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Studies on Nucleosides Analogs. XVIII.[1] Synthesis of Pyrimido-[4,5-*c*]pyridazine Nucleoside Analogs[2]

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The reactions of 6-hydrazino-1,3-dimethyluracil (**1**) with aldoses (**2a—e**), D-fructose, and D-glucuronolactone gave hydrazones (**3a—e**, **6**, and **8**) in good yields, and these products were converted to pyrimido[4,5-*c*]pyridazine nucleoside analogs (**4a—e**, **7**, and **9**) by cyclodehydration.

Stereoisomers were isolated from the reaction mixtures of pyrimido[4,5-*c*]pyridazine derivatives, and were examined by CD spectroscopy.

On the other hand, the hydrazones (**11a, b**) of **1** with glycolaldehyde or (±)-glyceraldehyde were converted only to acetates (**12a, b**). Formation of the pyrimido[4,5-*c*]-pyridazine derivatives (**13a, b**) was not observed.

Keywords——6-hydrazino-1,3-dimethyluracil; D-fructose; D-glucuronolactone; (±)-glyceraldehyde; glycolaldehyde; pyrimido[4,5-*c*]pyridazine nucleoside; CD; absolute configuration

As part of a series of synthetic studies of nucleoside analogs, we have reported the synthesis of theophylline and aminopyrazole[3,4-*d*]pyrimidine nucleoside analogs by the reaction of diamine and hydrazine derivatives with sugars.[3,4] While several synthetic methods for nucleosides[5] and nucleoside analogs[6] by the reaction of hydrazine derivatives are known, they are not very convenient and produce nucleoside derivatives only in low yields.

In this paper, we describe the facile synthesis of pyrimido[4,5-*c*]pyridazine nucleoside analogs and the isolation of diastereomers from the reaction mixtures of 6-hydrazino-1,3-dimethyluracil (**1**) with sugars.

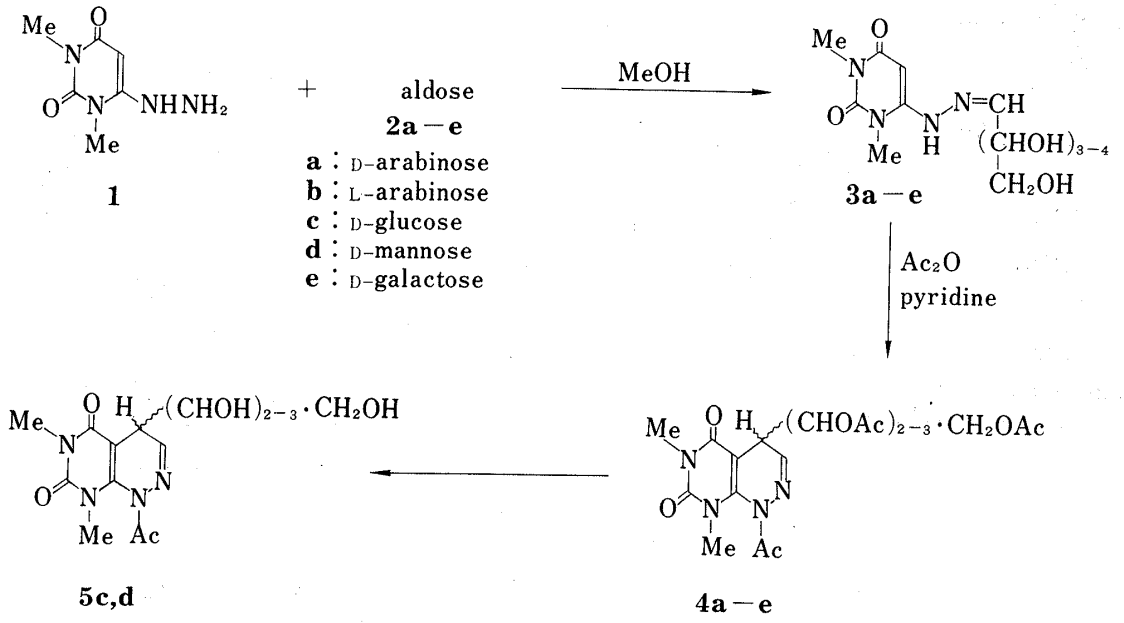
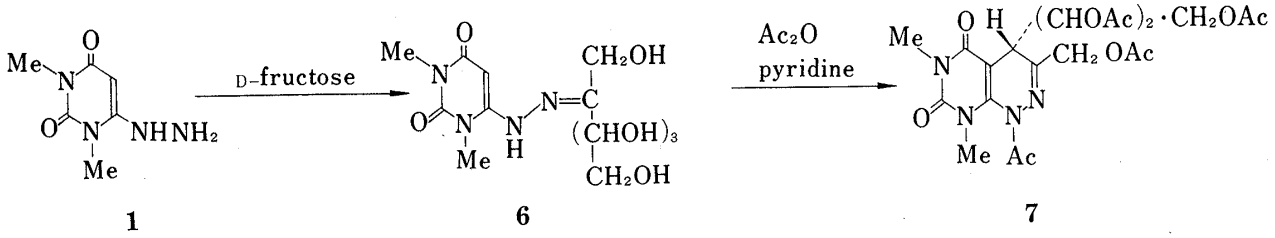


Chart 1

Hofmann,[7] Wolfrom *et al.*,[8] and Mester *et al.*[9] have reported the synthesis of acyclic sugar phenylhydrazones and acetylation of these hydrazones. By a similar procedure, hydrazones (**3a**—**e**) of 6-hydrazino-1,3-dimethyluracil (**1**) were obtained from refluxing mixtures of aldoses (**2a**—**e**) in good yields. These hydrazones (**3a**—**e**) were converted to the 1-acetyl-4-substituted pyrimido[4,5-*c*]pyridazines (**4a**—**e**) by cyclodehydration with acetic anhydride containing pyridine at room temperature. As shown in Chart 1, **4a**—**e** were converted to 1-acetyl-4-substituted pyrimido[4,5-*c*]pyridazines (**5a**—**e**) in good yields by deacetylation with methanolic ammonia at 0°.



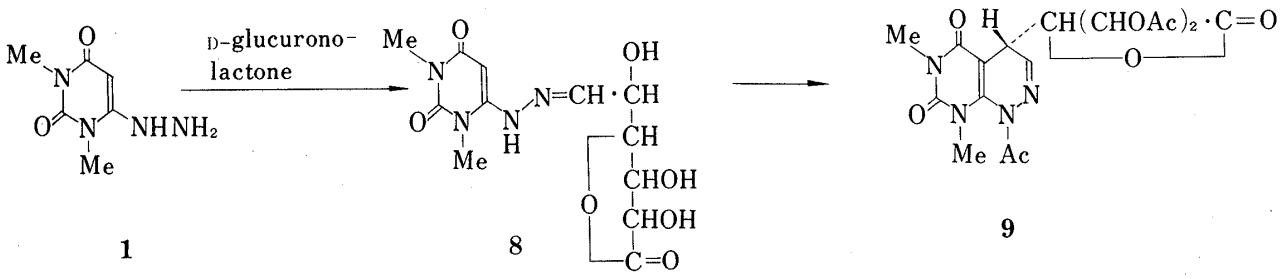
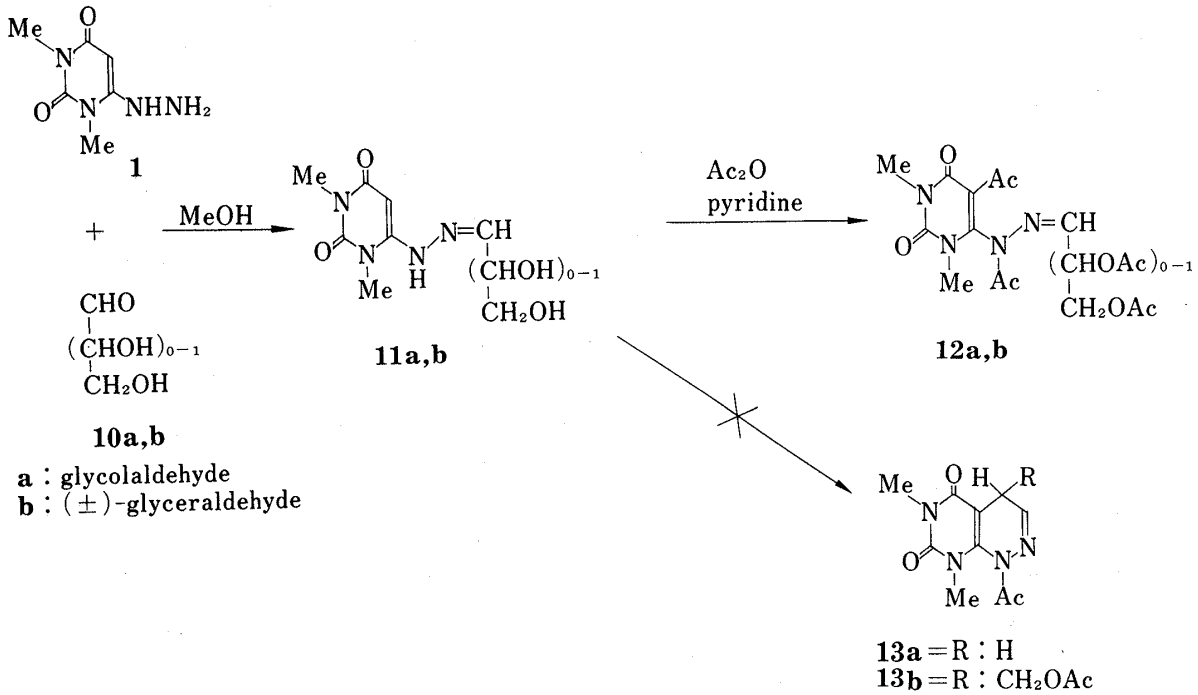


Chart 2



a : glycolaldehyde
b : (±)-glyceraldehyde

Chart 3

Similarly, the reactions of **1** with D-fructose and D-glucuronolactone in methanol gave the hydrazones (**6** and **8**) in good yields, and these products were converted to pyrimido[4,5-*c*]-pyridazine derivatives (**7** and **9**) by cyclodehydration with acetic anhydride as shown in Chart 2.

On the other hand, the hydrazones (**11a, b**) prepared by the reaction of **1** with glycolaldehydes (**10a**) or (±)-glyceraldehyde (**10b**) were converted to acetylated pyrimidine derivatives (**12a, b**), and the desired pyrimido[4,5-*c*]pyrimidines (**13a, b**) were not obtained (Chart 3).

Snatzke *et al.*[10] determined the configuration of acyclic sugar derivatives of benzothiazole and benzothiazoline by measuring the circular dichroism (CD) spectra. We also studied the relation of the stereochemistry of nucleoside analogs to the CD spectra by means of X-ray analysis.[11] From these data, nucleoside analogs having *S* configuration at the anomeric position give positive CD bands at around 250—260 nm and 210 nm, and negative ones at around 290 nm and 230 nm. Compounds having *R* configuration at the anomeric position give negative CD bands at around 250—260 nm and 210 nm, and positive ones at around 290 nm and 230 nm.

We obtained a pair of diastereomers (**4d**), 4-*R* and 4-*S*, from the reaction mixture of hydrazone (**3d**) with acetic anhydride after column chromatography and recrystallizations. These isomers showed symmetrical CD curves, as summarized in Table I.

Table I. Circular Dichroism Data for Pyrimido[4,5-*c*]pyridazine Derivatives (in Methanol)

Compound	Configuration at C-4	Sugar	CD maxima ($[\theta] \times 10^{-3}$)				
			I	II	III	IV	V
4a	*R*	D-Arabinose		208(−37.9)	224(+9.3)	248(−4.3)	290(+2.3)
4b	*S*	L-Arabinose		207(+51.7)	224(−2.5)	247(+9.0)	290(−1.0)
4c (**4d**)	*R*	D-Glucose (D-Mannose)		213(−29.9)		260(−5.1)	
4d	*S*	D-Mannose		211(+29.9)		260(+1.2)	
7	*S*	D-Fructose	202(−16.0)	215(+ 0.3)	225(−5.3)	258(+7.2)	
9	*S*	D-Glucurono-lactone		207(+47.2)		252(+5.8)	
5c (**5d**)	*R*	D-Glucose (D-Mannose)	203(+ 4.3)	213(−11.7)	245(+2.1)	263(−1.4)	
5d	*S*	D-Mannose		215(+21.4)	241(−3.1)	262(+4.8)	

On the basis of the data in Table I, compound (**4d**), having positive (260 nm)—positive (210 nm) Cotton effects, was considered to be 4-*S*, and the compound having negative (260 nm) —negative (210 nm) Cotton effects was considered to be 4-*R*.

From the reaction mixture of the hydrazone of D-glucose (**3c**) with acetic anhydride, only the 4-*R* compound (**4c**) was isolated; **4c** was confirmed to be the same compound as **4d**, which was obtained from the hydrazone of D-mannose (**3d**), by mixed melting point determination and comparison of infrared (IR), nuclear magnetic resonance (NMR), and ultraviolet (UV) spectrum data.

In the case of other sugar hydrazones (**3a, b, e, 6,** and **8**), only one compound (4-*R* or 4-*S* isomer) could be isolated. The CD data for these compounds are summarized in Table I.

From the CD data for these acyclic sugar-pyrimido[4,5-*c*]pyridazine derivatives (**4a—e, 7,** and **9**), their configurations at C-4 were assigned as shown in Table I.

Experimental

All melting points are uncorrected. NMR spectra were measured with a Varian T-60 or a JEOL PS100 spectrometer, and Me_4Si was used as an internal standard. Mass spectra (MS) were determined with a JEOL 01S spectrometer equipped with a direct inlet system at 75 eV. IR and UV spectra were obtained with a

JASCO IR A2 spectrometer and a Hitachi 340 spectrometer, respectively. CD curves were obtained on a JASCO J-20 spectropolarimeter in 1 mm and 0.1 mm cells; the concentration and length were adjusted to obtain the maximum signal.

General Procedure for the Reaction of Hydrazones (3a—e, 6, and 8) of Sugars with 6-Hydrazino-1,3-dimethyluracil (1)——6-Hydrazino-1,3-dimethyluracil (**1**) (0.01 mol) was added to a solution of a sugar (0.01 mol) in MeOH (80 ml), and the mixture was refluxed for 3 to 5 hr. After cooling, the separated crystalline products were collected by filtration, washed with EtOH, and recrystallized from 90% EtOH to give white or pale yellow crystals of the hydrazone (**3a**—**e**, **6**, and **8**). The results are summarized in Tables II and III.

1-Acetyl-4(*R*)-(D-*erythro*-triacetoxypropyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (4a)——A solution of 0.61 g (0.002 mol) of **3a** in 10 ml of pyridine was treated with 10 ml of acetic anhydride at room temperature for 16 hr. The clear reaction solution was then concentrated to one-third of its original volume

Table II. Yields and Analysis Results of Hydrazones (**3a**—**e**, **6**, **8**, and **11a**, **b**)

Compound	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
3a	93	183	$C_{11}H_{18}N_4O_6$	43.70	6.00	18.54	43.84	5.74	18.60
3b	93	178	$C_{11}H_{18}N_4O_6$	43.70	6.00	18.54	43.59	6.07	18.74
3c	94	165	$C_{12}H_{20}N_4O_7$	43.37	6.07	16.86	43.37	6.06	16.86
3d	87	192	$C_{12}H_{20}N_4O_7$	43.37	6.07	16.86	43.33	6.08	16.86
3e	93	175	$C_{12}H_{20}N_4O_7$	43.37	6.07	16.86	43.34	5.87	16.87
6	93	181	$C_{12}H_{20}N_4O_7$	43.37	6.07	16.86	43.38	6.04	16.63
8	94	157	$C_{12}H_{16}N_4O_7$	43.90	4.91	17.07	43.92	4.90	17.04
11a	71	159	$C_8H_{12}N_4O_3$	45.28	5.70	26.40	45.22	5.63	26.70
11b	74	192	$C_9H_{14}N_4O_4$	44.62	5.83	23.13	44.63	5.85	23.37

Table III. Physical Data for Hydrazones (**3a**—**e**, **6**, **8**, and **11a**, **b**)

Compound	IR ν_{max}^{KBr} cm^{-1} OH, C=O	NMR (in DMSO-d_6) δ	UV λ_{max}^{MeOH} nm (log ε)
3a	3350, 1685	3.13 (3H, s, NMe), 3.37 (3H, s, NMe), 3.58—5.10 (9H, m, sugar-H), 5.35 (1H, s, 5-H), 7.72 (1H, d, –N=CH–), 10.12 (1H, s, NH)	220(4.23) 288(4.22)
3b	3350, 1685	3.17 (3H, s, NMe), 3.38 (3H, s, NMe), 3.50—5.05 (9H, m, sugar-H), 5.40 (1H, s, 5-H), 7.78 (1H, d, –N=CH–), 10.17 (1H, s, NH)	220(4.11) 288(4.15)
3c	3350, 1680	3.17 (3H, s, NMe), 3.37 (3H, s, NMe), 3.35—5.35 (11H, m, sugar-H), 5.40 (1H, s, 5-H), 5.60 (1H, d, –N=CH–), 7.85 (1H, s, NH)	200(4.22) 268(4.25)
3d	3350, 1680	3.17 (3H, s, NMe), 3.37 (3H, s, NMe), 3.50—5.23 (11H, m, sugar-H), 5.43 (1H, s, 5-H), 7.77 (1H, d, –N=CH–), 10.20 (1H, s, NH)	200(4.20) 268(4.22)
3e	3350, 1680	3.17 (3H, s, NMe), 3.40 (3H, s, NMe), 3.00—5.40 (11H, m, sugar-H), 5.42 (1H, s, 5-H), 7.77 (1H, d, –N=CH–), 10.10 (1H, s, NH)	218(4.26) 250(3.59) 286(4.28)
6	3350, 1680	3.10 (3H, s, NMe), 3.30 (3H, s, NMe), 3.50—5.00 (12H, m, sugar-H), 5.33 (1H, s, 5-H), 8.20 (1H, s, NH)	207(3.99) 225(4.03) 272(4.13) 292(4.13)
8	3350, 1800 1680	3.16 (3H, s, NMe), 3.35 (3H, s, NMe), 4.30—5.90 (8H, m, 5-H and sugar-H), 7.80 (1H, d, –N=CH–), 10.27 (1H, s, NH)	220(4.24) 288(4.21)
11a	1685	3.10 (3H, s, NMe), 3.33 (3H, s, NMe), 4.07 (2H, m, CH_2), 5.10 (1H, m, OH), 5.30 (1H, s, 5-H), 7.67 (1H, t, –N=CH–), 10.00 (1H, bs, NH)	240(4.24) 288(4.30)
11b	1685	3.20 (3H, s, NMe), 3.40 (3H, s, NMe), 3.58 (2H, dd, CH_2OH), 4.17 (1H, m, CH), 4.78 (1H, t, CH_2OH), 5.30 (1H, d, CHOH), 5.40 (1H, s, 5-H), 7.52 (1H, d, –N=CH–), 10.17 (1H, s, NH)	240(4.21) 288(4.27)

at 35—40° under reduced pressure, and the resulting syrup was poured into 100 ml of ice-water under stirring. After extraction with $CHCl_3$, the extract was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield 0.63 g (69%) of a pale yellow syrup. Crystallization from EtOH gave 0.30 g (33%) of **4a** (4(*R*)-configuration) as colorless needles, mp 169°. UV λ_{max}^{MeOH} nm (log ε): 206 (4.5), 244 (4.0), 260 (4.0). MS *m/z*: 452 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740, 1715, 1660 (C=O). NMR ($CDCl_3$) δ: 1.88—2.17 (9H, s×3, OAc×3), 2.60 (3H, s, NAc), 3.40 (3H, s, NMe), 3.57 (3H, s, NMe), 4.26 (1H, m, 2′-H), 4.57 (2H, m, 3′-H), 5.37 (1H, m, 1′-H), 6.03 (1H, m, 4-H), 6.27 (1H, d, 3-H). *Anal.* Calcd for $C_{19}H_{24}O_9N_4$: C, 50.44; H, 5.35; N, 12.39. Found: C, 50.42; H, 5.35; N, 12.38.

1-Acetyl-4(*S*)-(L-*erythro*-triacetoxypropyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (4b)——Treatment of **3b** (0.61 g, 0.002 mol) in 10 ml of pyridine with 10 ml of acetic anhydride according to the method described above gave crude **4b** (0.63 g, 69%) as a pale yellow syrup. Crystallization from EtOH gave 0.31 g (34%) of **4b** as colorless needles, mp 153°. Further recrystallization from EtOH gave colorless needles, mp 155°. UV λ_{max}^{MeOH} nm (log ε): 206 (4.5), 244 (4.0), 260 (4.0). MS *m/z*: 452 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740, 1715, 1675 (C=O). NMR ($CDCl_3$) δ: 1.83—2.12 (9H, s×3, OAc×3), 2.57 (3H, s, NAc), 3.33 (3H, s, NMe), 3.50 (3H, s, NMe), 4.23 (1H, m, 4-H), 6.23 (1H, d, 3-H). *Anal.* Calcd for $C_{19}H_{24}N_4O_9$: C, 50.44; H, 5.35; N, 12.39. Found: C, 50.44; H, 5.36; N, 12.43.

1-Acetyl-4(*R*)-(D-*arabino*-tetraacetoxybutyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (4c-*R*) and 1-Acetyl-4(*S*)-(D-*arabino*-tetraacetoxybutyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (4c-*S*)——a) According to the method described above, **3c** (0.66 g, 0.002 mol) in 10 ml of pyridine was treated with 10 ml of acetic anhydride to give crude **4c** (0.72 g, 69%) as a gummy precipitate. Crystallization from EtOH yielded 0.45 g (38%) of pure **4c** (*R*-form) as colorless needles, mp 215°. UV λ_{max}^{MeOH} nm (log ε): 206 (4.3), 241 (4.1), 260 (4.0). MS *m/z*: 524 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1735, 1700 (C=O). NMR ($CDCl_3$) δ: 1.88—2.05 (12H, s×4, OAc×4), 2.68 (3H, s, NAc), 3.38 (3H, s, NMe), 3.43 (3H, s, NMe), 4.00—5.60 (6H, m, 4-H and sugar protons), 5.80 (1H, d, 3-H). *Anal.* Calcd for $C_{22}H_{28}N_4O_{11}$: C, 50.38; H, 5.38; N, 10.68. Found: C, 50.59; H, 5.38; N, 10.73.

b) According to the method described above, **3d** (0.66 g, 0.002 mol) in 10 ml of pyridine was treated with 10 ml of acetic anhydride to give **4c** (mixture of *R* and *S* form) (0.70 g, 67%) as a gummy precipitate. The precipitate was dissolved in $CHCl_3$ and chromatographed on a silica gel. Elution with CCl_4–$CHCl_3$ (5: 1) gave 0.32 g (31%) of **4c**-*R* (*R*-form) as colorless needles, mp and mixed mp 215°.

Subsequent elution with CCl_4–$CHCl_3$ (5: 1—4: 1) gave 0.30 g (29%) of **4c**-*S* (*S*-form) as colorless needles, mp 181°. UV λ_{max}^{MeOH} nm (log ε): 204 (4.4), 241 (3.9), 260 (3.9). MS *m/z*: 524 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1735, 1700 (C=O). NMR ($CDCl_3$) δ: 2.01—2.11 (12H, s×4, OAc×4), 2.67 (3H, s, NAc), 3.34 (3H, s, NMe), 3.46 (3H, s, NMe), 4.02—6.12 (7H, m, 3-H, 4-H, and sugar protons). *Anal.* Calcd for $C_{22}H_{28}O_{11}N_4$: C, 50.38; H, 5.38; N, 10.68. Found: C, 50.25; H, 5.38; N, 10.51.

1-Acetyl-4(*S*)-(D-*lyxo*-tetraacetoxybutyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (4e)——According to the method described above, **3e** (0.66 g, 0.002 mol) in 10 ml of pyridine was treated with 10 ml of acetic anhydride to give crude **4e** (0.75 g, 72%) as a gummy precipitate. Crystallization from EtOH yielded 0.37 g (36%) of **4e**-*S* (*S*-form) as colorless prisms, mp 200°. UV λ_{max}^{MeOH} nm (log ε): 204 (4.4), 240 (3.9), 260 (3.8). MS *m/z*: 524 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1730, 1705 (C=O). NMR ($CDCl_3$) δ: 1.83—2.01 (12H, s×4, OAc×4), 2.57 (3H, s, NAc), 3.35 (3H, s, NMe), 3.55 (3H, s, NMe), 3.80—6.20 (7H, m, 3-H, 4-H, and sugar protons). *Anal.* Calcd for $C_{22}H_{28}N_4O_{11}$: C, 50.38; H, 5.38; N, 10.68. Found: C, 50.22; H, 5.32; N, 10.61.

1-Acetyl-3-acetoxymethyl-4(*S*)-(D-*erythro*-triacetoxypropyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (7)——According to the method described above, **6** (0.66 g, 0.002 mol) in 15 ml of pyridine was treated with 15 ml of acetic anhydride to give crude **7** (0.73 g, 70%) as a gummy precipitate. Crystallization from EtOH yielded 0.40 g (38%) of **7** as colorless prisms, mp 141°. UV λ_{max}^{MeOH} nm (log ε): 204 (4.5), 240 (4.0), 260 (3.9). MS *m/z*: 524 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740, 1700 (C=O). NMR ($CDCl_3$) δ: 1.93—2.20 (12H, s×4, OAc×4), 2.83 (3H, s, NAc), 3.38 (3H, s, NMe), 3.45 (3H, s, NMe), 4.20—5.18 (6H, m, sugar protons), 6.60 (1H, d, 4-H). *Anal.* Calcd for $C_{22}H_{28}N_4O_{11}$: C, 50.38; H, 5.38; N, 10.68. Found: C, 50.33; H, 5.40; N, 10.62.

1-Acetyl-4(*S*)-(4′-D-*threo*-2′,3′-di-O-acetyl-1′-ketofuranosyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (9)——According to the method described above, **8** (0.66 g, 0.002 mol) in 15 ml of pyridine was treated with 15 ml of acetic anhydride to give crude **9** (0.54 g, 61%) as a gummy precipitate. Recrystallization from EtOH yielded 0.29 g (33%) of **9** (*S* form) as pale yellow prisms, mp 204°. UV λ_{max}^{MeOH} nm (log ε): 207 (4.4), 245 (3.9), 262 (4.0). MS *m/z*: 436 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1800 (lactone), 1745, 1700 (C=O). NMR ($CDCl_3$) δ: 1.87 (3H, s, OAc), 2.23 (3H, s, OAc), 2.62 (3H, s, NAc), 3.38 (3H, s, NMe), 3.50 (3H, s, NMe), 5.28 (1H, d, 2′-H), 5.43—5.53 (2H, m, 3′-H and 4′-H), 5.90 (1H, m, 4-H), 6.40 (1H, d, 3-H). *Anal.* Calcd for $C_{18}H_{20}N_4O_9$: C, 49.55; H, 4.62; N, 12.83. Found: C, 49.69; H, 4.68; N, 12.80.

General Procedure for the Reaction of Hydrazones (11a, b) of Glycolaldehyde (10a) or (±)-Glyceraldehyde (10b) with 6-Hydrazino-1,3-dimethyluracil (1)——Compound **1** (0.01 mol) was added to a solution of glycolaldehyde (**10a**) (0.01 mol) or (±)-glyceraldehyde (**10b**) (0.01 mol) in MeOH (80 ml), and the mixture was refluxed for 3 hr. The mixture was concentrated and the residue was treated with 30 to 50 ml of EtOH. The separated crystalline powder was collected by filtration, washed with EtOH, and recrystallized from EtOH to give pale yellow crystals of the hydrazone (**11a, b**). The results are summarized in Tables II and III.

Acetylation of Hydrazone (11a)——According to the method described above, **11a** (0.42 g, 0.002 mol)

in 10 ml of pyridine was treated with 10 ml of acetic anhydride to give crude **12a** (0.53 g, 79%) as a pale yellow crystalline powder. Recrystallization from 95% EtOH yielded 0.42 g (63%) of **12a** as pale yellow prisms, mp 120°. UV λ_{max}^{MeOH} nm (log ε): 204 (4.4), 240 (3.9), 260 (3.8). MS *m/z*: 338 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740, 1700 (C=O). NMR ($CDCl_3$) δ: 2.00—2.13 (6H, s×2, 5-Ac and OAc), 2.72 (3H, s, NAc), 3.35 (3H, s, NMe), 3.48 (3H, s, NMe), 4.63 (2H, d, CH_2), 6.80 (1H, t, –N=CH–). *Anal.* Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.80; H, 5.33; N, 16.54.

Acetylation of Hydrazone (11b)——According to the method described above, **11b** (0.48 g, 0.002 mol) in 12 ml of pyridine was treated with 12 ml of acetic anhydride to give crude **12a** (0.68 g, 84%) as a pale yellow crystalline powder. Recrystallization from 95% of EtOH yielded 0.50 g (62%) of **12a** as colorless prisms, mp 155°. UV λ_{max}^{MeOH} nm (log ε): 204 (4.5), 240 (4.0), 260 (3.9). MS *m/z*: 410 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740, 1700 (C=O). NMR ($CDCl_3$) δ: 2.13 (9H, s×3, OAc×2 and 5-Ac), 2.73 (3H, s, NAc), 3.33 (3H, s, NMe), 3.47 (3H, s, NMe), 3.45—4.65 (2H, m, CH_2), 5.83 (1H, m, CH), 6.77 (1H, d, –N=CH–). *Anal.* Calcd for $C_{17}H_{22}N_4O_8$: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.86; H, 5.41; N, 13.70.

1-Acetyl-4(*R*)-(D-*arabino*-tetrahydroxybutyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (5c-*R* Form and 5d-*R* Form)——A suspension of 1.01 g (0.002 mol) of compound **4c** (*R* form) or **4d** (*R* form) in 100 ml of saturated NH_3–MeOH was stirred at 0° for 5 hr. The solvent was removed at 30—35° under reduced pressure, and the dried residue was mixed with 15 ml of EtOH. The insoluble material was filtered off, and crystallized from EtOH to yield 0.67 g (98%) of **5c** (*R* form) as colorless needles, mp 252°. UV λ_{max}^{MeOH} nm (log ε): 204 (4.4), 240 (3.8), 258 (3.8). MS *m/z*: 356 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1700 (C=O). NMR ($CDCl_3$) δ: 2.68 (3H, s, NAc), 3.23 (3H, s, NMe), 3.37 (3H, s, NMe), 3.10—5.63 (11H, m, 3-H, 4-H, and sugar protons). *Anal.* Calcd for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 46.97; H, 5.62; N, 15.54.

1-Acetyl-4(*S*)-(D-*arabino*-tetrahydroxybutyl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione (5d-*S* Form)——According to the method described above, **4d** (*S* form) (1.01 g, 0.002 mol) was treated with 100 ml of saturated NH_3–MeOH to give crude **5d** (*S* form) (0.66 g, 96%) as a white crystalline powder. Recrystallization from EtOH yielded 0.62 g (90%) of **5d** (*S* form) as colorless needles, mp 201°. UV λ_{max}^{MeOH} nm (log ε): 204 (4.4), 240 (3.9), 258 (3.9). MS *m/z*: 356 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1700 (C=O). NMR ($CDCl_3$) δ: 2.57 (3H, s, NAc), 3.20 (3H, s, NMe), 3.37 (3H, s, NMe), 2.80—5.80 (11H, m, 3-H, 4-H, and sugar protons). *Anal.* Calcd for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.21; H, 5.44; N, 15.68.

References and Notes

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