Synthesis of Novel Bicyclic Pyridazine Nucleosides

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The synthesis of some [6:6]- or [6:5]-fused bicyclic pyridazin-6-one nucleosides, starting from 4,5-dichloro-3-nitro(or amino) and 3-hydrazinopyridazin-6-one nucleosides is described.

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Pyridazine nucleosides have been synthesized as the isosteric analogs of uridine [1]. Townsend *et al.* [2] also reported the anticancer activity of 4-hydroxy-1-(β-D-ribofuranosyl)pyridazin-6-one(3-deaza-6-azauridine). Some 3-glycosylated purine derivatives such as 3-β-D-ribofuranosyluric acid, isoadenosine and oxoallopurinol ribofuranoside has been isolated and reported the biological properties [3].

In connection with our research program for the synthesis of novel *N*-nucleosides containing pyridazine base related to some 3-glycosylated purine nucleosides, we attempted to synthesize some [6:6]- or [6:5]-fused bicyclic pyridazine nucleosides.

In this paper, we wish to report the cyclization of some pyridazine cyclonucleosides.

Our approach to the synthesis of the target bicyclic nucleosides involved the use of suitably substituted pyridazine nucleosides that would contain substituent in the 3- and/or 4-position. Therefore, we elected to use 4,5-dichloro-3-nitro(or amino)pyridazin-6-one nucleosides and 3-hydrazinopyridazin-6-one nucleoside as our starting materials.

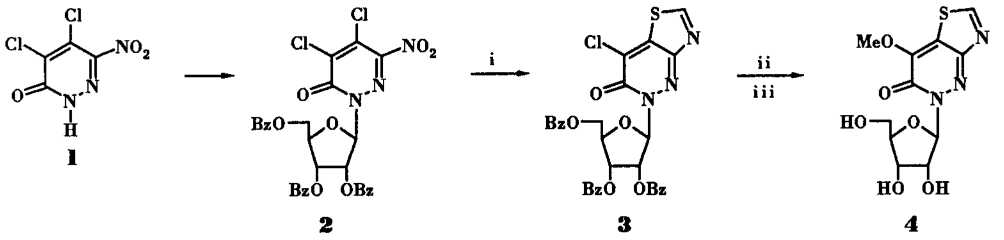
Cyclization of 4,5-dichloro-3-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**2**) with carbon disulfide and sodium bisulfite in ethanol at *p*H 3 gave 7-chloro-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[4,5-*c*]pyridazin-6(5*H*)-one (**3**) in low yield. The structure of **3** follows from elemental analysis, ir, pmr and mass spectrometry. We did not detect the absorption peak of nitro group in the infrared spectrum of **3**. Proton magnetic resonance spectrum of **3** showed protons of ribose ring in addition to a new proton at C-2 and aromatic protons at 8.12-7.19 ppm. Mass spectrum of **3** showed the typical pattern of common nucleosides [4], but we did not detect the molecular ion. Ions at m/e 189 (B + H), 295 (B + 108), 247 (B + 60), 218 (B + 30) and 445 (PS), where B is a base; PS is a tri-*O*-benzoylated sugar, formed by cleavage of the C–N glycosidic bond. And also, ions at m/z 341, 323, 322, 235, 122 and 105 formed by fragmentation of the protected sugar.

Debenzoylation of **3** with sodium methoxide in methanol-tetrahydrofuran (1:1 v/v) afforded 7-methoxy-5-β-D-ribofuranosylthiazolo[4,5-*c*]pyridazin-6(5*H*)-one (**4**) in good yield. The infrared spectrum of **4** showed the absorption peaks of hydroxy and amide carbonyl groups. The proton magnetic resonance spectrum for compound **4** showed protons of C-2 position and methoxy group at 7.85 and 3.51 ppm, and also showed proton signals of ribose ring and three hydroxy groups.

On the other hand, treatment of 2-amino-4,5-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**5**) [5] with chloroacetone in ethanol gave 3-(2-oxopropylamino)-4,5-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**6**) in 34% yield and 7,8-dichloro-2-methyl-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyridazin-6(5*H*)-one (**8**) in 41% yield.

The infrared spectra of **6** and **8** showed two carbonyl peaks. The proton magnetic resonance spectrum of **6** showed proton signals of NH, CH_2 and CH_3 for the 2-oxopropylamino group involving signals of the aromatic and the ribose ring protons, whereas the proton magnetic resonance spectrum of **8** showed proton signals of methyl and CH at C-3 position involving signals of the aromatic and the ribose ring protons. Therefore, we distinguished the

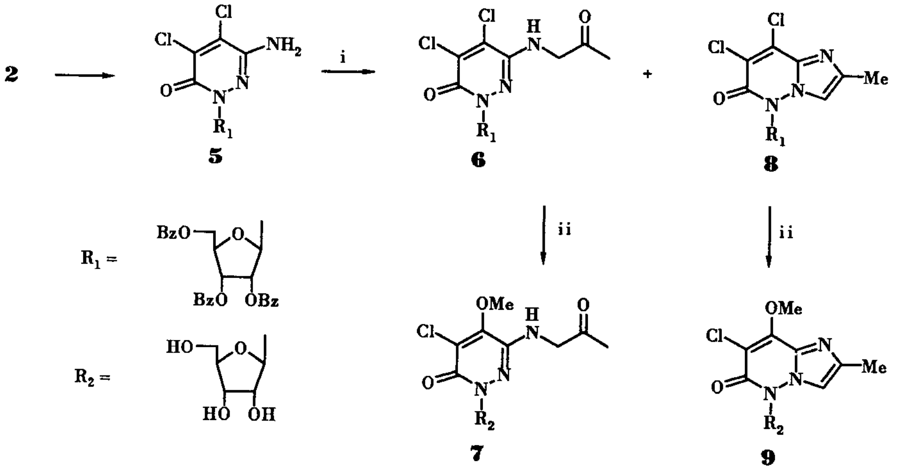
Scheme I



i) CS_2, EtOH, $NaHSO_3$, *p*H 3

ii) NaOMe, MeOH iii) Amberlite IRC-50 H^+

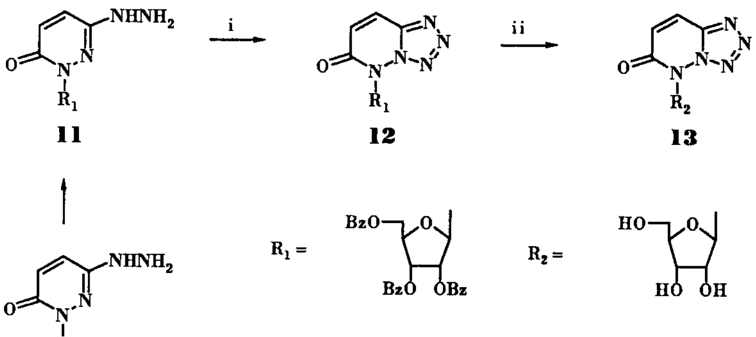
Scheme II



i) Chloroactone, EtOH or AcOH

ii) NaOMe, MeOH; Amberlite IRC-50 H^+

Scheme III



i) KNO_2, AcOH-EtOH

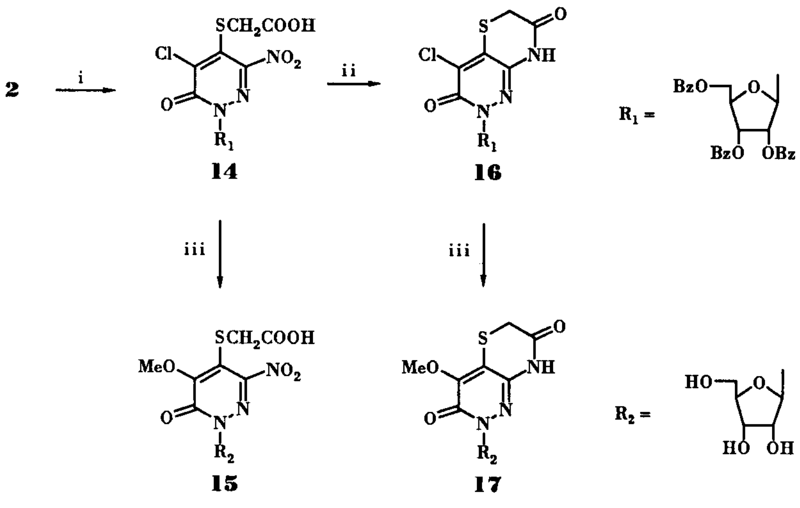
ii) NaOMe, THF-MeOH; Amberlite IRC-50 H^+

structure of these two isomers from pmr data. The mass spectrum of **6** showed the protected sugar ion (PS; m/z 445) and the BH ion (m/z 236). The mass spectrum of **8** showed the protected sugar ion (PS; m/z 445), the base ion (B; m/z 217) and B-CH(OH)CH$^+$OH (B + 60), m/z 277).

Debenzolyation of **6** and **8** with methanolic sodium methoxide afforded 5-chloro-4-methoxy-3-(2-oxopropylamino)-1-β-D-ribofuranosylpyridazin-6-one (**7**) and 7-chloro-8-methoxy-2-methyl-5-β-D-ribofuranosylimidazo[1,2-*b*]pyridazin-6(5*H*)-one (**9**), respectively. The infrared spectra of **7** and **9** showed only one absorption peak for the carbonyl group, respectively. The proton magnetic spectrum of compound **7** showed proton signals of NH (5.76-5.60), CH_3O (3.95), CH_3 (3.70) and CH_2 (3.20) involving proton signals of the sugar moiety. Whereas, the proton magnetic spectrum of **9** showed proton signals of CH at the 3-position (7.80), CH_3O (3.52) and CH_3 (2.94) involving signals of the ribose ring protons. The positon of the methoxy for compounds **7** and **9** was proved by further reactions of these compound [6].

On the other hand, we attempted to synthesize the nucleoside containing the tetrazolopyridazin-6-one heterocycle. Reaction of 3-hydrazino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**11**) [5] with aqueous potassium nitrite in acetic acid-ethanol gave 7,8-dihydro-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)tetrazolo[1,5-*b*]pyridazin-6(5*H*)-one (**12**) in low yield. The infrared spectrum of **12** showed two absorption peaks for carbonyl groups. The proton magnetic spectrum of **12** showed proton signals of two C-H at the C-7 (6.89) and the C-8 (7.06) positions as doublets involving signals of the aromatic and ribose ring protons. Debenzolyation of **12** with sodium methoxide afforded 7,8-dihydro-5-β-D-ribofuranosyltetrazolo[1,5-*b*]pyridazin-6(5*H*)-one (**13**). The infrared spectrum of **13** showed one absorption peak of an amide carbonyl. The proton magnetic resonance spectrum of **13** showed proton signals of C-H at the C-7 and the C-8 positions and an anomeric proton involving other proton signals of the ribose ring. The mass spectrum of **13** showed ion peaks for the molecular ion (M$^+$; m/z 269), M-30 (m/z 239), M-89 (m/z

Scheme IV



i) $HSCH_2COOH$, EtOH ii) $NaBH_4SnCl_2 \cdot H_2O$, $CHCl_3$
iii) NaOMe, MeOH; Amberlite IRC-50 H^+

180), B + 2H (m/z 139) and sugar moiety (S; m/z 133).

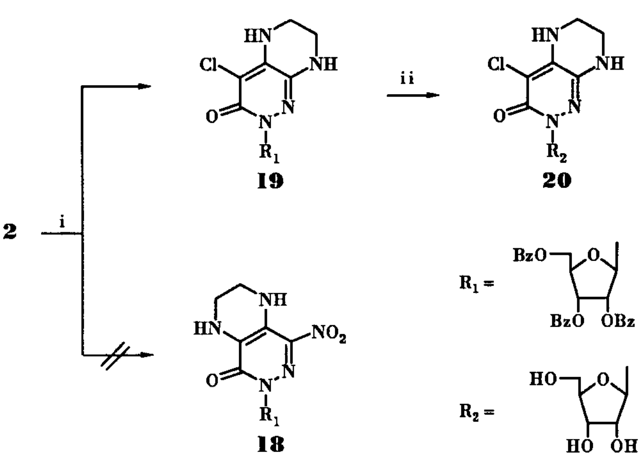
In order to synthesize [6:6]-fused heterocyclic nucleosides containing sulfur and nitrogen, reaction of **2** with thioglycolic acid and sodium hydroxide gave 4-carboxymethylthio-5-chloro-3-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**14**). Debenzolyation of **14** with methanolic sodium methoxide furnished 4-carboxymethylthio-5-methoxy-3-nitro-1-β-D-ribofuranosylpyridazin-6-one (**15**).

The infrared spectrum of **15** showed the absorption peaks for the O-H, a nitro group and two carbonyl groups. The proton magnetic resonance spectrum also showed proton signals for CH_2, OCH_3 and three OH groups involving other protons of the ribose ring. The mass spectrum of **15** showed ions M-30 (m/z 363), M-89 (m/z 304) and the sugar moiety (S; m/z 133).

Reductive cyclization of **14** with sodium borohydride and stannous chloride dihydrate in chloroform-ethyl acetate gave 2*H*,4*H*-8-chloro-6-(2,3,5-tri-*O*-benzoly-β-D-ribofuranosyl)pyridazino[3,2-*c*][1,4]thiazin-3(4*H*),7(6*H*)-dione (**16**) in low yield. Debenzoylation of methanolic sodium methoxide furnished 2*H*,4*H*-8-methoxy-6-β-D-ribofuranosylpyridazino[3,2-*c*][1,4]thiazin-3(4*H*),7(6*H*)-dione (**17**). The proton magnetic resonance spectrum of **17** showed proton signals for N-H, CH_2, CH_3O, O-H and other protons on the ribose ring. The mass spectrum of this compound showed ion peaks for M-30 (m/z 315), M-89 (m/z 256) and the sugar moiety (S; m/z 133).

Treatment of **2** with ethylenediamine in tetrahydrofuran gave 8-chloro-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-piperazino[2,3-*c*]pyridazin-7(6*H*)-one (**19**), but we did not obtain compound **18**. We did not detect the absorption peak of the nitro group in the infrared spectrum of **19**, but the peak of N-H was observed. The proton magnetic resonance spectrum of **19** also showed a proton signals of the N-H and two CH_2 groups also involving aromatic and ribose ring protons. Debenzoylation of compound **19** with methanolic sodium methoxide afforded 8-methoxy-6-β-D-ribofuranosylpiperazino[2,3-*c*]pyridazin-7(6*H*)-one (**20**) in good yield. The structure of this compound was determined from ir, pmr and mass spectral data. The infrared spectrum of **20** showed an absorption peak of the carbonyl group. The proton magnetic resonance spectrum of **20** also showed proton signals for NH (6.78), OCH_3 (3.78) and CH_2 (3.25) involving the OH protons and the ribose ring protons. The mass spectrum of **20** showed ion peaks for M^+ (m/z 314), M-89 (m/z 225), B + 30 (m/z 211), B + H (m/z 182) and the sugar moiety (S; m/z 133).

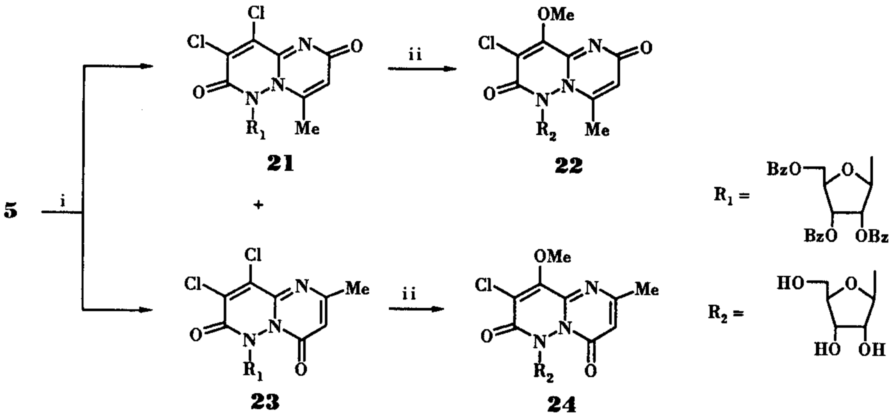
Scheme V



i) Ethylenediamine, THF
ii) NaOMe, MeOH; Amberlite IRC-50 H^+

Also, we attempted to synthesize a pyrimidinopyrid-

Scheme VI



i) Ethyl acetoacetate, EtOH-AcOH

ii) NaOMe, MeOH; Amberlite IRC-50 H^+

Table 1

Elemental Analyses of some Bicyclic Pyridazine Nucleosides

Compound No.	Molecular Formula	Calcd./Found(%) C	H	N
3	$C_{31}H_{22}N_3O_8SCl \cdot H_2O$	57.28 57.48	3.72 3.47	6.46 6.15
4	$C_{11}H_{13}N_3O_6S$	41.90 41.91	4.16 4.09	13.33 13.79
6	$C_{33}H_{27}N_3O_9Cl_2$	58.25 58.02	4.00 4.12	6.18 6.55
7	$C_{13}H_{18}N_3O_7Cl$	42.93 42.82	4.99 4.98	11.55 11.89
8	$C_{33}H_{25}N_3O_8Cl_2$ $\cdot 3/2H_2O$	57.49 57.37	4.09 3.80	6.09 6.20
9	$C_{13}H_{16}N_3O_6Cl$	45.16 45.17	4.66 4.53	12.15 11.84
12	$C_{30}H_{23}N_5O_8$	61.96 61.94	3.99 3.97	12.04 12.44
13	$C_9H_{11}N_5O_5$	40.15 40.18	4.12 3.97	26.01 25.84
14	$C_{32}H_{24}N_3O_{12}SCl$	54.13 54.17	3.41 3.19	5.92 6.29
15	$C_{12}H_{15}N_3O_{10}S$ $\cdot 1/2H_2O$	35.82 36.01	4.01 4.00	10.44 10.17
16	$C_{32}H_{24}N_3O_9SCl$	58.05 57.78	3.65 3.93	6.35 6.45
17	$C_{12}H_{15}N_3O_7S$	41.74 41.77	4.38 4.07	12.17 12.07
19	$C_{32}H_{27}N_4O_8Cl$ $\cdot 1/2H_2O$	60.05 60.41	4.41 4.40	8.75 8.40
20	$C_{12}H_{18}N_4O_6$	45.86 46.33	5.77 5.51	17.83 17.62
21	$C_{34}H_{25}N_3O_9Cl_2$	59.14 58.85	3.65 3.62	6.09 6.39
22	$C_{14}H_{16}N_3O_7Cl \cdot H_2O$	42.92 43.02	4.63 5.01	10.73 11.04
23	$C_{34}H_{25}N_3O_9Cl_2$	59.14 59.89	3.65 3.67	6.09 5.97
24	$C_{14}H_{16}N_3O_7Cl \cdot H_2O$	42.92 43.31	4.63 4.29	10.73 11.06

azine nucleoside from a pyridazine nucleoside. Cyclization of **5** with ethyl acetoacetate in acetic acid-ethanol gave **21** and **23** as a mixture of two isomers. Two isomers were separated by silica gel column chromatography, but we could not determine the structure of the two isomers because the ir and pmr spectra of these isomers were very similar. Thus, the assignment of the structure for these isomers was based on the ir and pmr spectra obtained for the debenzoylated nucleosides **22** and **24** by treatment of **21** and **23** with sodium methoxide in methanol. The infrared spectrum of **22** showed two absorption peaks for carbonyl groups at 1630 and 1615 cm^{-1}, whereas the infrared spectrum of **24** showed two absorption peaks for carbonyl groups at 1640 and 1620 cm^{-1}. The proton signal at the 3-position were observed at 5.58 ppm for **22** and at 6.11 ppm for **24** in the proton magnetic resonance spectrum, respectively. The mass spectrum of **22** showed M-30 (m/z 343), M-89 (m/z 284), B + H (m/z 241) and sugar moiety (S; m/z 133). The mass spectrum of **24** also showed M^+ (m/z 376), M-30 (m/z 343), M-89 (m/z 284), B + H (m/z 241) and sugar moiety (S; m/z 133). Recently, Matyus, *et al.* [7] determined the structures of some pyrimido[1,2-*b*]pyridazin-2(2*H*)-ones and pyrimido[1,2-*b*]pyridazin-4(4*H*)-ones based on the ir and nmr data. Therefore, the structures of our compounds **22** and **24** could well be determine by the comparison of our spectral data with the data of Matyus. The position of the methoxy group for compounds **22** and **24** was proved by further reactions [6].

Additional chemical transformations of the novel compounds, along with an evaluation of their biological properties, are currently under investigation in our laboratory.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The infrared spectra were recorded on a Hitachi 270-50 spectrophotometer. The ^{1}H-nmr spectra were ob-

Table 2

^{1}H-NMR Spectral Data for Certain Bicyclic Pyridazine Nucleosides

Compound No.	Solvent [a]	$H_{1'}$	$J_{1',2'}$ (Hz)	Others [b]
3	C	6.71	2	8.12-7.8 (m, bz H's + H_2), 6.20-5.58 (m, $H_{2'}$ + $H_{3'}$), 5.0-4.6 (m, $H_{4'}$ + $H_{5'}$)
4	D	6.25	2	7.85 (s, H_2), 5.82 (d, $OH_{2'}$, J = 4), 5.60 (d, $OH_{3'}$, J = 4), 4.61-4.55 (m, $OH_{5'}$), 4.53-4.32 (m, $H_{2'}$ + $H_{3'}$), 4.09-3.86 (m, $H_{4'}$ + $H_{5'}$), 3.51 (s, OCH_3)
6	D	6.78	2	8.10-7.30 (m, bz H's), 6.47 (t, NH), 6.08 (m, $H_{2'}$ + $H_{3'}$), 4.98-4.61 (m, $H_{4'}$ + $H_{5'}$), 3.28 (s, CH_3), 3.20 (d, CH_2, J = 2)
7	D	6.17	4	5.76-5.60 (t, NH), 5.21 (d, $OH_{2'}$, J = 4), 4.80 (m, $OH_{3'}$), 4.46-4.30 (m, $OH_{5'}$), 4.30-3.78 (m, $H_{2'}$ + $H_{3'}$ + $H_{4'}$ + $H_{5'}$), 3.95 (s, OCH_3), 3.70 (s, CH_3), 3.20 (d, CH_2, J = 2)
8	C	6.86	2	8.21-7.07 (m, H_3 + bz H's), 6.21-5.91 (m, $H_{2'}$ + $H_{3'}$), 4.91-4.55 (m, $H_{4'}$ + $H_{5'}$), 4.35 (s, CH_3)
9	D	6.17	3	7.80 (s, H_3), 5.20-4.30 (m, $OH_{2'}$ + $OH_{3'}$ + $OH_{5'}$), 4.2-3.6 (m, $H_{2'}$ + H_3 + $H_{4'}$ + $H_{5'}$), 3.52 (s, OCH_3), 2.94 (s, CH_3)
12	C	6.80	4	8.20-7.19 (m, bz H's), 7.06 (d, H_8, J = 6), 6.89 (d, H_7, J = 6), 6.18-5.91 (m, $H_{2'}$ + $H_{3'}$), 4.90-4.48 (m, $H_{4'}$ + $H_{5'}$)
13	D	6.20	3	7.50 (d, H_8, J = 8), 7.01 (d, H_7, J = 8), 5.25 (d, $OH_{2'}$, J = 4), 5.05 (d, $OH_{3'}$, J = 4), 4.64 (m, $OH_{5'}$), 4.41-3.80 (m, $H_{2'}$ + $H_{3'}$), 3.71-3.51 (m, $H_{4'}$ + $H_{5'}$)
14	D	6.61	2	8.25-6.82 (m, bz H's), 6.2-5.8 (m, $H_{2'}$ + $H_{3'}$), 4.6 (s, CH_2), 4.2-3.5 (m, $H_{4'}$ + $H_{5'}$)
15	D	6.18	3	5.25 (d, $OH_{2'}$, J = 3), 5.01 (d, $OH_{2'}$, J = 3), 4.52 (m, $OH_{5'}$), 4.5-3.8 (m, $H_{2'}$ + $H_{3'}$ + $H_{4'}$ + $H_{5'}$ + CH_2 + OCH_3)
16	D	6.75	2	8.04-7.11 (m, bz H's), 6.20 (bs, NH), 6.19-5.85 (m, $H_{2'}$ + $H_{3'}$), 4.76-4.52 (m, $H_{4'}$ + $H_{5'}$), 4.0 (s, CH_2)
17	D	6.20	6	5.97 (bs, NH), 4.5-3.4 (m, 3OH + $H_{2'}$ + $H_{3'}$ + $H_{4'}$ + $H_{5'}$ + CH_2 + OCH_3)
19	C	6.60	2	8.21-7.27 (m, bz H's), 6.02-5.67 (m, $H_{2'}$ + $H_{3'}$), 4.78-4.30 (m, $H_{4'}$ + $H_{5'}$), 3.25 (m, $2CH_2$)
20	D	6.13	2	6.78 (bs, NH), 6.01-5.89 (m, $H_{2'}$ + $H_{3'}$), 4.20-3.00 (m, 3OH + $H_{4'}$ + $H_{5'}$), 3.78 (s, OCH_3), 3.25 (m, $2CH_2$)
21	C	6.76	3	8.19-7.08 (m, bz H's + H_3), 6.18-5.95 (m, $H_{2'}$ + $H_{3'}$), 4.95-4.45 (m, $H_{4'}$ + $H_{5'}$ + CH_3)
22	D	6.11	4	5.58 (s, H_3), 4.61-3.63 (m, $H_{2'}$ + $H_{3'}$ + $H_{4'}$ + $H_{5'}$ + 3OH + OCH_3), 3.51 (s, CH_3)
23	C	6.80	3	8.19-7.08 (m, bz H's), 6.18-5.95 (m, $H_{2'}$ + $H_{3'}$), 4.95-4.47 (m, $H_{4'}$ + $H_{5'}$ + CH_3)
24	D	6.20	3	6.11 (s, H_3), 5.21 (d, $OH_{2'}$, J = 6), 4.90 (d, $OH_{3'}$, J = 6), 4.69-4.43 (m, $OH_{5'}$), 4.33-3.43 (m, $H_{2'}$ + $H_{3'}$ + $H_{4'}$ + $H_{5'}$ + OCH_3 + CH_3)

[a] C = deuteriochloroform: D = DMSO-d_6. [b] Coupling constant (J) in hertz. All NH of OH signals were exchangeable with deuterium oxide, Abbreviations used: Bz = benzoyl, s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet.

tained on a Bruker AW-80 MHz spectrometer. Chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Elemental analyses were performed with a LECO Micro Carbon Hydrogen Nitrogen Determinator (CHN-800). The presence of water of crystallization in the elemental analyses was verified by proton magnetic resonance spectroscopy. Ultraviolet absorption spectra (uv) were recorded on a Gilford Response UV-VIS spectrophotometer. The mass spectra were obtained from the Korean Research Institute of Chemical Technology (Taejon, Korea). Nucleosides were detected by the treatment with sulfuric acid followed by charring. Open-bed column chromatography was carried out on silica gel 60 (70-230 mesh, Merck) using gravity flow. The columns were packed as slurries with the elution solvent.

7-Chloro-5-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)[1,3]thiazolo[4,5-*c*]pyridazin-6(5*H*)-one (**3**).

A mixture of **2** (3 g, 4.58 mmoles) [1c], carbon disulfide (0.3 ml, 3.9 mmoles), sodium bisulfite (0.32 g, 3.1 mmoles) and ethanol (50 ml) was adjusted to *p*H **3** using aqueous hydrochloric acid (20%), and then refluxed for 24 hours. After cooling, the mixture was poured into ice water (200 ml), filtered and dried in air. The resulting product was dissolved in chloroform (10 ml). The product solution was applied to the top of an open-bed silica gel column (2.5 x 40 cm). The column was eluted with chloroform-methanol (50:1 v/v). The fractions containing the product were combined, and the solvent was evaporated under reduced pressure to give **3** in 25% (0.72 g) yield. Recrystallization of a small sample from ethanol yielded a powder, mp 80-82°; ir (potassium bromide): 3070, 1740, 1700, 1650 cm^{-1}; uv (methanol): λ max nm (log ε) 228 (3.49), 300 sh (3.19); ms: m/z (relative intensity) 445 (23.9, PS), 341 (3.8, PS-C_7H_5O), 323 (22, PS-122), 295 (20, B + 108), 247 (9.8, B + 60), 235 (8.5, $C_{12}H_{11}O_5^+$), 218 (4.5, B + 30), 189 (16.1, B + H), 122 (9.3, $C_7H_6O_2^+$), 105 (100, $C_7H_5O^+$).

7-Methoxy-5-β-D-ribofuranosyl[1,3]thiazolo[4,5-*c*]pyridazin-6(5*H*)-one (**4**).

A mixture of **3** (0.5 g, 0.79 mmole), sodium methoxide (0.38 g, 8.27 mmoles), tetrahydrofuran (15 ml) and methanol (15 ml) was stirred for 24 hours at room temperature. Amberlite IRC-50 resin (H^+ form, 2 g) was added and the mixture was stirred for additional 16 hours, filtered and the residue washed with boiling methanol (20 ml). The combined filterates were coevaporated with silica gel (2 g) and the silica gel then applied to the top of an open-bed silica gel column (1.5 x 40 cm). The column was eluted with a chloroform-methanol (9:1 v/v) mixture. The eluent containing product was evaporated under reduced pressure to give **4** as a form. Recrystallization of a small sample from ethanol yielded a powder, mp 85-89°; ir (potassium bromide): 3400, 2970, 1620, 1580 cm^{-1}; uv (methanol): λ max nm (log ϵ) 262 (3.46), 314 (3.60), 322 (3.60); (*p*H 1): 214 (2.00), 230 (2.83), 248 (2.63); (*p*H 11): 212 (2.41), 298 (2.60), 346 sh (2.45), 356 sh (2.41), 372 (2.36).

3-(2-Oxopropylamino)-4,5-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**6**) and 7,8-Dichloro-2-methyl-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyridazin-6(5*H*)-one (**8**).

A mixture of **5** (2.0 g, 3.2 mmoles) [5], chloroacetone (0.32 ml, 3.5 mmoles) and ethanol was refluxed for 40 hours. After cooling, the reaction mixture was coevaporated with silica gel (4 g) under reduced pressure, and the silica gel was then applied to the top of an open-bed silica gel column (2.5 x 40 cm). The column was eluted with a chloroform-methanol (200:0.3 v/v) mixture. After the first 160 ml of solvent, 6 ml fractions were then collected. Nucleoside products were detected in fractions 35-56 and fractions 80-105. Fractions 35-56 were combined and evaporated under reduced pressure to give **6** in 34% (0.76 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 133-135°; ir (potassium bromide): 3390, 3100, 1750, 1670, 1630, 1600, 1540, 1470 cm^{-1}; uv (methanol): λ max nm (log ϵ) 228 (5.35), 332 (3.60); ms: m/z (relative intensity) 445 (10.5, PS), 341 (9.8, PS-C_7H_5O), 236 (7.8, B + H), 122 (3.4, $C_7H_6O_2^+$), 105 (100, $C_7H_5O^+$). Fractions 80-105 were combined and evaporation under reduced pressure to give **8** in 41% (0.89 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 172-174°; ir (potassium bromide): 3050, 1730, 1670, 1625, 1460, 1370, 1250 cm^{-1}; uv (methanol): λ max nm (log ϵ) 230 (2.04), 240 (2.20), 320 (1.78); ms: m/z (relative intensity) 445 (4.0, PS), 341 (5.7, PS-C_7H_5O), 277 (24, B + 60), 217 (37, B), 201 (80, B-CH_4), 122 ($C_7H_6O_2^+$), 105 (100, $C_7H_5O^+$).

3-(2-Oxopropylamino)-5-chloro-4-methoxy-1-β-D-ribofuranosylpyridazin-6-one (**7**).

After a mixture of **6** (0.3 g, 0.429 mmole), sodium methoxide (0.27 g, 5.0 mmoles, 80%), tetrahydrofuran (20 ml) and methanol (20 ml) was stirred for 20 hours at room temperature, Amberlite IRC-50 resin (H^+ form, 2.0 g) was added. The reaction mixture was then stirred for additional 18 hours at room temperature. After the mixture was filtered, and the resin was washed with boiling methanol (20 ml). The combined filterates were coevaporated with silica gel (3 g) and applied to the top of an open-bed silica gel column (1.5 x 40 cm). The column was eluted with chloroform-methanol (8:2 v/v). The eluent containing the product was combined and evaporated under reduced pressure to give **7** in 73% (0.12 g). Recrystallization of a small sample from ethanol yielded an analytical sample, mp 181-182°; ir (potassium bromide); 3400, 3350, 2950, 1620, 1580, 1540, 1480, 1370 cm^{-1}; uv (methanol): λ max nm (log ϵ) 382 (3.11); (*p*H 1): 230 (2.11), 344 (2.75); (*p*H 11): 230 (3.81), 32 (3.58).

7-Chloro-8-methoxy-2-methyl-5-β-D-ribofuranosylimidazo[1,2-*b*]pyridazin-6(5*H*)-one (**9**).

After compound **8** (0.5 g, 0.73 mmole) was dissolved in tetrahydrofuran (20 ml)-methanol (20 ml), sodium methoxide (0.47 g, 7.4 mmoles) was added and the mixture was then stirred for 17 hours at room temperature. Amberlite IRC-50 resin (H^+ form, 2 g) was added to the reaction mixture, and the mixture was then stirred for additional 14 hours. The mixture was filtered and the resin was then washed with boiling methanol (15 ml). The combined filterates were coevaporated with silica gel (3 g) and applied to the top of an open-bed silica gel column (1.5 x 40 cm). The column was eluted with a chloroform-methanol (8:2 v/v) mixture. The eluents containing the product were combined and evaporated under reduced pressure to give **9** in 86% (0.23 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 221-223°; ir (potassium bromide): 3400, 2950, 1620, 1520, 1450, 1370 cm^{-1}; uv (methanol): λ max nm (log ϵ) 262 (3.46), 352 (3.75); (*p*H 1): 208 (2.03); (*p*H 11): 206 (2.60), 212 (1.69), 228 sh (1.70), 244 (1.84).

7,8-Dihydro-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)tetrazolo[1,5-*b*]pyridazin-6(5*H*)-one (**12**).

After compound **11** (1.2 g, 2.10 mmoles) was dissolved in acetic acid (10 ml)-ethanol (2 ml), potassium nitrites (0.5 g, 4.95 mmoles) and water (5 ml) were added. The mixture was stirred for 0.5 hour at 0° and then for additional 7 hours at room temperature. The reaction mixture was poured into cold water (100 ml). The resulting pricipitate was filtered and dried in air. Recrystallization of the crude product from ethanol gave **12** in 39% (0.48 g) yield, mp 137-139°; ir (potassium bromide): 1740, 1700, 1600, 1530, 1460 cm^{-1}; uv (methanol): λ max nm (log ϵ) 320 (2.71), 345 (2.76).

7,8-Dihydro-5-β-D-ribofuranosyltetrazolo[1,5-*b*]pyridazin-6(5*H*)-one (**13**).

A mixture of **12** (0.5 g, 0.859 mmole), sodium methoxide (0.38 g, 7.0 mmoles, 80%), tetrahydrofuran (15 ml) and methanol (15 ml) was stirred for 17 hours at room temperature. Amberlite IRC-50 resin (H^+ form, 1.8 g) was added, and the mixture was then stirred for additional 18 hours at room temperature. The reaction mixtures was filtered and the resin was then washed with boiling methanol (15 ml). The combined filterates were coevaporated with silica gel (3 g) under reduced pressure and applied to the top of an open-bed silica gel column (1.5 x 40 cm). The column was eluted with a chloroform-methanol (9:1 v/v) solvent. The fractions containing the nucleoside were combined and evaporated under reduced pressure to give **13** in 84% (0.19 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 167-169°; ir (potassium bromide): 3400, 2930, 1620, 1580 cm^{-1}; uv (methanol): λ max nm (log ϵ) 243 (1.90), 270 (2.11); (*p*H 1): 214 (2.67), 348 (3.23); (*p*H 11): 226 (3.47), 246 (3.47); ms: m/z (relative intensity) 269 (31, M^+), 239 (47, M-30), 180 (23, M-89), 133 (100, S).

4-Carboxymethylthio-5-chloro-3-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**14**).

After sodium hydroxide (0.8 g, 22 mmoles) was dissolved in water, the solution was cooled to 10°. Thioglycolic acid (1 g, 10.8

mmoles) was added, and the reaction mixture was then stirred for 0.5 hour at same temperature. To this solution was added **2** (2 g, 3.05 mmoles) in tetrahydrofuran (40 ml), and the mixture was refluxed for 12 hours. After cooling, the reaction mixture was poured into water (100 ml). The resulting precipitate was filtered and dried in air. The crude product was dissolved in chloroform (5 ml) and applied to the top of an open-bed silica gel column (3 x 30 cm). The column was eluted with a chloroform-methanol (9.5:0.5 v/v) solvent. Fractions containing nucleoside was combined and evaporated under reduced pressure to give **14** as white powder in 26% (0.56 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 112-115°; ir (potassium bromide): 3450, 3100, 2970, 1740, 1620 cm^{-1}; uv (methanol): λ max nm (log ϵ) 234 (3.38), 318 (3.07).

4-Carboxymethylthio-5-methoxy-3-nitro-1-β-D-ribofuranosylpyridazin-6-one (**15**).

A mixture of **14** (0.6 g, 0.84 mmoles), sodium methoxide (0.4 g, 7.4 mmoles, 80%), tetrahydrofuran (20 ml) and methanol (20 ml) was stirred for 18 hours at room temperature. Amberlite IRC-50 resin (H$^+$ form, 2 g) was added, and the mixture was then stirred for additional 20 hours at room temperature. The mixture was filtered, and the resin was washed with boiling methanol (20 ml). The combined filterates were coevaporated with silica gel (3 g) under reduced pressure and applied to the top of an open-bed silica gel column (1.5 x 40 cm). The column was eluted with a chloroform-methanol (9:1 v/v) mixture. Fractions containing nucleoside were combined and evaporated under reduced pressure to give **15** in 84% (0.26 g) yield. Recrystallization of a small sample from methanol (or ethanol) yielded an analytical sample, mp 112-115°; ir (potassium bromide): 3400, 2940, 1730, 1670, 1590, 1270 cm^{-1}; uv (methanol): λ max nm (log ϵ) 234 (3.49), 344 (2.75); (*p*H 1): 218 (3.48), 268 (3.51), 330 (3.42); (*p*H 11): 242 (3.29), 320 (3.09); ms: m/z (relative intensity) 363 (3.4, M-30), 304 (22.2, M-89), 133 (100, S).

2*H*,4*H*-8-Chloro-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazino[3,2-*c*][1,4]thiazin-3(4*H*),7(6*H*)-dione (**16**).

After compound **14** (0.7 g, 0.985 mmole) was dissolved in chloroform (20 ml)-ethyl acetate (30 ml), sodium borohydride (0.11 g, 4.0 mmoles) and stannous chloride dihydrate 0.77 g, 4.05 mmoles) were added. The mixture was stirred for 27 hours at room temperature. The reaction mixture was filtered, and the residue was then washed with hot ethyl acetate (20 ml). The combined filterates were coevaported with silica gel (4 g) under reduced pressure and applied to the top of an open-bed silica gel column (1.5 x 40 cm). The column was eluted with a chloroform-methanol (9.5:0.5 v/v) solvent. Fractions containing the nucleoside were combined and evaporated under reduced pressure to give **16** in 20% (0.135 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 243-245°; ir (potassium bromide): 3250, 2940, 1730, 1650, 160 cm^{-1}; uv (methanol) λ max nm (log ϵ) 206 (3.12), 230 sh (3.41), 308 (3.26).

2*H*,4*H*-8-Methoxy-6-β-D-ribofuranosylpyridazino[3,2-*c*][1,4]thiazin-3(4*H*),7(6*H*)-dione (**17**).

A mixture of 16 (0.37 g, 0.558 mmole), tetrahydrofuran (15 ml), methanol (15 ml) and sodium methoxide (0.35 g, 6.48 mmoles, 80%) was stirred for 24 hours at room temperature. After Amberlite IRC-50 resin (H$^+$ form, 2 g) was added, the reaction mixture was stirred for additional 24 hours at room temperature. The mixture was filtered and the resin was then washed with boiling methanol (20 ml). The combined filterate were coevaporated with silica gel (2 g) and applied to the top of an open-bed silica gel column (1.5 x 40 cm). The column was washed with a chloroform-methanol (9:1 v/v) mixture (400 ml) to remove methyl benzoate. The product was then eluted with chloroform-methanol (1:1 v/v). Fractions containing nucleoside were combined and evaporated under reduced pressure to give **17** in 83% (0.156 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 300° dec; ir (potassium bromide): 3500, 3450, 2830, 1740, 1685, 1630, 1580 cm^{-1}; uv (methanol): λ max nm (log ϵ) 298 (3.55): ms: m/z (relative intensity) 315 (11.0, M-30), 256 (24, M-89), 133 (35, S).

8-Chloro-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)piperazino[2,3-*c*]pyridazin-7(6*H*)-one (**19**).

A mixture of **2** (2 g, 3.04 mmoles), ethylenediamine (0.4 ml, 6.6 mmoles) and tetrahydrofuran (40 ml) was stirred for 8 hours at room temperature. The reaction mixture was poured into water (200 ml). The product was extracted with ethyl acetate (100 ml x 2). The ester layer was dried over anhydrous magnesium sulfate and coevaporated with silica gel (4 g) under reduced pressure. The silica gel was applied to the top of an open-bed silica gel column (2 x 40 cm). The column was eluted with a chloroform-methanol (9.5:0.5 v/v) solvent. Fractions containing nucleoside were combined and evaporated under reduced pressure to give **19** in 51% (0.82 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 91-93°; ir (potassium bromide): 3450, 3060, 3040, 2930, 1730, 1650 cm^{-1}; uv (methanol): λ max nm (log ϵ) 252 (3.03), 286 (3.60), 318 (3.67).

8-Methoxy-6-β-D-ribofuranosylpiperazino[2,3-*c*]pyridazin-7(6*H*)-one (**20**).

A mixture of **19** (0.45 g, 0.713 mmole), sodium methoxide (0.38 g, 7.1 mmoles, 80%), tetrahydrofuran (20 ml) and methanol (20 ml) was stirred for 24 hours at room temperature. Amberlite IRC-50 resin (H$^+$ form, 2 g) was added and the reaction mixture was stirred for additional 24 hours. The mixture was filtered, and the resin was then washed with boiling methanol (20 ml). The combined filterates were coevaporated with silica gel (3 g) under pressure and applied to the top of an open bed silica gel column (2 x 40 cm). The column was eluted with a ethyl acetate-methanol (7:3 v/v) mixture. Fractions containing nucleoside were combined and evaporated under reduced pressure to give 20 in 84% (0.191 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 169-170°; ir (potassium bromide): 3400, 2980, 1665, 1620, 1580 cm^{-1}; uv (methanol): λ max nm (log ϵ) 268 (3.44); (*p*H 1): 236 (2.20), 242 (1.9), 284 (1.78); (*p*H 11): 240 (1.90), 270 (2.20), 282 (2.36); ms: m/z (relative intensity) 314 (21.4, M$^+$), 225 (55.1, M-89), 211 (67, B+30), 182 (58.1, B+H), 133 (48, S).

8,9-Dichloro-4-methyl-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidino[1,2-*b*]pyridazin-2(2*H*),7(6*H*)-dione (**21**) and 8,9-Dichloro-2-methyl-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidino[1,2-*b*]pyridazin-4(4*H*),7(6*H*)-dione (**23**).

A mixture of **5** (1.5 g, 2.4 mmoles), acetic acid (10 ml) and ethyl acetoacetate (0.4 g, 2.8 mmoles) was refluxed for 6 hours. After cooling, the reaction mixture was poured into ice water (100 ml). The resulting pericipetate was filtered and dried in air. After the crude product was dissolved in chloroform (6 ml), the chloroform solution was applied to the top of an open-bed silica gel column (2 x 40 cm). The column was eluted with a chloroform-methanol (10:0.2 v/v) solvent. After the first 110 ml of solvent, 6 ml fractions were then collected. Nucleoside products were detected in fractions 5-41 and fractions 106-127. Fractions 5-41 were combined and evaporated under reduced pressure to furnish **23** in 31% (0.513 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 96-97°; ir (potassium bromide): 3070, 1750, 1630, 1530, 1470 cm^{-1}; uv (methanol): λ max nm (log ε) 242 (2.45), 272 (2.04), 316 (2.32); ms: m/z (relative intensity) 445 (5.3, PS), 276 (2.6, B + 30), 246 (50, B + H), 122 (3.6, $C_7H_6O_2^+$), 105 (100, $C_7H_5O^+$).

Fractions 106-127 were combined and evaporated under reduced pressure to give **21** in 23% (0.38 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 104-105°; ir (potassium bromide): 3050, 1750, 1630, 1580, 1530, 1460 cm^{-1}; uv (methanol): λ max nm (log ε) 252 (2.11), 352 (2.71); ms: m/z (relative intensity) 445 (25.9, PS), 246 (3.5, B + H), 276 (11, B + 30), 122 (5.2, $C_7H_6O_2^+$), 105 (100, $C_7H_5O^+$).

8-Chloro-4-methyl-9-methoxy-6-β-D-ribofuranosylpyrimidino[1,2-*b*]pyridazin-2(2*H*),7(6*H*)-dione (**22**).

A mixture of **21** (0.5 g, 0.725 mmole), sodium methoxide (0.5 g, 9.25 mmoles, 80%) and tetrahydrofuran (20 ml) was stirred for 16 hours at room temperature. Amberlite IRC-50 resin (H$^+$ form, 2 g) was added, and the reaction mixture was stirred for additional 24 hours at room temperature. The mixture was filtered, and the resin was then washed with boiling methanol (20 ml). The combined filterates were coevaporated with silica gel (2 g) and applied to the top of an open-bed silica gel column (1.0 x 40 cm). The column was eluted with a dichloromethane-methanol (9:1 v/v) solvent. Fractions containing nucleoside were combined and evaporated under reduced pressure to give **22** in 89% (0.24 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 170-171°; ir (potassium bromide): 3360, 2950, 1630, 1615, 1580, 1525, 1480 cm^{-1}; uv (methanol): λ max nm (log ε) 262 (3.46), 298 sh (3.28); (*p*H 1): 226 (3.45), 262 sh (3.46), 396 (3.26); (*p*H 11), 232 (2.84), 332 (2.64), 342 (2.66); ms: m/z (relative intensity) 343 (6.5, M-30), 284 (4.9, M-89), 241 (4.6, B + H), 133 (84, S).

8-Chloro-2-methyl-9-methoxy-6-β-D-ribofuranosylpyrimidino[1,2-*b*]pyridazin-4(4*H*),7(6*H*)-dione (**24**).

A mixture of **23** (0.4 g, 0.58 mmole), sodium methoxide (0.35 g, 6.48 mmoles, 80%), tetrahydrofuran (20 ml) and methanol (20 ml) was stirred for 20 hours at room temperature. Amberlite IRC-50 resin (H$^+$ form, 2 g) was added, and the mixture was stirred for additional 14 hours at room temperature. The reaction mixture was filtered and the resin was then washed with boiling methanol (20 ml). The combined filterates were coevaporated with silica gel (3 g) under reduced pressure and applied to the top of an open-bed silica gel column (1.5 x 40 cm). The column was eluted with a chloroform-methanol (8:2 v/v) solvent. Fractions containing nucleoside were combined and evaporated under reduced pressure to furnish **24** in 82% (0.19 g) yield. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 170-171°; ir (potassium bromide): 3400, 2640, 1640, 1620, 1540, 1480 cm^{-1}; uv (methanol): λ max nm (log ε) 268 (1.78), 270 (2.08), 318 (2.04); (*p*H 1): 276 (3.51), 318 (3.41); (*p*H 11): 250 (3.45), 268 (3.43), 318 (2.11); ms: m/z (relative intensity) 373 (6, M^+), 343 (23, M-30), 284 (32, M-89), 241 (12.6, B + H), 133 (94, S).

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