClN_4O_4$ Calcd: C, 56.65; H, 4.76; N, 13.91 Found: C, 56.47; H, 4.76; N, 13.67
11	75	175-180 dec (from absolute ethanol) $[\alpha]^{22}_D$ -58.4° (c = 1.01, $(CH_3)_2SO$)	$C_{13}H_{15}ClN_4O_6S$ Calcd: C, 39.95; H, 3.87; N, 14.34 Found: C, 39.79; H, 3.65; N, 14.43
12	56	204-206 dec (from absolute ethanol)	$C_{12}H_{11}ClN_4O_3$ Calcd: C, 48.91; H, 3.76; N, 19.01 Found: C, 48.83; H, 3.63; N, 19.24
13	72	175-178 dec (from absolute ethanol)	$C_{16}H_{19}ClN_4O_5$ Calcd: C, 50.20; H, 5.00; N, 14.63 Found: C, 50.14; H, 4.85; N, 14.61
14	91	>280 dec (from absolute ethanol)	$C_{12}H_{12}N_4O_4$ Calcd: C, 52.17; H, 4.38; N, 20.28 Found: C, 51.86; H, 4.38; N, 20.31

Table 2

^{1}H NMR Data

Compound	MHz Solvent	(Tetramethylsilane)
6	300 $CDCl_3$	1.36 (3H, s, CH_3), 1.51 (3H, s, CH_3), 4.55 (1H, d, CH_a H_bPh), 4.75 (1H, d, H_2 or H_3), 4.79 (1H, d, CH_a H_bPh), 4.92 (1H, d, H_4), 5.16 (1H, d, H_2 or H_3), 5.22 (1H, s, H_1), 7.18-7.23 (5H, m, *Ph*CH_2), 7.26 (1H, d, $H_{5'}$), 7.48 (1H, d, $H_{4'}$), 7.62 (1H, d, H_5), 11.27 (1H, s, N*H*-Het), J_{HaHb} = 12.2 Hz, J_{H2H3} = 6.0 Hz, J_{H4H5} = 4.7 Hz, $J_{H4'H5'}$ = 9.4 Hz
7	300 $(CD_3)_2SO$	1.30 (3H, s, CH_3), 1.47 (3H, s, CH_3), 3.28 (3H, s, SO_2CH_3), 4.78 (1H, dd, H_4), 4.87 (1H, d, H_3), 5.22 (1H, d, H_2), 6.05 (1H, d, H_1), 7.41 (1H, d, H_5), 7.51 (1H, d, $H_{5'}$), 7.65 (1H, d, $H_{4'}$), 11.61 (1H, s, N*H*-Het), J_{H1H2} = 3.8 Hz, J_{H3H4} = 2.9 Hz, J_{H4H5} = 6.6 Hz, $J_{H4'H5'}$ = 9.4 Hz
8	300 $(CD_3)_2SO$	1.35 (3H, s, CH_3), 1.37 (3H, s, CH_3), 5.39 (1H, dd, H_2), 5.69 (1H, d, H_1 or H_3), 6.21 (1H, d, H_1 or H_3), 7.48 (1H, d, $H_{5'}$), 7.66 (1H, d, $H_{4'}$), 7.68 (1H, d, H_5), 11.84 (1H, broad peak, N*H*-Het), J_{HH2} = 2.6 Hz, J_{H2H} = 5.3 Hz, $J_{H4'H5'}$ = 9.5 Hz
9	300 $(CD_3)_2SO$	1.30 (6H, s, $2CH_3$), 1.39 (3H, s, CH_3), 1.49 (3H, s, CH_3), 4.31-4.36 (2H, m, H_4 and H_5), 4.39 (1H, dd, H_2), 4.65 (1H, dd, H_3), 5.53 (1H, d, H_1), 7.38 (1H, d, H_6), 7.43 (1H, d, $H_{5'}$), 7.62 (1H, d, $H_{4'}$), 11.46 (1H, s, N*H*-Het), J_{H1H2} = 5.0 Hz, J_{H2H3} = 2.3 Hz, J_{H3H4} = 7.8 Hz, J_{H4H5} = 1.8 Hz, J_{H5H6} = 6.3 Hz, $J_{H4'H5'}$ = 9.4 Hz
10	300 $(CD_3)_2SO$	1.38 (3H, s, CH_3), 1.50 (3H, s, CH_3), 4.08 (1H, d, CH_a H_bPh), 4.24 (1H, d, CH_a H_bPh), 4.87 (1H, d, H_2 or H_3), 5.29 (1H, s, H_4), 5.67 (1H, s, H_1), 5.89 (1H, d, H_2 or H_3), 6.65-6.69 (2H, m, *Ph*CH_2), 7.07-7.13 (3H, m, *Ph*CH_2), 7.45 (1H, d, $H_{7'}$), 8.38 (1H, d, $H_{8'}$), J_{HaHb} = 11.9 Hz, J_{H2H3} = 5.8 Hz, $J_{H7'H8'}$ = 9.8 Hz
11	300 $(CD_3)_2SO$	1.38 (3H, s, CH_3), 1.56 (3H, s, CH_3), 3.06 (3H, s, SO_2CH_3), 5.05 (1H, d, H_2), 5.48 (1H, d, H_4), 5.91 (1H, d, H_3), 6.26 (1H, d, H_1), 7.57 (1H, d, $H_{7'}$), 8.51 (1H, d, $H_{8'}$), J_{H1H2} = 3.7 Hz, J_{H3H4} = 3.2 Hz, $J_{H7'H8'}$ = 9.7 Hz
12	300 $(CD_3)_2SO$	1.38 (3H, s, CH_3), 1.43 (3H, s, CH_3), 5.61 (1H, dd, H_2), 6.39 (1H, d, H_1 or H_3), 6.40 (1H, d, H_1 or H_3), 7.64 (1H, d, $H_{7'}$), 8.58 (1H, d, $H_{8'}$), J_{HH2} = 2.5 Hz, J_{H2H} = 5.3 Hz, $J_{H7'H8'}$ = 9.7 Hz
13	300 $(CD_3)_2SO$	1.25 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.56 (3H, s, CH_3), 4.57 (1H, dd, H_2), 4.68 (1H, dd, H_4), 4.83 (1H, dd, H_3), 5.46 (1H, d, H_5), 5.72 (1H, d, H_1), 7.52 (1H, d, $H_{7'}$), 8.47 (1H, d, $H_{8'}$), J_{H1H2} = 5.0 Hz, J_{H2H3} = 2.6 Hz, J_{H3H4} = 7.7 Hz, J_{H4H5} = 2.0 Hz, $J_{H7'H8'}$ = 9.7 Hz
14	300 $(CD_3)_2SO$	1.37 (3H, s, CH_3), 1.42 (3H, s, CH_3), 5.60 (1H, dd, H_2), 6.37 (1H, d, H_1), 6.49 (1H, d, H_3), 7.04 (1H, d, $H_{7'}$), 8.31 (1H, d, $H_{8'}$), 12.60 (1H, broad peak, O*H*-Het), $J_{H7'H8'}$ = 9.8 Hz

Scheme 2



11 Intermediate **12** **14**

Table 3

Fractional Coordinates and Equivalent Temperature Factors (Å^2). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U_{eq}
Cl	0.74795(7)	0.41414(8)	0.97359(4)	0.0565(2)
S	-0.11102(6)	0.18906(5)	0.72778(3)	0.0387(1)
O(1)	0.3771(2)	0.2015(2)	0.77962(9)	0.0444(5)
O(2)	0.5156(2)	0.2170(2)	0.6680(1)	0.0545(6)
O(3)	0.3168(2)	0.3232(2)	0.61756(9)	0.0425(5)
O(4)	0.0599(2)	0.1890(2)	0.75565(9)	0.0376(4)
O(5)	-0.1149(2)	0.2142(3)	0.6490(1)	0.0626(7)
O(6)	-0.1688(2)	0.0746(2)	0.7571(1)	0.0634(7)
N(1)	0.1044(2)	0.3825(2)	0.9634(1)	0.0492(6)
N(2)	0.0980(2)	0.3465(2)	0.8883(1)	0.0465(6)
N(4)	0.3357(2)	0.3703(2)	0.9172(1)	0.0348(5)
N(5)	0.4900(2)	0.3766(2)	0.9117(1)	0.0386(5)
C(3)	0.2357(2)	0.3389(2)	0.8615(1)	0.0364(6)
C(6)	0.5524(3)	0.4041(2)	0.9757(1)	0.0425(7)
C(7)	0.4780(3)	0.4277(3)	1.0462(1)	0.0483(8)
C(8)	0.3253(3)	0.4251(3)	1.0486(1)	0.0451(7)
C(9)	0.2488(3)	0.3959(2)	0.9802(1)	0.0400(6)
C(1')	0.2837(2)	0.3115(2)	0.7823(1)	0.0345(5)

Table 3 (continued)

Fractional Coordinates and Equivalent Temperature Factors (Å2). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U_{eq}
C(2')	0.1598(2)	0.2841(2)	0.7248(1)	0.0322(5)
C(3')	0.2525(3)	0.2255(2)	0.6609(1)	0.0357(6)
C(4')	0.3878(3)	0.1659(2)	0.7025(1)	0.0385(6)
C(5')	0.4760(3)	0.3032(3)	0.6095(1)	0.0410(6)
C(6')	0.5538(4)	0.4259(3)	0.6227(2)	0.064(1)
C(7')	0.5098(4)	0.2475(4)	0.5328(2)	0.076(1)
C(8')	-0.1930(3)	0.3126(3)	0.7772(2)	0.0549(8)

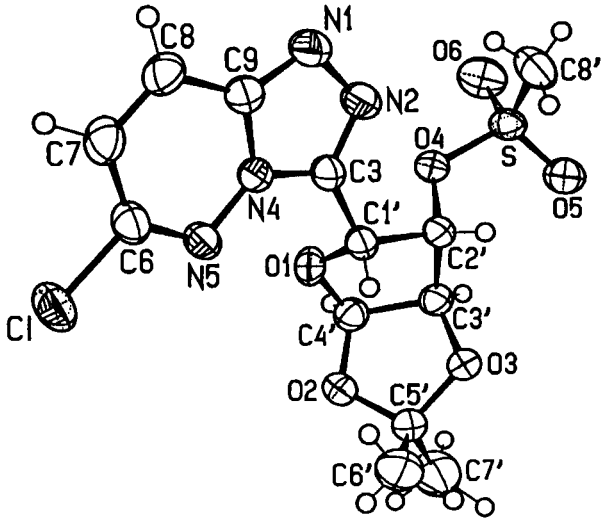


Figure 1. Ortep view of the molecule **11** wtih labeling of non-hydrogen atoms. (Ellipsoids are drawn at 50% probability level.)

reaction mixture at the end. When the reaction was carried out under milder conditions at room temperature by using potassium carbonate instead of potassium hydroxide, followed by extraction with chloroform, compound **12** was isolated in small yield as an intermediate. The structure of this compound was established by an independent synthesis. Compound **14** was also obtained from compound **12** under the same conditions in 64% yield (Scheme 2, Tables 1 and 2).

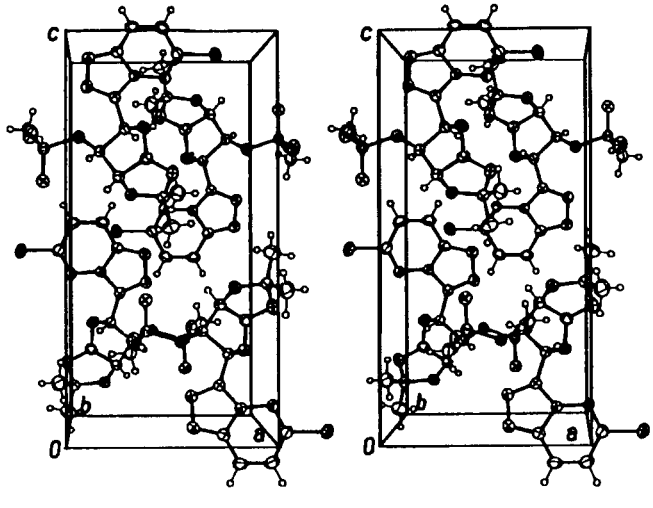


Figure 2. Ortep stereoview of the molecular packing in the unit cell of **11**.

The structures of compounds **6-14** were determined by elemental analyses for C, H, and N and ^{1}H nmr spectra. The structure and stereochemistry for compound **11** was confirmed also by X-ray analysis (Figures 1 and 2, Tables 3 and 4).

Table 4

Bond Distances (Å) and Bond Angles (°) with e.s.d.'s in parentheses

Cl-C(6)	1.734(2)	N(2)-C(3)	1.309(3)
S-O(4)	1.590(2)	N(4)-N(5)	1.370(3)
S-O(5)	1.416(2)	N(4)-C(3)	1.364(3)
S-O(6)	1.423(2)	N(4)-C(9)	1.379(3)
S-C(8')	1.740(3)	N(5)-C(6)	1.292(3)
O(1)-C(1')	1.437(3)	C(3)-C(1')	1.490(3)
O(1)-C(4')	1.417(3)	C(6)-C(7)	1.429(4)
O(2)-C(4')	1.396(3)	C(7)-C(8)	1.352(4)
O(2)-C(5')	1.428(3)	C(8)-C(9)	1.418(3)
O(3)-C(3')	1.415(3)	C(1')-C(2')	1.522(3)
O(3)-C(5')	1.432(3)	C(2')-C(3')	1.527(3)
O(4)-C(2')	1.453(3)	C(3')-C(4')	1.541(3)
N(1)-N(2)	1.381(3)	C(5')-C(6')	1.499(4)
N(1)-C(9)	1.319(3)	C(5')-C(7')	1.507(4)
O(4)-S-O(5)	109.1(1)	C(7)-C(8)-C(9)	117.0(2)
O(4)-S-O(6)	103.2(1)	N(1)-C(9)-N(4)	109.7(2)
O(4)-S-C(8')	104.0(1)	N(1)-C(9)-C(8)	132.6(2)
O(5)-S-O(6)	120.7(1)	N(4)-C(9)-C(8)	117.6(2)
O(5)-S-C(8')	109.7(2)	O(1)-C(1')-C(3)	110.8(2)
O(6)-S-C(8')	108.7(1)	O(1)-C(1')-C(2')	103.6(2)
C(1')-O(1)-C(4')	106.8(2)	C(3)-C(1')-C(2')	117.2(2)
C(4')-O(2)-C(5')	111.7(2)	O(4)-C(2')-C(1')	108.8(2)
C(3')-O(3)-C(5')	109.8(2)	O(4)-C(2')-C(3')	108.4(2)
S-O(4)-C(2')	117.5(1)	C(1')-C(2')-C(3')	100.6(2)
N(2)-N(1)-C(9)	106.6(2)	O(3)-C(3')-C(2')	108.1(2)
N(1)-N(2)-C(3)	109.0(2)	O(3)-C(3')-C(4')	104.5(2)
N(5)-N(4)-C(3)	127.4(2)	C(2')-C(3')-C(4')	103.6(2)
N(5)-N(4)-C(9)	127.1(2)	O(1)-C(4')-O(2)	111.6(2)
C(3)-N(4)-C(9)	105.6(2)	O(1)-C(4')-C(3')	107.1(2)
N(4)-N(5)-C(6)	112.0(2)	O(2)-C(4')-C(3')	105.1(2)
N(2)-C(3)-N(4)	109.1(2)	O(2)-C(5')-O(3)	105.4(2)
N(2)-C(3)-C(1')	128.1(2)	O(2)-C(5')-C(6')	109.8(2)
N(4)-C(3)-C(1')	122.6(2)	O(2)-C(5')-C(7')	110.2(3)
Cl-C(6)-N(5)	114.9(2)	O(3)-C(5')-C(6')	107.8(2)
Cl-C(6)-C(7)	117.9(2)	O(3)-C(5')-C(7')	110.1(2)
N(5)-C(6)-C(7)	127.2(2)	C(6')-C(5')-C(7')	113.2(3)
C(6)-C(7)-C(8)	118.9(2)		

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and on a Büchi 535 melting point apparatus. The ^{1}H nmr spectra were obtained on a Bruker AVANCE DPX 300 (300 MHz) spectrometer with dimethyl-d_6 sulfoxide or deuteriochloroform as solvents and tetramethylsilane as internal standard. The elemental analyses for C, H and N were obtained on a Perkin-Elmer CHN Analyser 2400. The optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter.

The following compounds were prepared according to the procedures described in the literature: benzyl 2,3-*O*-isopropylidene-β-*D*-*ribo*-pentodialdo-1,4-furanoside (**2**) [17], 1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-*D*-*xylo*-pentodialdo-1,4-furanose (**3**) [18], 1,2-*O*-isopropylidene-α-*D*-*glycero*-pent-3-enodialdo-1,4-furanose (**4**) [18], 1,2:3,4-di-*O*-isopropylidene-α-*D*-*galacto*-hexodialdo-1,5-pyranose (**5**) [19].

Hydrazinopyridazine *D*-Pentodialdo-1,4-furanose Hydrazones **6, 7, 8** and Hydrazinopyridazine *D*-Hexodialdo-1,5-pyranose Hydrazone **9**. General Procedure.

A mixture of *D*-pentodialdo-1,4-furanose **2, 3, 4** or *D*-hexodialdo-1,5-pyranose **5** (0.003 mole), and 6-chloro-3-hydrazinopyridazine (**1**) (0.003 mole), in anhydrous ethanol (12 ml) was stirred at room temperature for 30 minutes, the precipitate was collected by filtration to give the hydrazone. The following compounds were prepared in this manner: 6-chloro-3-hydrazinopyridazine benzyl 2,3-*O*-isopropylidene-β-*D*-*ribo*-pentodialdo-1,4-furanoside hydrazone (**6**), 6-chloro-3-hydrazinopyridazine 1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-*D*-*xylo*-pentodialdo-1,4-furanose hydrazone (**7**), 6-chloro-3-hydrazinopyridazine 1,2-*O*-isopropylidene-α-*D*-*glycero*-pent-3-enodialdo-1,4-furanose hydrazone (**8**), and 6-chloro-3-hydrazinopyridazine 1,2:3,4-di-*O*-isopropylidene-α-*D*-*galacto*-hexodialdo-1,5-pyranose hydrazone (**9**). Experimental and analytical data are given in Tables 1 and 2.

4(*R*)-(6-Chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,4-furanoses **10, 11** and 5(*R*)-(6-Chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,5-pyranose **13**. General Procedure.

To a mixture of hydrazinopyridazine *D*-pentodialdo-1,4-furanose hydrazones **6, 7** or hydrazinopyridazine *D*-hexodialdo-1,5-pyranose hydrazone **9** (0.003 mole), sodium acetate (anhydrous, 1.23 g, 0.015 mole), anhydrous methanol (10 ml), a solution of bromine (0.16 ml, 0.003 mole) in anhydrous methanol (3 ml) was added dropwise while stirring at room temperature. The resulting solution was stirred for 30 minutes. The precipitate was collected by filtration to give the product. The following compounds were prepared in this manner: benzyl 4(*R*)-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidene-β-*D*-*erithro*-1,4-furanoside (**10**), 4(*R*)-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-*L*-*threo*-1,4-furanose (**11**) and 5(*R*)-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,2:3,4-di-*O*-isopropylidene-α-*L*-*arabino*-1,5-pyranose (**13**). Experimental and analytical data are given in Tables 1 and 2.

2(*S*),3(*R*)-Dihydro-5-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidenefurane (**12**).

A mixture of 6-chloro-3-hydrazinopyridazine 1,2-*O*-isopropylidene-α-*D*-*glycero*-pent-3-enodialdo-1,4-furanose hydrazone (**8**) (0.002 mole), lead(IV) acetate (1.15 g, 0.0026 mole), methylene chloride (10 ml) was stirred at room temperature for 3 hours. The mixture was filtered and the filtrate was then evaporated *in vacuo*. The residue was triturated with anhydrous ethanol (4 ml) and the precipitate was collected by filtration to give 2(*S*),3(*R*)-dihydro-5-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidenefuran (**12**). Experimental and analytical data are given in Tables 1 and 2.

2(*S*),3(*R*)-Dihydro-5-(6-hydroxy-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidenefuran (**14**).

This compound was prepared by two different methods:

a) From Compound **11**.

A mixture of 4(*R*)-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-*L*-*threo*-1,4-furanose (**11**) (0.001 mole), potassium hydroxide (0.028 g, 0.0005 mole) in a mixture of water (1 ml) and dioxan (3 ml) was stirred at reflux temperature for 2 hours, cooled to room temperature and the solution was adjusted with hydrochloric acid (36%) to *p*H = 2. The precipitate was collected by filtration to give 2(*S*),3(*R*)-dihydro-5-(6-hydroxy-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidenefuran (**14**). Experimental and analytical data are given in Tables 1 and 2.

b) From Compound **12**.

A mixture of 2(*S*),3(*R*)-dihydro-5-(6-chloro-*s*-triazolo[4,3-*b*]-pyridazinyl-3)-2,3-*O*-isopropylidenefuran **12** (0.001 mole), potassium hydroxide in methanol (3*M*, 0.5 ml) and dioxan (6 ml) was stirred at reflux temperature for 30 minutes. Water (10 ml) was added and the solution was adjusted with hydrochloric acid (36%) to *p*H = 2. The precipitate was collected by filtration to give 2(*S*),3(*R*)-dihydro-5-(6-hydroxy-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-*O*-isopropylidenefuran (**14**). Experimental and analytical data are given in Tables 1 and 2.

X-ray Structure Determination.

A colorless crystal with dimensions 0.68 x 0.39 x 0.28 mm was used for data collection on Enraf Nonius CAD-4 diffractometer with graphite monochromatized MoKα radiation. Accurate unit-cell parameters were obtained from a least-squares refinement of the angular settings of 100 reflections in the range $8.2° < \theta < 17.5°$. Crystals are orthorhombic with cell dimensions a = 8.846(1), b = 10.689(1), c = 17.644(1) Å and space group $P2_12_12_1$ (no. 19). Other crystal data are $C_{13}H_{15}ClN_4O_6S$, M_r = 390.8, V = 1668.4(1) Å^3, Z = 4, D_x = 1.556 Mg/m^3, μ = 0.3841 mm^{-1}, T = 293(2) K. Intensity data were collected in the ω-2θ scan mode with a scan width $(0.85+0.3\text{tg}\theta)°$, aperture (2.4+0.9tgθ) mm and maximum scan time 60 seconds. Background was measured at 1/4 of the scan at each limit. An entire sphere to θ_{max} 28° of data was measured with an index range $-11 \le h \le 11$, $-14 \le k \le 14$ and $-23 \le l \le 23$. The intensity check reflections (3,4,5; 3,2,2; 3,1,6) were monitored periodically every 20000 seconds of the scanning time. A change of -1.40% of intensities of check reflections was observed and correction applied. Orientation control using reflections (-3,-4,1; -5,4,-4; 6,-1,-1) was every 600 reflections. The data were corrected for absorption using an analytical method [20] with T_{min} and T_{max} 0.8094 and 0.9143, respectively. 16173 reflections were collected, averaging gave 4009 independent reflections with R_{int} = 0.026; 3608 of them were observed ($I>2.5\sigma(I)$). Friedel pairs were not merged.

Structure was solved by direct methods using SIR92 [21] program. The positions of hydrogen atoms were obtained from an

intermediate difference Fourier map. Full-matrix least-squares refinement minimizing $\Sigma w(|F_o|-|F_c|)^2$ with empirical weighting scheme was employed. Hydrogen atoms positions with their isotropic temperature factors were not refined. The absolute configuration on chiral centers was confirmed by the refinement of Flack parameter with the final value -0.07(7). Also the correction for secondary extinction [22] was applied with g = $0.26(8)\cdot10^{4}$. In the final cycle of the refinement we used 2162 contributing reflections (including were those unobserved reflections for which F_c was greater than F_o) and 228 parameters. The final R and R_w values were 0.027 and 0.034, respectively. Average and maximum shift to e.s.d. ratio were $2.98\cdot10^{-5}$ and $3.39\cdot10^{-4}$. The residual density in the final difference map was max. 0.209 and min. -0.256 e/Å^3.

The Xtal3.2 [23] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. ORTEPII [24] was used to produce molecular graphics.

Final atomic coordinates and equivalent isotropic thermal parameters with their e.s.d.'s are reported in Table 3. Bond lengths and bond angles for non-hydrogen atoms are listed in Table 4. They are in the agreement with the expected standard values [25]. An ORTEP [24] drawing of the asymmetric unit showing the atom-labeling scheme is presented in Figure 1 and molecular packing in Figure 2. Intermolecular contacts which result in the molecular packing are dominated by van der Waals interactions.

REFERENCES AND NOTES

[1] U. Hacksell and G. D. Daves, Jr., *Prog. Med. Chem.*, **22**, 1 (1985).

[2] A. P. Kozikowski and X.-M. Cheng, *J. Chem. Soc., Chem. Commun.*, 680 (1987).

[3] I. Maeba, K. Kitaori, Y. Itaya and C. Ito, *J. Chem. Soc., Perkin Trans. 1*, 67 (1990).

[4] M. Yokoyama, T. Tanabe, A. Toyoshima and H. Togo, *Synthesis*, 517 (1993).

[5] Antiviral Agents: The Development and Assessment of Antiviral Chemotherapy, H. J. Field, ed, CRC Press, Boca Raton, FL, 1988.

[6] M. Cornia, G. Casiraghi, and L. Zetta, *J. Org. Chem.*, **56**, 5466 (1991).

[7] M. S. Solomon and P. B. Hopkins, *Tetrahedron Letters*, **32**, 3297 (1991).

[8] T. Watanabe, S. Nishiyama, S. Yamamura, K. Kato, M. Nagai and T. Takita, *Tetrahedron Letters*, **32**, 2399 (1991).

[9] D. E. Bergstrom and P. Zhang, *Tetrahedron Letters*, **32**, 6485 (1991).

[10] M. Yokoyama, A. Toyoshima, T. Akiba, and H. Togo, *Chem. Letters*, 265 (1994).

[11] J. Streith, A. Boiron, A. Frankowski, D. Le Nouen, H. Rudyk, and T. Tschamber, *Synthesis*, 944 (1995).

[12] B. Stanovnik, *Tetrahedron*, **47**, 2925 (1991).

[13] M. Žličar, B. Stanovnik, and M. Tišler, *Tetrahedron*, **48**, 7965 (1992).

[14] B. Stanovnik, B. Jelen, and M. Žličar, *Il Farmaco*, **48**, 231 (1993).

[15] J. Svete, L. Golič, and B. Stanovnik, *J. Heterocyclic. Chem.*, **34**, 1115 (1997).

[16] N. Takahayashi, *J. Pharm. Soc. Japan*, **76**, 765 (1965); *Chem. Abstr.*, **51**, 1192 (1957).

[17] W. Karpiesiuk and A. Banaszek, *Tetrahedron*, **50**, 2965 (1994).

[18] K. M. Sun and B. Fraser-Reid, *Synthesis*, 28 (1982).

[19] R. F. Butterworth and S. Hanessian, *Synthesis*, 70 (1971).

[20] J. de Meulenaer and H. Tompa, *Acta Cryst.*, **19**, 1014 (1965).

[21] A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi and G. Polidori, *J. Appl. Cryst.*, **27**, 435 (1994).

[22] A. C. Larson, Crystallographic Computing, F. R. Ahmed, S. R. Hall and C. P. Huber, eds, Copenhagen: Munksgaard, 291 (1970).

[23] S. R. Hall, H. D. Flack and J. M. Stewart, Xtal3.2 Reference Manual, Universities of Western Australia, Geneva and Maryland, 1992.

[24] C. K. Johnson, ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA, 1976.

[25] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, S1 (1987).