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Novel Synthesis of (+)-Hydantocidin Based on the Plausible Biosynthetic Pathway

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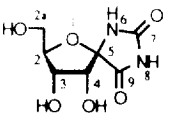
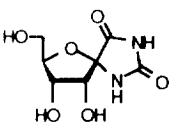
Abstract: *The title synthesis was examined by employing two synthetic schemes which feature N,O-spiroketal formation as a key step. Although the stepwise synthesis starting with D-fructose and proceeding through the D-psicose derivatives successfully produced a mixture of (+)-hydantocidin (**1**) and its C5-epimer [(-)-5-epi-hydantocidin (**2**)], the one-step synthesis utilizing D-isoascorbic acid and urea as starting materials was found to give **2** more selectively than **1**. Studies on the key N,O-spiroketal formation and epimerization between **1** and **2** were also carried out to explore some novel aspects of the obtained results.*

(+)-Hydantocidin (**1**) isolated from the culture broth of *Streptomyces hygroscopicus* SANK 63584,[1] Tu-2474[2] and A1491,[3] is the first example of natural products carrying a spirohydantoin nucleus at the anomeric position of D-ribofuranose. This unique structural characteristic has never been found in the family of nucleoside antibiotics.[4] **1** shows an interesting profile of herbicidal and plant growth regulatory activity without any toxicity against microorganisms, fishes, and animals.[5] From the studies on structure-activity relationships of **1**, its spiro isomer, (-)-5-*epi*-hydantocidin (**2**), also displays a herbicidal activity being approximately 60% of that for **1**.[6] These interesting features make **1** and **2** exceptionally attractive targets for total synthesis. Since Sankyo group achieved the first total synthesis of (+)-**1** in 1991,[7a,b] leading to confirmation of its absolute configuration, synthetic studies on **1** itself[7] and its stereoisomers[8,9] and analogues[10] have been reported.

We embarked on the total synthesis of **1** by taking into account its intriguing structure and remarkable herbicidal activity. This report concerns with the novel synthesis of **1** and **2** accomplished by employing two synthetic schemes designed based on the plausible biosynthetic pathway of **1**.[11] This paper



(+)-Hydandocidin (**1**)



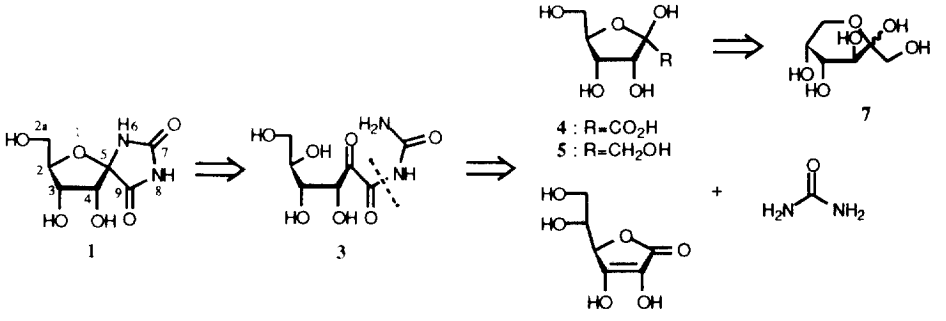
(-)-5-*epi*-Hydandocidin (**2**)

also details the studies on key intramolecular *N,O*-spiroketal formation and epimerization between **1** and **2**.[12]

Synthetic strategy

Although no obvious biosynthetic pathway of **1** has hitherto been proposed, we designed the synthetic strategy of **1** based on the plausible biosynthetic pathway as shown in **Scheme 1**.[11] Thus, the *N,O*-spiroketal moiety of **1** can be disconnected retrosynthetically to afford open-chain *N*-acylurea **3**. Removal of the urea unit in **3** leads back to the C_6 sugar unit such as carboxylic acid **4** or D-isoascorbic acid (**6**). The former carboxylic acid **4** is accessible from D-psicose (**5**), which, in turn, can be readily prepared from D-fructose (**7**). The key step in this approach is envisioned to be the intramolecular *N,O*-spiroketal formation of **3** to furnish **1**, wherein the stereochemistry at the C_5 position of **1** is controllable by selecting reaction conditions. This strategic analysis obviously suggests that **1** might be produced *in vivo* from two simple building blocks, a hexose derivative and urea, through the biogenetic precursor **3**.

Scheme 1



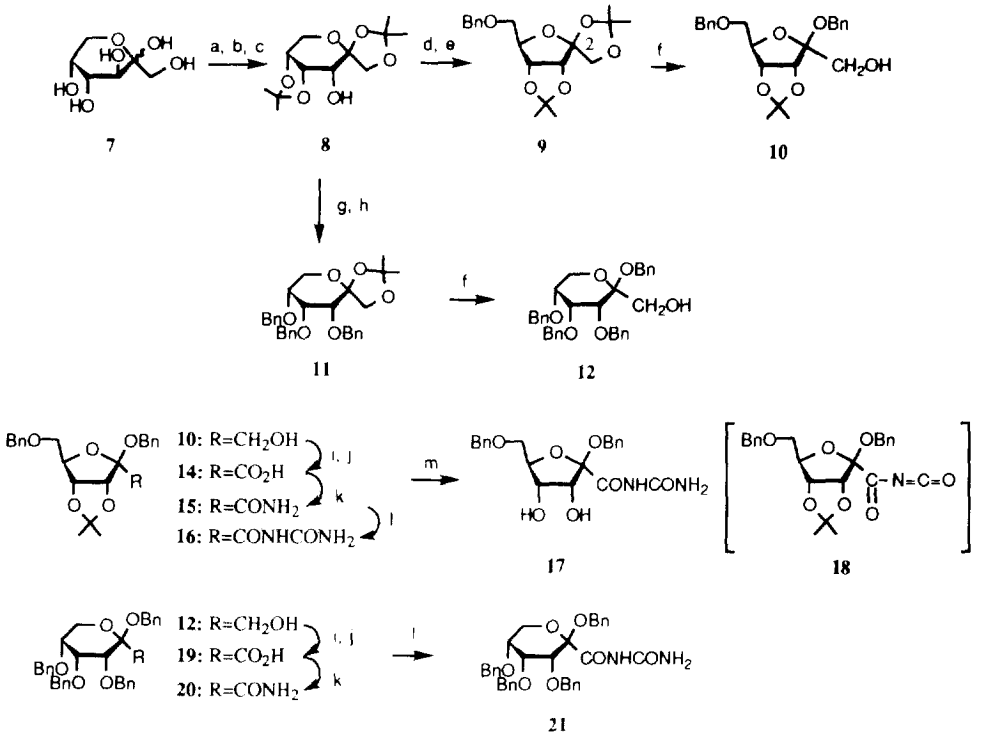
Results and Discussion

1. Stepwise Synthesis of a Mixture of (+)-Hydantocidin (1) and (-)-*epi*-Hydantocidin (2) from D-Fructose (7).

At the outset, it was anticipated that the D-ribofuranose **22** and the D-ribopyranose **23** might be subjected to the *N,O*-spiroketal formation as synthetic equivalents of **3**. Accordingly, preparation of **22** and **23** was first examined starting with inexpensive **7** as shown in **Scheme 2**. Thus, following to the Moffat[13] and Mio methods,[7b] 6-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-D-psicofuranose (**9**) was synthesized from **7** in 5 steps and in 38% overall yield by way of 1,2:3,4-di-*O*-isopropylidene-D-psicopyranose (**8**). Benzyl glycoside formation of **9** was found to be effected in a stereoselective manner by treating **9** with benzyl alcohol in the presence of trifluoromethanesulfonic acid (TfOH) or methanesulfonic acid (MsOH) at ambient temperature, giving rise to benzyl glycoside **10**, in 74% or 66% yield, respectively.

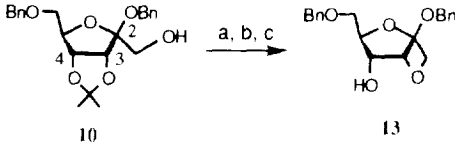
The stereochemical issue with respect to the anomeric center in **10** was confirmed unambiguously by its successful conversion to the oxetane **13** according to the Mio method.[7b] Thus, as shown in **Scheme 3**,

Scheme 2



reagents and conditions : a) H_2SO_4, Me_2CO, rt, 73% b) Ac_2O, DMSO, rt, 77% c) $NaBH_4$, EtOH, rt, 95% d) H_2SO_4, Me_2CO, rt, 73% e) BnCl, $BnEt_3NCl$, aq. NaOH, 100°C, 92% f) TfOH, BnOH, rt, 74% for **10**, 71% for **12** or MsOH, BnOH, rt, 66% for **10** , 41% for **12** g) p-TsOH, MeOH, rt, 86% h) BnCl, KOH, 130°C, 100% i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, 100% j) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-butene, ^tBuOH-H_2O, rt, 100% k) $ClCO_2{}^iPr$, Et_3N, THF, 0°C; NH_3(gas), rt, 92% for **15** from **14** , 85% for **20** from **19** l) $(COCl)_2$, $Cl(CH_2)_2Cl$, 80°C; NH_3(gas), rt, 87% for **16**, 87% for **21** m) HCl, ^iPrOH, 90°C, 99%

Scheme 3



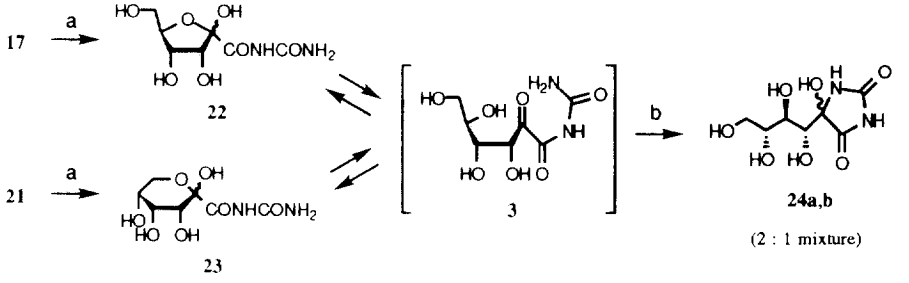
reagents and conditions : a) MsCl, CH_2Cl_2, Et_3N, DMAP, rt, 100% b)1M HCl/THF (1/3), 50°C, 88% (based on the recovery of SM) c) $NaN(TMS)_2$, THF, 0°C, 84%

sequential mesylation of **10**, removal of the acetonide group, and oxetane ring formation cleanly produced **13**. The oxetane ring structure was confirmed by the coupling constant of 4.7 Hz between H_3 and H_4 in the 400MHz ^{1}H-NMR spectrum of **13**.[7b] Based on this chemical transformation, the C_2 hydroxymethyl and the C_3 hydroxy groups in **10** were assigned to have *cis* -configuration. This results appeared that benzyl alcohol attacks the C_2-position of **9** from the less hindered convex β-side of 3,4-isopropylidene-D-psicofuranose ring system.

As shown in **Scheme 2**, **10** was derived to carboxylic acid **14** by Swern oxidation followed by sodium chlorite oxidation[14] of the resulting aldehyde. For introducing a urea unit required for *N,O*-spiroketal formation, direct access to *N*-acylurea **16** from **14** was first examined. However, contrary to our expectation, all the attempts to directly acylate urea with the activated carboxylic acid derivatives of **14**[15] such as mixed anhydride, acid chloride, imidazolide, and so on, met with failure. These unsuccessful results presumably depend upon low nucleophilicity of urea as well as steric hindrance of the carbonyl group in **14**. However, success was eventually realized by the following stepwise reaction sequence. Thus, the mixed acid anhydride derived from **14** and isopropyl chloroformate was allowed to react with ammonia, yielding amide **15**. *In situ* generation of reactive *N*-acylisocyanate **18**[16] by treating **15** with oxalyl chloride followed by the reaction with ammonia, cleanly gave rise to **16** in 80 % overall yield from **14**. Acidic hydrolysis of the acetonide moiety in **16** afforded the protected D-ribofuranose **17**, the precursor to **22**, in a quantitative yield.

The protected D-ribopyranose **21**, the precursor to **23**, was also prepared from **8** which had been produced from **7** in three steps when the synthesis of **9** from **7** was examined (*vide supra*). Selective acidic hydrolysis of the 4,5-*O*-isopropylidene moiety in **8** followed by complete benzylation of the resulting triol provided tribenzyl ether **11**. By employing the same five-step sequence as utilized for preparing **16** from **9**; benzyl glycoside formation, Swern and sodium chlorite oxidation, and amide and urea formation, **11** was converted to **21** *via* **12**, **19**, and **20**. Taking into account the selective formation of **10** from **9**, the configuration at the anomeric position in **21** was tentatively assigned. These results are summarized in **Scheme 2**.

Scheme 4



reagents and conditions: a) H_2 (4atm), 10% Pd-C, EtOH, rt, 96% from **17**, 87% from **21**. b) H_2O, 80°C, 100% from a *ca.* 1 : 1 mixture of **22** and **23**

With completion of the synthesis of **17** and **21** carrying the requisite carbon frameworks and functional groups with correct stereochemistries at the C_2, C_3, and C_4 positions (hydantocidin numbering), we next examined debenzylation of **17** and **21** to obtain **22** and **23** which are synthetically equivalent to **3**. As shown in **Scheme 4**, hydrogenolysis of **17** over Pd-C was found to undergo complete deprotection, furnishing a *ca.* 1 : 1 mixture of **22** and **23** in 96 % yield.[17] Structural assignments of **22** and **23** were achieved by the ^{13}C-NMR spectrum of the mixture. While, at the beginning, the *N,O*-spiroketal formation was examined directly using the mixture of **22** and **23**, only a very low yield (less than 10 %) of the mixture of **1** and **2** could be obtained. After experimentation, we found that the mixture of **22** and **23** can be

isomerized to a *ca.* 2 : 1 mixture of the hydantoins, **24a** (major) and **24b** (minor), by simple thermal treatment. These hydantoins **24a,b** were anticipated to be usable as synthetic equivalents to **3**. On the other hand, **21** could be completely debenzylated under the same conditions as for **17**, producing the same mixture of **22** and **23** as obtained from **17**. The mixture of **22** and **23** thus obtained was also converted to the same mixture of **24a,b** by the thermal treatment. These observations obviously suggest that **22** and **23** initially produced from **17** and **21**, respectively, promptly undergo isomerization through **3**, producing an equilibrium mixture of **22** and **23**. Subsequent hydantoin ring formation occurs from **3** which intervenes between **22** and **23**, ultimately yielding thermodynamically most stable isomers **24a,b**. Although **24a,b** were able to be cleanly separated by HPLC, their absolute stereochemistries could not be determined by their spectral data.

With **24a,b** in hand, we next focused our attention to the crucial *N,O*-spiroketal formation of **24a,b** as shown in **Scheme 5**. At the outset, since Sankyo group had not isolated **2** from the fermentation broth, it was anticipated that **1** should be thermodynamically more stable than **2**. Accordingly, *N,O*-spiroketal formation of **24a,b** to **1** was expected to proceed in a highly stereoselective manner through the iminium intermediate **25** whose conformation might be restricted by the intramolecular hydrogen bonding, affording **1** as a sole product. However, this expectation turned out not to be the case. Moreover, it appeared that **1** is thermodynamically less stable than **2**.

Scheme 5

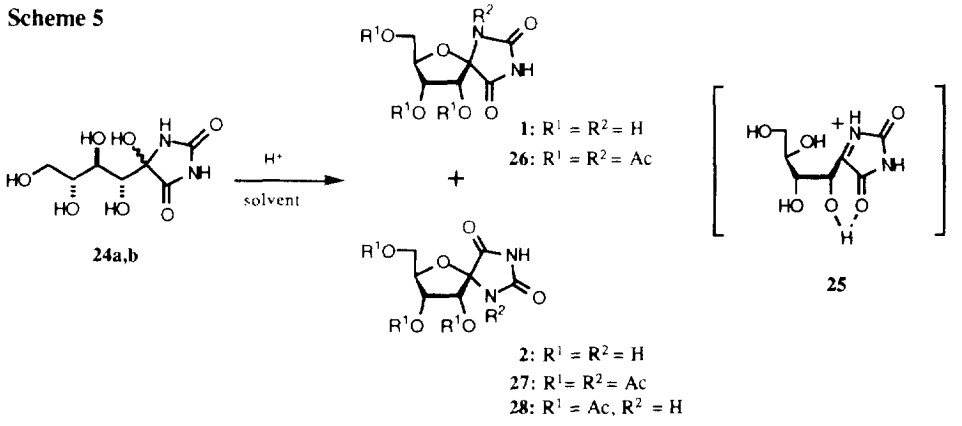


Table 1 summarized the results of cyclization of **24a,b** (*ca.* 2:1 mixture) under various conditions for 3.5h. The formation ratios of **1** to **2** were determined by HPLC analysis.[18] Although the *N,O*-spiroketal formation was not induced by using HCl, H_2SO_4, TsOH, CuI_2, and ZnI_2 as a catalyst (entries 1-5), trifluoroacetic acid (TFA) was found to undergo the reaction in 44 % yield (entry 6). Since good yields were obtained by employing ion-exchange resin (Dowex® 50W-X8 or Amberlist® 15, H^+ form) as a catalyst, we further pursued the *N, O*-spiroketal formation by uses of these catalysts (entries 7-21). Ultimately, it was found that mixtures of **1** and **2** can be produced in ratios of 17 : 83 ~ 36 : 64.[18] Higher reaction temperature yielded **1** with better selectivity (36 : 64) but in a lower isolation yield (56 %) (entry 14). The best result was obtained by subjecting **24a,b** to Dowex® 50W-X8 (H^+) in ^{n}PrOH/H_2O = 2/1 (v/v) at 45°C, giving rise to a

mixture of **1** and **2** in a ratio of 30 : 70 in 90% yield (entry 13). Spectroscopic properties (IR, ^{1}H-NMR, MS) of **1** and **2** separated by HPLC were identical with those of authentic samples.[1,7b]

The structures of **1** and **2** were definitely established by converting them to the corresponding tetraacetates **26** and **27**. Thus, treatments of **1** and **2** with Ac_2O-pyridine (1/2) in the presence of 4-dimethylaminopyridine (DMAP) (10 mol %) at room temperature for 1 and 12 h gave **26** and **27** in 89 % and 90 % yields, respectively. When acetylation of **2** was examined in the presence of a smaller amount of DMAP (3 mol %) and for a short period of time (1 h), triacetate **28** was found to be produced in 52 % yield in addition to **27** (46 % yield). On the other hand, the acetylation of **1** even performed at room temperature for 10 min in the absence of DMAP, cleanly afforded **26** as a sole product in 79 % yield and no formation of the triacetate corresponding to **28** was observed. The different behavior between **1** and **2** in acetylation might be explained by the steric hindrance of 3,4-diol moiety (hydantocidin numbering).

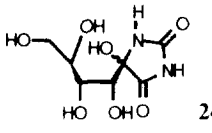
Table 1. Intramolecular *N,O*-Spiroketal formation of the Hydantoins **24a,b** (**24a/b** = *ca.* 2/1) to (+)-Hydantocidin (**1**) and (-)-5-*epi*-Hydantocidin (**2**) under Various Conditions

entry	solvent (v/v)	acidic catalyst	temp., °C	yield, %[a]	**1** : **2**[b]
1	MeOH	CuI_2	50	-[c]	-
2	MeOH	ZnI_2	50	-[c]	-
3	MeOH/H_2O = 2/1	HCl	40	-[c]	-
4	MeOH/H_2O = 2/1	H_2SO_4	40	NR	-
5	MeOH/H_2O = 2/1	TsOH	40	NR	-
6	CF_3CO_2H: H_2O = 2/1	CF_3CO_2H	25	44	21 : 79
7	MeOH/H_2O = 2/1	Dowex® 50W-X8	45	81	27 : 73
8	EtOH/H_2O = 2/1	Dowex® 50W-X8	45	88	28 : 72
9	MeCN/H_2O = 2/1	Dowex® 50W-X8	45	77	17 : 83
10	Dioxane/H_2O = 2/1	Dowex® 50W-X8	45	88	32 : 68
11	$MeNO_2$/H_2O = 2/1	Dowex® 50W-X8	45	82	18 : 82
12	^{i}PrOH/H_2O = 2/1	Dowex® 50W-X8	45	76	24 : 76
13	^{n}PrOH/H_2O = 2/1	Dowex® 50W-X8	45	90	30 : 70
14	^{n}PrOH/H_2O = 2/1	Dowex® 50W-X8	90	56	36 : 64
15	^{n}PrOH/H_2O = 2/1	Amberlist® 15	45	90	27 : 73
16	^{n}BuOH (H_2O saturated)	Dowex® 50W-X8	45	91	25 : 75
17	^{s}BuOH (H_2O saturated)	Dowex® 50W-X8	45	92	18 : 82
18	^{t}BuOH/H_2O = 2/1	Dowex® 50W-X8	45	79	18 : 82
19	^{n}PrOH	Dowex® 50W-X8	45	NR	-
20	H_2O	Dowex® 50W-X8	45	NR	-
21	H_2O	Dowex® 50W-X8	90	-[d]	-

a) Isolated yield. b) Determined by HPLC analysis.[18] c) Decomposition d) Unknown compound

Contrary to our initial expectation, **1** could not be produced in a high stereoselectivity from **24a,b**. This result obviously suggests that **2** might be thermodynamically more stable than **1**. In order to explore the stereoselectivity for *N,O*-spiroketal formation, the detailed studies were next carried out by employing separated **24a** and **24b**. These results were summarized in **Table 2**. Thus, a *ca.* 2 : 1 mixture of **24a,b** had afforded a 30 : 70 mixture of **1** and **2** when treated with Dowex® 50W-X8 in ^{n}PrOH/H_2O = 2/1 at 45°C for 3.5 h (entry 1). However, treatment of **24a** with Dowex® 50W-X8 in ^{n}PrOH/H_2O = 2/1 at 45°C for 30 min (47 % conversion) provided a mixture of **1** and **2** with 49 : 51 selectivity.[18] After 1.5 h (87% conversion),

Table 2. Intramolecular *N,O*-Spiroketal Formation of the Separated Hydantoins **24a** and **24b** in the Presence of Ion-Exchange Resin.



24a,b

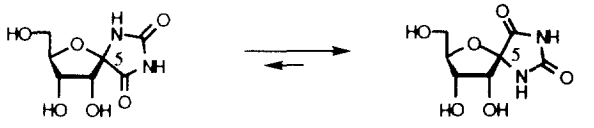
Dowex® 50W-X8
^{n}PrOH/H_2O = 2/1, 45°C

1 / 2

entry	starting material	reaction time, h	conversion, %[a]	**1** : **2**[a]
1	**24** (**24a/24b** = ca. 2/1)	3.5	100	30 : 70
2	**24a**	0.5	47	49 : 51
3	**24a**	1.0	76[b]	48 : 52
4	**24a**	1.5	87	43 : 57
5	**24b**	0.5	88	8 : 92
6	**24b**	1.0	95	9 : 91
7	**24b**	2.0	100	9 : 91

a) Determined by HPLC analysis.[18] b) **24a** was recovered in 20 % yield.

Table 3. Equilibrium between (+)-Hydantocidin (**1**) and (-)-5-*epi*-Hydantocidin (**2**) under the Acidic Condition.[a]



1 **2**

entry	starting material	reaction time, h	**1** : **2**[b]
1	**1**	6	51 : 49
2	**1**	12	8 : 92
3	**2**	6	4 : 96
4	**2**	28	9 : 91

a) Dowex® 50W-X8 in ^{n}PrOH/H_2O = 2/1 at 45°C. b) Determined by HPLC analysis.[18]

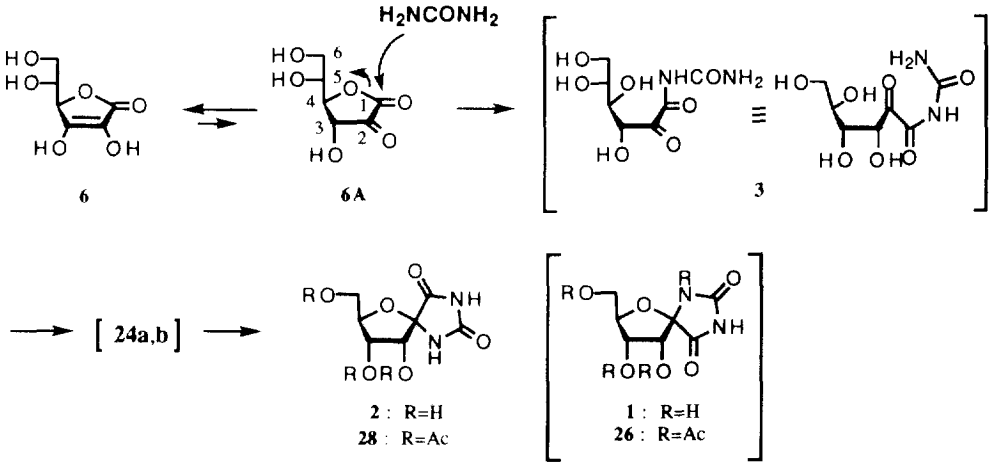
the ratio had changed to 43 : 57 (entries 2-4). In the case of 1 h reaction, **24a** was recovered in 20 % yield without isomerization to **24b** (entry 3). When **24b** was treated under the same conditions, the ratio of **1** to **2** was 8 : 92 after 30 min (95 % conversion) and no further change was observed for the ratio after 2 h (100 % conversion)(entries 6-7). These observations definitely indicate that **24a** provides a *ca.* 1 : 1 mixture of **1** and **2**, and that *N,O*-spiroketal formation of **24b** is faster than that of **24a**, providing **2** with a high selectivity.

It was clearly suggested by the experiments summarized in **Table 2** that **1** and **2** can readily epimerize under the same acidic conditions as employed for the *N,O*-spiroketal formation. Therefore, epimerization of separated **1** and **2** were examined by treating with Dowex® 50W-X8 at 45°C. Results summarized in **Table 3** show that the half time value ($t_{1/2}$) of epimerization of **1** to **2** is *ca.* 6 h and the equilibrium ratio of **1** to **2** can be estimated as *ca.* 1 : 10 in favor of **2**. Fleet *et al.* have also reported that **2** is thermodynamically more stable than **1** and the equilibrium ratio of **1** to **2** is *ca.* 1 : 4 in 80 % TFA at room temperature.[8] Considering the facts disclosed above, the results summarized in **Table 1** might be construed as a sum of the stereoselectivities of *N,O*-spiroketal formations of **24a** and **24b** and the thermal equilibrium between produced **1** and **2**.

2. *One-step* Synthesis of (-)-5-*epi*-Hydantocidin (2) from D-Isoascorbic Acid (6) and Urea

With completion of the synthesis of **1** and **2** based on the plausible biosynthetic pathway of **1**, we next examined the one-step synthesis of **1** and **2** starting from two simple building blocks, **6** and urea, as shown in **Scheme 6**. It was envisioned that nucleophilic addition of urea to the reactive C_1 carbonyl group in **6A** being one of the four possible tautomers of **6**,[19] prompts cleavage of the lactone ring, leading to **3**. Subsequent *N,O*-spiroketal formation of **24a,b** which can be produced from **3** in the reaction mixture, gives rise to **1** and **2** in a similar fashion to that of the previous stepwise synthesis.

Scheme 6

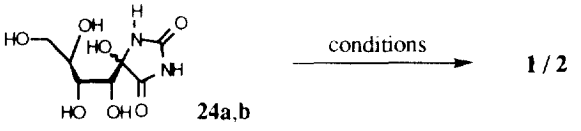


Thus, a stirred mixture of **6** and urea was heated at 130°C for 3.5 h without any solvent, and the resulting dark brown caramel was treated with Dowex® 50W-X8 in $^{n}PrOH/H_2O$=2/1. After purification by

ODS column chromatography, acetylation, and further purification by silica gel column chromatography, **28** was isolated in 0.21 % yield as the sole product to be identified. Any amounts of **26** excepted to be obtainable from **1** were not isolated. The reaction performed at 100° for 3.5 h or at 130°C for 2 h gave no trace amounts of **26** and/or **28** after acetylation and separation. The yields of **28** obtained after the prolonged reaction time at 130°C are as follows: 0.04 % (3 h), 0.07 % (4 h), 0.05 % (4.5 h). When the reaction was performed by using a solvent such as water, *N*,*N*-dimethylformamide (DMF), or dimethylsulfoxide (DMSO), and/or by employing Molecular Sieves, $MgSO_4$, *p*-TsOH, H_2SO_4, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), DMAP as an additive, none of **1** and/or **2** were detected in the reaction mixture.

Unsuccessful isolation of **1** completely differs from the previous stepwise synthesis affording the mixture of **1** and **2** (30 : 70, see **Table 1**, entry 13). With an aim to explore the reason why **26** could not be isolated from the one-step synthesis, studies on the *N*,*O*-spiroketal formation were carried out employing separated **24a,b** under two thermal conditions (A and B). The obtained results were shown in **Table 4** along with the previous ones (condition C). Thus, treatment of the mixture of **24a,b** at 130°C (condition A) for 3.5 h (73 % conversion) provided a mixture of **1** and **2** in a ratio of 12 : 88 (entry 1). When the mixture of **24a,b** was heated at 130°C in the presence of **6** (1 equiv.) (condition B) for 3.5 h, a 14 : 86 ratio of **1** to **2** was also obtained with increased conversion (93 %)(entry 2). Treatment of separated **24a** under the condition A formed **2** with 10 : 90 selectivity and separated **24b** also provide **2** with 13 : 87 selectivity (entries 4 and 8). In the presence of **6** (condition B), the reactions proceeded more smoothly and the conversion yields

Table 4. Intramolecular *N*,*O*-Spiroketal Formation of the Hydantoins **24a**, **b** in the Presence or Absence of D-Isoascorbic Acid (**6**).



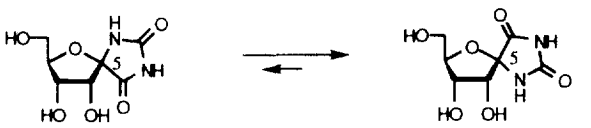
24a,b

entry	substrate	conditions[a]	reaction time, h	conversion, %[b]	**1** : **2**[b]
1	**24** (**24a**/**24b** = 2/1)	A	3.5	73	12 : 88
2	**24** (**24a**/**24b** = 2/1)	B	3.5	93	14 : 86
3	**24** (**24a**/**24b** = 2/1)	C	3.5	100	30 : 70
4	**24a**	A	3.5	85	10 : 90
5	**24a**	B	3.5	91	15 : 85
6	**24a**	C	0.5	47	49 : 51
7	**24a**	C	1.5	87	43 : 57
8	**24b**	A	3.5	62	13 : 87
9	**24b**	B	3.5	94	8 : 92
10	**24b**	C	0.5	95	8 : 92
11	**24b**	C	2.0	100	9 : 91

a) Condition A: heating at 130°C without solvent. Condition B: heating at 130°C in the presence of **6** (1 equiv.) without solvent. Condition C: Dowex® 50W-X8 in ^{n}PrOH/H_2O = 2/1 at 45°C. b) Determined by HPLC analysis.[18]

increased up to over 90 % with the selectivities similar to those obtained under the condition A (entries 5 and 9). These observations obviously suggest that *N,O*-spiroketal formation of **24a** and **24b** under the conditions A and B may take place through different reaction mechanisms from that proposed for the condition C. Thus, under the condition C, **24a** provided a 1 : 1 mixture of **1** and **2** (entry 6), whereas **24b** gave **2** with a high selectivity (entry 10). On the other hand, the conditions A and B under which the *N,O*-spiroketal formation was examined at 130°C, resulted in the formation of thermodynamically more stable **2** from the both starting materials (**24a,b**) with high selectivity .

Table 5. Equilibrium between (+)-Hydantocidin (**1**) and (-)-5-*epi*-Hydantocidin (**2**) in the Presence or Absence of D-Isoascorbic Acid (**6**).



1 **2**

entry	substrate	conditions[a]	time, h	**1** : **2**[b]
1	**1**	A	3.5	100 : 0
2	**1**	B	3	49 : 51
3	**1**	B	6	52 : 48
4	**1**	C	6	51 : 49
5	**1**	C	12	8 : 92
6	**2**	A	3.5	0 : 100
7	**2**	B	1.5	8 : 92
8	**2**	B	3	9 : 91
9	**2**	C	6	4 : 96
10	**2**	C	28	9 : 91

a) Condition A: heating at 130°C without solvent. Condition B: heating at 130°C in the presence of **6** (1 equiv.) without solvent. Condition C: Dowex® 50W-X8 in ^{n}PrOH/H_2O = 2/1 at 45°C. b) Determined by HPLC analysis.[18]

Next, equilibrium between **1** and **2** was also studied under the conditions A, B and C. Although both **1** and **2** underwent no epimerization by simple heating (condition A)(**Table 5**, entries 1 and 6), the epimerization of **1** readily took place in the presence of **6** (1 equiv.)(condition B), giving **2** in 49 : 51 ratio after 3 h and no further change of the ratio was observed after 6 h (entries 2 and 3). Under the same conditions, more thermodynamically stable **2** also epimerized to a mixture of **1** and **2** in 9 : 91 ratio after 3 h (entries 7 and 8).

On the basis of these observations, no isolation of **26** obtainable from **1** in the one-step synthesis might be explained by the very low yield of **1** (less than 0.02 %) provided by the *N,O*-spiroketal formation

more selectively producing **2** and/or the rapid epimerization of **1** to **2** in the presence of a large excess amount of **6**.

Conclusion

We have succeeded in developing novel synthetic schemes to **1** and **2** based on the proposed biosynthetic pathway of **1**. The former stepwise route starting with **7** might be fairly efficient due to uses of inexpensive and less toxic reagents. Although the latter one-step synthesis utilizing **6** and urea as starting materials is of interest in light of its directness, it obviously lacks practicality due to the very low chemical yield and selective formation of **2**. Our successful synthesis of **1** and/or **2** clearly suggests feasibility of the proposed biosynthetic pathway in which **1** might be produced *in vivo* from a hexose derivative and urea.

Experimental

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz ^{1}H , 100 MHz ^{13}C) spectrometer in deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) or deuterowater (D_2O) with either tetramethylsilane (TMS) (0.00 ppm ^{1}H, 0.00 ppm ^{13}C) or chloroform (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as an internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated [br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), exch (exchangeable)]; coupling constants, *J*, are reported (Hz); integration is provided, and assignment is indicated. Infrared spectra were measured with a Jasco A-202 and a Jasco FT/R-5300 spectrometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium 40-67%), w (weak 20-40%), and br (broad). Low and high resolution Electron Impact (EIMS) and Secondary Ion mass spectra (SIMS) were taken with a Hitachi M-80A or a Hitachi M-80B spectrometer with ionization voltages of 70 and 15 eV. Chemical ionization mass spectra (CIMS) were recorded with isobutane as an ionization mass. Data are reported in the form of *m/e* (intensity relative to base = 100). Measurements of optical rotations were carried out with a Horiba Sepa-200 digital polarimeter and rotation values are reported as follows: $[\alpha]_{wavelength}^{temperature}$, (concentration in g/100 mL, solvent). Analytical thin-layer chromatography was performed using Merck silica gel plates with F-254 indicator. Column chromatography was performed with indicated solvents on Merck silica gel 60 (230-400 mesh ASTM). Visualization was accomplished by UV light, iodine, $KMnO_4$, *para*-anisaldehyde or pancardi solution. Analytical high-pressure liquid chromatography (HPLC) was performed on a Toso HLC-803 liquid chromatograph with a Shimazu SPD-1 spectrophotometric detector. The column used was Asahipak® Hikarisil C-18 and the detector wavelength was 210 nm. Retention times (t_R)and integrated ratios were obtained from a Shimazu C-R3A recorder. Melting points (mp) were determined on a Yanaco MP-21 micro melting point apparatus and are uncorrected.

Benzyl 6-*O*-benzyl-3,4-*O*-isopropylidene-β-D-psicofuranoside (10)

a) Preparation using TfOH: A solution of **9**[7b, 12] (350 mg, 1.0 mmol) and TfOH (5 μL, 57 μmol) in benzyl alcohol (3.5 mL) were stirred at 0°C for 2 h. The reaction was quenched with aqueous NH_4OH solution (1 mL) at the same temperature. The mixture was concentrated *in vacuo* to remove excess benzyl alcohol. The residue was purified by silica gel column chromatography (hexane/EtOAc, 4/1) to afford **10** as a white solid (294 mg, 74 %). An analytical sample was obtained as colorless needles by recrystallization from hexane/EtOAc: mp 83-84°C; $[\alpha]_D^{20}$ = -29.8° (c = 1.55, $CHCl_3$); ^{1}H-NMR (400 MHz) 7.36-7.25 (10 H, m, HC(Ar)), 4.72 (1 H, dd, *J* = 1.4, 6.1, HC(4)), 4.68 (1 H, d, *J* = 6.1, HC(3)), 4.61 (1 H, d, *J* = 11.8, CH_2Ph), 4.54 (1 H, d, *J* = 11.8, CH_2Ph), 4.49 (1 H, d, *J* = 12.1, CH_2Ph), 4.44 (1 H, d, *J* = 12.1, CH_2Ph), 4.42 (1 H, ddd, *J* = 1.4, 7.1, 7.4, HC(5)), 3.91 (1 H, br d, *J* = 12.2, HC(1)), 3.85 (1 H, br d, *J* = 12.2, HC(1)), 3.52 (1 H, dd, *J* = 7.1, 9.6, HC(6)), 3.47 (1 H, dd, *J* = 7.3, 9.6, HC(6)), 1.95 (1 H, br s, OH), 1.53 (3 H, s, Me), 1.33 (3 H, s, Me); ^{13}C-NMR (100 MHz) 137.9, 137.6, 128.4 (x2), 127.72, 127.70, 127.5, 127.3, 113.0, 110.3, 85.5, 85.1, 82.3, 73.2, 70.6, 63.2, 59.7, 26.3, 24.8; IR (KBr) 3350 (m), 2950 (m), 1500 (m), 1455 (m), 1385 (m), 1375 (m) 1215 (s), 1080 (s), 1040 (s), 910 (m), 870 (s), 730 (s), 700 (s); MS (15 eV) 370 (1), 369 (M^+-CH_2OH, 4.5), 293 (5), 277 (2), 251 (2), 189 (2), 181 (10), 127 (3), 91 (100); HRMS. Calcd for $C_{22}H_{25}O_5$ (369.1700): Found: 369.1679; Anal. Calcd for $C_{23}H_{28}O_6$ (400.47): C, 68.98; H, 7.05. Found: C, 68.84; H, 7.09.

b) Preparation using MsOH: A solution of **9** (350 mg, 1.0 mmol) and MsOH (32 μL, 0.50 mmol) in benzyl alcohol (3.5 mL) was stirred at 0°C for 2 h. Treatment of the reaction mixture in the same manner as described in a) gave **10** as a white solid (263 mg, 66 %) after purification by silica gel column chromatography (hexane/EtOAc, 4/1). The ^{1}H-NMR spectrum of this sample was identical with that described in a).

Benzyl 6-*O*-benzyl-1,3-anhydro-β-D-psicofuranoside (13)

Trifluoromethanesulfonyl chloride (45 μL, 0.59 mmol) and DMAP (1.2 mg, 2 mol %) were added to a solution of **10** (196 mg, 0.49 mmol) and Et_3N (0.20 mL, 0.59 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After stirring for 30 min, the reaction was quenched with H_2O (3 mL) and the mixture was extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (50 mL) dried (Na_2SO_4), then filtered. Concentration of the filtrate *in vacuo* followed by purification by silica gel column chromatography (hexane/EtOAc, 4/1) afforded the mesylate as a colorless oil (234 mg, 100 %): ^{1}H-NMR (200 MHz) 7.38-7.20

(10 H, m, HC(Ar)), 4.72 (1 H, dd, J = 1.5, 6.0, HC(4)), 4.64 (1 H, d, J = 6.0, HC(3)), 4.63 (1 H, d, J = 11.5, CH_2Ph), 4.62 (1 H, d, J = 11.5, CH_2Ph), 4.57 (1 H, d, J = 10.9, CH_2Ph), 4.50 (1 H, d, J = 12.1, HC(1)), 4.47 (1 H, d, J = 12.1, HC(1)), 4.44-4.37 (1 H, m, HC(5)), 4.38 (1 H, d, J = 10.9, CH_2Ph), 3.51 (1 H, dd, J = 7.2, 9.6, HC(6)), 3.43 (1 H, dd, J = 7.3, 9.6, HC(6)), 3.02 (3 H, s, SO_3Me), 1.52 (3 H, s, Me), 1.32 (3H, s, Me); IR (neat) 3000 (m), 2875 (m), 2840 (m), 1500 (w), 1460 (m), 1365 (s), 1245 (s), 1220 (s), 1180 (s), 1090 (s), 1015 (s), 985 (s), 875 (m), 830 (s), 725 (s), 705 (s); MS (CI) 478 (M^+), 463 (M^+-15); MS (70 eV) 463 (M^+-15, 0.4), 371 (M^+-107, 1), 281 (0.4), 261 (0.5), 181 (1.2), 149 (3), 127 (5), 91 (100), 69 (11).

A solution of the mesylate (64 mg, 0.13 mmol) in THF/1M HCl (3/1) (2 ml) was stirred for 12 h at 50°C. The reaction was quenched by adding of powdered $NaHCO_3$, and the mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (10 mL) and H_2O (10 mL). The separated aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1/1) to afford the starting mesylate as a colorless oil (29 mg, 45 % recovery) from the first fraction and the diol as a colorless solid [28 mg, 48 %(88% corrected for the recovery of the starting mesylate)] from the second fraction: mp 90-91°C (hexane/EtOAc); ^{1}H-NMR (200 MHz) 7.38-7.21 (10 H, m, HC(Ar)), 4.66 (1 H, d, J = 11.1, CH_2Ph), 4.58 (1 H, d, J = 11.7, HC(1)), 4.55 (2 H, s, CH_2Ph), 4.50 (1 H, d, J = 11.1, CH_2Ph), 4.41 (1 H, d, J = 11.7, HC(1)), 4.41 (1 H, ddd, J = 4.8, 7.9, 8.4, HC(4)), 4.16 (1 H, ddd, J = 3.8, 6.0, 8.4, HC(5)), 4.11 (1 H, dd, J = 3.5, 4.7, HC(3)), 3.65 (1 H, dd, J = 3.8, 10.2, HC(6)), 3.51 (1 H, dd, J = 6.1, 10.2, HC(6)), 3.48 (3 H, d, J = 3.5, OH), 3.03 (3 H, s, SO_3Me), 2.57 (1H, d, J =8.4, OH); IR (KBr) 3370 (s), 3040 (m), 2950 (m), 1740 (w), 1500 (w), 1460 (m), 1340 (s), 1230 (s), 1170 (s), 1125 (s), 1070 (s), 1050 (s), 975 (s), 905 (w), 850 (w), 830 (m), 785 (w), 745 (m), 700 (m); MS (10 eV) 421 (M^+-17, 0.3), 331 (M^+-OBn, 35), 313 (3), 251 (7), 235 (81), 217 (18), 181 (65), 145 (45), 133 (20), 107 (29), 91 (100).

A solution of $NaN(TMS)_2$ (1.0 M solution in THF, 0.27 mL, 0.27 mmol) was added to a solution of the diol (53 mg, 0.12 mmol) in THF (2 mL) at 0 °C. After stirring for 60 min at 0 °C, the reaction was quenched with sat. aqueous NH_4Cl solution (3 mL) and the mixture was extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), then filtered. Concentration of the filtrate *in vacuo* followed by purification by silica gel column chromatography (hexane/EtOAc, 1/1) gave **13** as a colorless oil (35 mg, 84 %): ^{1}H-NMR (400 MHz) 7.39-7.27 (10 H, m, HC(Ar)), 4.90 (1 H, d, J = 7.4, HC(1)), 4.84 (1 H, d, J = 4.7, HC(3)), 4.69 (1 H, d, J = 11.7, CH_2Ph), 4.65 (2 H, s, CH_2Ph), 4.59 (1 H, d, J = 7.4, HC(1)), 4.50 (1 H, d, J = 11.7, CH_2Ph), 4.16 (1 H, ddd, J = 2.7, 5.2, 7.9, HC(5)), 3.93 (1 H, ddd, J = 4.7, 7.9, 10.5, HC(4)), 3.93 (1 H, dd, J = 2.7, 10.8, HC(6)), 3.78 (1 H, dd, J = 5.2, 10.8, HC(6)), 2.27 (1 H, d, J = 10.5, OH); ^{13}C-NMR (100 MHz) 137.9, 136.8, 128.4 (x 4), 128.0 (x 2), 127.7 (x 4), 104.4 (C(2)), 88.1 (C(5)), 82.0 (C(1)), 81.9 (C(3)), 73.6 (OCH_2Ph), 71.2 (C(4)), 69.2 (C(6)), 66.6 (OCH_2Ph); IR (neat) 3450 (m), 2960 (m), 2895 (m), 1500 (w), 1460 (w), 1340 (s), 1340 (s), 1265 (m), 1230 (w), 1090 (m), 1165 (m), 1110 (s), 1060 (s), 1050 (m), 960 (m), 940 (m), 860 (w), 740 (m), 700 (m); MS (70 eV) 251 (M^+-Bn, 1.5), 221 (0.5), 181 (0.3), 145 (1.4), 104 (7), 91 (100), 65 (8); MS (CI) 343 (MH^+), 325 (MH^+-18), 313 (MH^+-OCH_2).

Benzyl 5-*O*-benzyl-1-carboxyl-1-dehydro-2, 3-*O*-isopropylidene-β-D-ribofuranoside (14)

A solution of **10** (27.9 g, 70 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $(COCl)_2$ (15.2 mL, 0.17 mol) and DMSO (24.7 mL, 0.35 mol) in CH_2Cl_2 (150 mL) at -78°C. After stirring for 20 min at -78°C, Et_3N (67.9 mL, 488 mmol) was added to the mixture. The reaction mixture was warmed to room temperature over 45 min, and the reaction was quenched by adding sat. aqueous $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine (500 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*, affording the crude aldehyde as a pale yellow oil (28.0 g, 100 %): ^{1}H-NMR (400 MHz) 9.52 (1 H, s, HC(1)), 7.40-7.21 (10 H, m, HC(Ar)), 4.84 (1 H, d, J = 5.8, HC(3)), 4.77 (1 H, dd, J = 1.2, 5.8, HC(4)), 4.67 (1 H, ddd, J = 1.2, 6.9, 7.5, HC(5)), 4.53 (1 H, d, J = 12.4, CH_2Ph), 4.50 (1 H, d, J = 11.1, CH_2Ph), 4.48 (1 H, d, J = 12.4, CH_2Ph), 4.38 (1 H, d, J = 11.1, CH_2Ph), 3.59 (1 H, dd, J = 6.7, 9.7, HC(6)), 3.49 (1 H, dd, J = 7.5, 9.7, HC(6)), 1.47 (3 H, s, Me), 1.28 (3 H, s, Me); IR (neat) 3100 (w), 2995 (w), 2875 (m), 2820 (m), 1742 (s), 1492 (w), 1375 (m), 1315 (w), 1275 (w), 1205 (m), 1155 (s), 1070 (s), 865 (m), 740 (s), 695 (s); MS (70 eV) 383 (M^+-15, 0.5), 369 (M^+-29, 2), 292 (0.8), 189 (2), 81 (8), 149 (3), 138 (1), 105 (3), 91 (100).

Sodium chlorite (25.3 g, 0.28 mol) was slowly added to a solution of the aldehyde (28.0 g, 70 mol), 2-methyl-2-butene (36.9 mL, 0.35 mol), and NaH_2PO_4-H_2O (43.6 g, 0.28 mol) in a mixture of t-BuOH (300 mL) and H_2O (90 mL). After stirring for 60 min at room temperature, the mixture was concentrated *in vacuo* to a half of the original volume, and the residual solution was extracted with Et_2O (4 x 150 mL). The combined organic layers were washed with 2 % HCl solution (500 mL) and brine (500 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*, giving **14** as a white solid (28.9 g, 100 % from **10**): ^{1}H-NMR (400 MHz, CD_3OD) 7.38-7.25 (10 H, m, HC(Ar)), 4.92-4.40 (7 H, m, HC(2), HC(3), HC(4), 2xCH_2Ph), 3.62-3.55 (1 H, br s, HC(5)), 3.55-3.47 (1 H, br s, HC(5)), 1.50 (3 H, s, Me), 1.33 (3 H, s, Me); IR (KBr) 3450 (br, m), 2940 (m), 2860 (m), 1725 (w), 1640 (s), 1500 (w), 145 (m), 1410 (m), 1380 (m), 1280 (m), 1250 (m), 1210 (m), 1165 (m), 1110 (s), 1090 (s), 1070 (s), 1025 (s), 865 (m), 778 (w), 740 (m), 700 (s); MS (15 eV) 369 (M^+-45, 10), 368 (21), 308 (5), 159 (21), 91 (100).

Benzyl 5-*O*-benzyl-1-carbamoyl-1-dehydro-2, 3-*O*-isopropylidene-β-D-ribofuranoside (15)

Isopropyl chloroformate (24.4 mL, 0.21 mol) was added to a solution of **14** (28.9 g, 0.70 mol) and Et_3N (38.8 mL, 0.28 mol) in THF (350 mL) at 0°C. The mixture was warmed to room temperature and the stirring was continued until the reaction was over (30 min). After passing NH_3 (gas) for 30 min, the mixture was concentrated *in vacuo* to a half of the original volume. The residual solution was extracted with CH_2Cl_2 (4 x 150 mL), and the combined organic layers were washed with brine (500 mL), dried (Na_2SO_4), then filtered. Concentration of the filtrate *in vacuo* followed by purification by silica gel column chromatography (hexane/EtOAc, 1/1) afforded **15** as a white solid (26.5 g, 92 %). An analytical sample was obtained as colorless prisms by

recrystallization from hexane/EtOAc: mp 142-143°C; $[\alpha]_D^{20}$ = -37.4° (c = 1.23, $CHCl_3$); ^{1}H-NMR (400 MHz) 7.36-7.26 (10 H, m, HC(Ar)), 6.73 (1 H, br s, NH), 4.83 (1 H, d, *J* = 5.8, HC(3)), 4.68 (1 H, dd, *J* = 1.2, 5.8, HC(4)), 4.56 (1 H, ddd, *J* = 1.2, 7.0, 7.7, HC(5)), 4.54 (1 H, d, *J* = 10.7, CH_2Ph), 4.50 (1 H, d, *J* = 12.0, CH_2Ph), 4.48 (1 H, d, *J* = 10.7, CH_2Ph), 4.43 (1 H, d, *J* = 12.0, CH_2Ph), 3.55 (1 H, dd, *J* = 7.7, 9.7, HC(6)), 3.48 (1 H, dd, *J* = 7.0, 9.7, HC(6)), 1.49 (3 H, s, Me), 1.29 (3 H, s, Me); ^{13}C-NMR (100 MHz) 168.7 (C(1)), 137.4, 136.9, 128.4, 128.3 (x2), 127.9 (x2), 127.82, 127.78 (x2), 127.70, 113.0, 109.6 (C(2)), 86.3 (C(3)), 86.0 (C(5)), 81.7 (C(4)), 73.3 (CH_2Ph), 70.4 (C(6)), 65.8 (CH_2Ph), 26.2, 24.5; IR (KBr) 3480 (m), 3260 (m), 2970 (m), 1720 (m), 1695 (s), 1455 (m), 1390 (m), 1380 (m), 1250 (m) 1220 (m), 1165 (m), 1110 (s), 1080 (s), 1050 (m), 875 (m), 760 (m), 740 (m), 700 (m); MS (CI) 414 (MH^+); MS (15 eV) 398 (M^+-15, 1.2), 369 (M^+-$CONH_2$, 3.5), 307 (20), 249 (1), 216 (1), 181 (14), 158 (3), 143 (7.5), 128 (7.5), 107 (1), 91 (100); HRMS. Calcd for $C_{22}H_{24}NO_6$ (398.1602): Found: 398.1602; Anal. Calcd for $C_{23}H_{27}NO_6$ (413.47): C, 66.81; H, 6.58; N, 3.39. Found: C, 66.77; H, 6.57; N, 3.33.

Benzyl 1-allophanoyl-5-*O*-benzyl-1-dehydro-2, 3-*O*-isopropylidene-β-D-ribofuranoside (16)

A mixture of $(COCl)_2$ (7.3 mL, 84 mmol) and **15** (17.3 g, 42 mmol) in CH_2Cl_2 (500 mL) were stirred for 30 min at room temperature, then for 2h at 90°C. After cooling to room temperature, NH_3 (gas) was induced to the mixture. The mixture was partitioned between CH_2Cl_2 (200 mL) and water (200 mL). The separated aqueous phase was further extracted with CH_2Cl_2 (3 x 500 mL). The combined organic layers were washed with brine (500 mL), dried (Na_2SO_4), filtered, then concentration *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1/1) giving **16** as a white solid (16.6 g, 87 %). An analytical sample was obtained as colorless prisms by recrystallization from hexane/EtOAc: mp 112-113°C; $[\alpha]_D^{20}$ = -68.1° (c = 1.06, $CHCl_3$); ^{1}H-NMR (400 MHz) 8.64 (1 H, br s, NH), 8.05 (1 H, br s, NH), 7.36-7.26 (10 H, m, HC(Ar)), 5.39 (1 H, br s, NH), 4.81 (1 H, d, *J* = 5.8, HC(3)), 4.72 (1 H, dd, *J* = 1.0, 5.8, HC(4)), 4.63 (1 H, ddd, *J* = 1.0, 7.2, 7.3, HC(5)), 4.54 (1 H, d, *J* = 10.8, CH_2Ph), 4.51 (1 H, d, *J* = 12.0, CH_2Ph), 4.46 (1 H, d, *J* = 12.0, CH_2Ph), 4.38 (1 H, d, *J* = 10.8, CH_2Ph), 3.56 (1 H, dd, *J* = 7.3, 9.8, HC(6)), 3.48 (1 H, dd, *J* = 7.2, 9.8, HC(6)), 1.46 (3 H, s, Me), 1.27 (3 H, s, Me); ^{13}C-NMR (100 MHz) 167.8 (C(1)), 152.5 ($NHCONH_2$), 137.4, 136.3, 128.52 (x 2), 128.45 (x 2), 128.08, 128.05 (x 2), 128.0, 127.8 (x 2), 113.4, 109.6 (C(2)), 86.8 (C(3)), 86.4 (C(5)), 81.7 (C(4)), 73.4 (CH_2Ph), 69.9 (C(6)), 66.5 (CH_2Ph), 26.0, 24.3; IR (KBr) 3450 (m), 3050 (w), 2950 (m), 2890 (w), 1725 (s), 1580 (m), 1480 (m), 1460 (m), 1385 (m), 1380 (m), 1280 (w) 1245 (w), 1220 (m), 1165 (m), 1095 (s), 1055 (m), 1030 (w). 870 (m), 760 (s), 700 (m); MS (CI) 457 (MH^+); MS (15 eV) 441 (M^+-15, 0.3), 398 (0.3), 369 (M^+-$CONHCONH_2$, 2), 350 (M^+-OBn, 4), 307 (5), 181 (7), 128 (3), 91 (100); HRMS. Calcd for $C_{23}H_{25}N_2O_7$ (441.1660): Found: 441.1661; Anal. Calcd for $C_{24}H_{28}N_2O_7$ (456.53): C, 63.14; H, 6.18; N, 6.14. Found: C, 62.95; H, 6.13; N, 5.93.

Benzyl 1-allophanoyl-5-*O*-benzyl-1-dehydro-β-D-ribofuranoside (17)

Aqueous 12% HCl solution (90 μL) was added to a solution of **16** (105 mg, 0.23 mmol) in ^{i}PrOH (3 mL), and the mixture was stirred at 90°C for 1.5 h. The reaction was quenched with sat. aqueous NH_4OH solution (1 mL) at the same temperature. Concentration of the mixture *in vacuo* afforded **17** as a colorless solid (95.4 mg, 99 %). An analytical sample was obtained as colorless prisms by recrystallization from EtOH: mp 157-158°C; $[\alpha]_D^{20}$ = -40.7° (c = 0.67, MeOH/$CHCl_3$ = 1/1); ^{1}H-NMR (400 MHz) 7.38-7.19 (10 H, m, HC(Ar)), 4.60 (1 H, d, *J* = 11.9, CH_2Ph), 4.59 (1 H, d, *J* = 10.8, CH_2Ph), 4.56 (1 H, d, *J* = 11.9, CH_2Ph), 4.38 (1 H, ddd, *J* = 2.3, 5.9, 8.3, HC(5)), 4.32 (1 H, dd, *J* = 4.2, 8.3, HC(4)), 4.25 (1 H, d, *J* = 10.8, CH_2Ph), 4.09 (1 H, d, *J* = 4.2, HC(3)), 3.80 (1 H, dd, *J* = 2.3, 10.8, HC(6)), 3.57 (1 H, dd, *J* = 5.9, 10.8, HC(6)); ^{13}C-NMR (100 MHz) 169.2 (C(1)), 153.6 ($NHCONH_2$), 137.5, 136.7, 127.6 (x 2), 127.4 (x 2), 127.3 (x 2), 127.2 (x 2), 126.92, 126.86, 107.6 (C(2)), 83.0 (C(5)), 75.9 (C(3)), 72.5 (C(4)), 70.4 (CH_2Ph), 69.8 (C(6)), 65.0 (CH_2Ph); IR (KBr) 3440 (m), 3370 (s), 2955 (w), 1730 (m), 1685 (s), 1610 (m), 1460 (m), 1420 (m), 1240 (w), 1130 (m), 1100 (m), 1060 (m), 945 (m), 920 (w), 740 (m), 700 (m); MS (CI) 417 (MH^+); MS (70 eV) 329 (M^+-$CONHCONH_2$, 1.6), 293 (6), 267 (2.5), 249 (2), 237 (1), 181 (11), 149 (3), 128 (1.3), 107 (3), 92 (12), 91 (100); HRMS. Calcd for $C_{19}H_{21}O_5$ (329.1388): Found: 329.1414; Anal. Calcd for $C_{21}H_{24}N_2O_7$ (416.43): C, 60.57; H, 5.81; N, 6.73. Found: C, 60.51; H, 5.72; N, 6.56.

3, 4, 5-Tri-*O*-benzyl-1, 2-*O*-isopropylidene-β-D-psicopyranose (11)

P-Toluenesulfonic acid (294 mg, 1.6 mmol) was added to a solution of **8**[7b, 12] (8.03g, 31 mmol) in MeOH (20 mL), and the mixture was stirred at room temperature for 1 h. The reaction was quenched with a sat. aqueous NH_4OH solution (2 mL) at the same temperature. Filtration of the precipitates gave the triol as a white solid (5.83 g, 86 %): mp 174-176°C; $[\alpha]_D^{20}$ = -111° (c = 0.83, H_2O); ^{1}H-NMR (400 MHz, D_2O) 4.17 (1 H, d, *J* = 9.9, HC(6)), 4.13 (1 H, d, *J* = 9.9, HC(6)), 3.99-3.92 (3 H, m), 3.85-3.78 (2 H, m), 1.52 (3 H, s, Me), 1.42 (3 H, s, Me); IR (neat) 3430 (m), 3330 (m), 2960 (m), 2950 (m), 2900 (m), 2550 (s), 2480 (m), 1460 (m), 1390 (m), 1375 (w), 1270 (m), 1255 (m), 1225 (m), 1200 (m), 1140 (m), 1090 (s), 1075 (s), 1050 (s), 1020 (m), 970 (m), 940 (m), 862 (s), 825 (w), 800 (w), 750 (m); Anal. Calcd for $C_9H_{16}O_6$ (456.53): C, 48.82; H, 7.18. Found: C, 49.09; H, 7.32.

A mixture of the triol (1.90 g, 8.6 mmol), benzyl chloride (16 mL, 16 mmol), and KOH (9.25 g, 17 mmol) was heated at 130°C for 3 h. After cooling to room temperature, the mixture was partitioned between $CHCl_3$ (50 mL) and brine (50 mL). The separated aqueous layer was further extracted with $CHCl_3$ (3 x 50 mL). The combined organic phases were washed with water (150 mL) and brine (150 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (hexane/EtOAc, 19/1 to 3/1) afforded **11** as a colorless oil (4.23 g, 100 %): $[\alpha]_D^{20}$ = +1.0° (c = 7.78, $CHCl_3$); ^{1}H-NMR (400 MHz) 7.39-7.26 (15 H, m, HC(Ar)), 4.82 (1 H, d, *J* = 11.9, CH_2Ph), 4.79 (1 H, d, *J* = 12.0, CH_2Ph), 4.75 (1 H, d, *J* = 12.0, CH_2Ph), 4.68 (1 H, d, *J* = 11.9, CH_2Ph), 4.52 (2 H, s, CH_2Ph), 4.21 (1 H, d, *J* = 9.9, HC(1)), 4.17 (1 H, d, *J* =

9.9, HC(1)), 4.03 (1 H, dd, J = 2.4, 2.5, HC(4)), 3.82 (1 H, dd, J = 7.0, 10.0, HC(6)), 3.79 (1 H, dd, J = 7.1, 10.0, HC(1)), 3.55 (1 H, d, J = 2.4, HC(3)), 3.52 (1 H, ddd, J = 2.4, 7.0, 7.1, HC(5)), 1.51 (3 H, s, Me), 1.38 (3 H, s, Me); ^{13}C-NMR (100 MHz) 138.6, 138.3, 138.0, 128.32, 128.26, 128.1, 127.7, 127.6, 127.55 (x 2), 127.47, 127.40, 110.2, 105.9, 77.3, 75.4, 74.1, 73.7, 73.4, 71.3, 68.4, 61.8, 27.4, 25.7; IR (neat) 3075 (w), 3050 (m), 3000 (m), 2950 (m), 2900 (m), 1570 (w), 1468 (m), 1390 (m), 1340 (m), 1270 (m), 1250 (m), 1225 (m), 1200 (m), 1155 (s), 1100 (s), 1070 (s), 1050 (m), 995 (m), 940 (m), 885 (m), 840 (m), 750 (s), 715 (s); MS (15 eV) 490 (M^+, 0.05), 475 (M^+-15, 0.2), 399 (M^+-Bn, 0.6), 341 (0.6), 253 (14), 181 (6), 160 (3), 91 (100); HRMS. Calcd for $C_{30}H_{34}O_6$ (490.2352): Found: 490.2331.

Benzyl 3, 4, 5-tri-*O*-benzyl-β-D-psicofuranoside (12)

a) Preparation using TfOH: A solution of **11** (139 mg, 0.28 mmol) and TfOH (5 μL, 57 μmol) in benzyl alcohol (10 mL) was stirred at room temperature for 2 h, and the reaction was quenched with sat. aqueous NH_4OH solution (3 mL). Concentration of the mixture *in vacuo* followed by purification by silica gel column chromatography (hexane/EtOAc, 3/2) afforded **12** as a colorless oil (109 mg, 71 %): $[\alpha]_D^{20}$ = -80.2° (c = 1.34, $CHCl_3$); ^{1}H-NMR 7.43-7.23 (20 H, m, HC(Ar)), 5.00 (1 H, d, J = 11.7, CH_2Ph), 4.85 (1 H, d, J = 12.6, CH_2Ph), 4.83 (1 H, d, J = 11.7, CH_2Ph), 4.73 (1 H, d, J = 12.6, CH_2Ph), 4.61 (1 H, d, J = 12.0, CH_2Ph), 4.53 (1 H, d, J = 12.0, CH_2Ph), 4.06 (1 H, dd, J = 8.3, 12.3, CH_2Ph), 4.00 (1 H, dd, J = 3.0, 3.1, HC(4)), 3.97 (1 H, dd, J = 2.7, 12.3, HC(6)), 3.93 (1 H, dd, J = 1.0, 3.0, HC(3)), 3.74 (1 H, dd, J = 5.0, 12.2, HC(1)), 3.74 (1 H, dddd, J = 1.0, 2.3, 2.7, 3.0, HC(5)), 3.63 (1 H, dd, J = 2.3, 12.3, HC(6)), 1.59 (1 H, dd, J = 5.0, 8.3, HO); ^{13}C-NMR (100 MHz) 138.8, 138.7, 138.2, 138.1, 128.5 (x2), 128.4 (x2), 128.2 (x2), 127.9 (x2), 127.61, 127.58, 127.50, 127.46 (x2), 127.38, 102.1, 76.0, 74.4, 74.2, 72.3, 72.1, 71.2, 63.5, 62.5, 60.6; IR (neat) 3500 (br m), 3080 (w), 3050 (m), 2940 (m), 2895 (m), 1500 (m), 1455 (m), 1360 (m), 1310 (m), 1210 (m), 1135 (m), 1080 (s), 1060 (s), 1025 (s), 740 (s), 700 (s); MS (70 eV) 509 (M^+-CH_2OH, 0.13), 341 (1.2), 181 (8.5) 91 (100); HRMS. Calcd for $C_{33}H_{33}O_5$ (509.2326): Found: 509.2326.

b) Preparation using MsOH: A solution of **11** (274 mg, 0.56 mmol) and MsOH (18 μL, 0.28 mmol) in benzyl alcohol (2.7 mL) was stirred at 0°C for 2 h. Treatment of the reaction mixture in the same manner as described in a) gave **12** as a white solid (123 mg, 41 %) after purification by silica gel column chromatography (hexane/EtOAc, 4/1). The ^{1}H-NMR spectrum of this sample was identical with that described in a).

Benzyl 2, 3, 4-tri-*O*-benzyl-1-carbamoyl-1-dehydro-β-D-ribopyranoside (20)

A solution of **12** (267 mg, 0.49 mmol) in CH_2Cl_2 (3 mL) was added to a solution of $(COCl)_2$ (0.173 mL, 2.0 mmol) and DMSO (0.28 mL, 4.0 mmol) in CH_2Cl_2 (6 mL) at -78°C. After stirring for 25 min at -78°C, Et_3N (0.69 mL, 4.9 mmol) was added to the reaction mixture. The mixture was warmed to room temperature over 1h, and the reaction was quenched by adding sat. aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), then filtered. Concentration of the filtrate *in vacuo* gave the crude aldehyde as a pale yellow oil (270 mg, 100 %): ^{1}H-NMR (200 MHz) 9.63 (1 H, s, HCO), 7.41-7.17 (20 H, m, HC(Ar)), 4.87 (1 H, d, J = 11.6, CH_2Ph), 4.78-4.58 (6 H, m, 2 x CH_2Ph, HC(4), HC(6)), 4.54 (1 H, d, J = 11.5, CH_2Ph), 4.39 (1 H, d, J = 11.5, CH_2Ph), 4.12 (1 H, dd, J = 11.7, 4.4, CH_2Ph), 3.97-3.90 (2 H, HC(3), HC(5)), 3.83-3.68 (1 H, HC(6)).

A solution (1 mL) of $NaClO_2$ (134 mg, 1.5 mmol) and NaH_2PO_4-H_2O (231 mg, 1.5 mmol) in H_2O (1 mL) was slowly added to a solution of the aldehyde (270 mg) and 2-methyl-2-butene (0.52 mL, 4.94 mmol) in t-BuOH (2.5 mL) at 0°C. After stirring at room temperature for 1 h, the mixture was concentrated *in vacuo* to a half of the original volume. The residual solution was extracted with Et_2O (4 x 10 mL), and the combined organic layers were washed with 2 % HCl solution (30 mL) and brine (30 mL), dried (Na_2SO_4), then filtered. Concentration of the filtrate *in vacuo* afforded crude **19** as a white solid (295 mg, 100 %): ^{1}H-NMR (400 MHz) 4.90-4.59 (6 H, m, 3 x CH_2Ph), 4.30 (2 H, br s, CH_2Ph), 4.17 (1 H, m, HC(4)), 4.02-3.78 (1 H, m, HC(6)), 3.75-3.67 (1 H, m, HC(3)), 3.64-3.58 (1 H, m, HC(5)), 3.50-3.38 (1 H, m, HC(6)).

Isopropyl chloroformate (0.128 mL, 1.0 mmol) was added to a solution of **19** (295 mg, 0.49 mmol) and Et_3N (0.28 mL, 2.0 mmol) in THF (2 mL) at 0°C. The reaction mixture was stirred for 75 min at 0°C, then at room temperature until the reaction was over (45 min). After passing NH_3 (gas) for 10 min, the mixture was concentrated *in vacuo* to a half of the original volume. The residual solution was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The separated aqueous layer was further extracted with $CHCl_3$ (4 x 10 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3/2) to give **20** as a colorless oil (233 mg, 85 % from **19**): $[\alpha]_D^{20}$ = -5.3° (c = 1.10, $CHCl_3$); ^{1}H-NMR (400 MHz) 7.41-7.21 (20 H, m, HC(Ar)), 6.90 (1 H, br d, J = 3.0, NH), 5.60 (1 H, br d, J = 3.0, NH), 4.93 (1 H, d, J = 11.1, CH_2Ph), 4.80 (2 H, s, CH_2Ph), 4.74 (1 H, d, J = 11.1, CH_2Ph), 4.60 (1 H, d, J = 12.0, CH_2Ph), 4.54 (1 H, d, J = 12.0, CH_2Ph), 4.51 (1 H, d, J = 11.2, CH_2Ph), 4.44 (1 H, d, J = 11.2, CH_2Ph), 4.29 (1 H, dd, J = 1.0, 3.0, HC(3)), 4.03 (1 H, dd, J = 1.8, 12.3, HC(6)), 3.90 (1 H, dd, J = 3.0, 3.3, HC(4)), 3.74 (1 H, dddd, J = 1.0, 1.8, 2.0, 3.3, HC(5)), 3.68 (1 H, dd, J = 2.0, 12.3, HC(6)); ^{13}C-NMR (100 MHz) 169.9 (C(1)), 138.8, 138.6, 138.0, 137.1, 128.2, 128.1, 128.0, 127.92, 127.86, 127.6, 127.5, 127.3, 127.1, 101.0 (C(2)), 75.9 (C(3)), 75.7 (CH_2Ph), 75.0 (CH_2Ph), 72.4 (CH_2Ph), 72.2 (C(5)), 70.7 (CH_2Ph), 65.1 (CH_2Ph), 64.0 (C(6); IR (neat) 3510 (m), 3380 (w), 3100 (m), 3050 (m), 2950 (m), 2900 (m), 1710 (s), 1590 (m), 1505 (m), 1460 (m), 1395 (m), 1365 (m), 1320 (m), 1260 (m), 1225 (m), 1145 (s), 1120 (s), 1070 (s), 1050 (s), 1020 (m), 935 (m), 770 (s), 750 (s), 710 (s); MS (15 eV) 554 (MH^+, 0.15), 553 (M^+, 0.03), 509 (M^+-$CONH_2$, 0.1), 462 (M^+-Bn, 4), 354 (4), 311 (93), 262 (3), 248 (5), 219 (3), 181 (25) 91 (100); HRMS. Calcd for $C_{27}H_{28}NO_6$ (462.1915): Found: 462.1921.

Benzyl 1-allophanoyl-2, 3, 4-tri-*O*-benzyl-1-dehydro-β-D-ribopyranoside (21)

Oxalyl chloride (68 μL, 0.77mmol) was added to a solution of **20** (121 mg, 0.22 mmol) in $ClCH_2CH_2Cl$ (5 mL), and the mixture was stirred at room temperature for 20 min, then at 100°C for 2 h until the reaction was over (30 min). The reaction was quenched with NH_3 (gas) at 0°C, and the mixture was partitioned between EtOAc (30 mL) and water (30 mL). The separated aqueous layer was further extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), filtered, then evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (CCl_4/Et_2O, 1/4) afforded **21** as a colorless oil (166 mg, 87 %): $[\alpha]_D^{20}$ = -20.0° (c = 1.99, $CHCl_3$); ^{1}H-NMR (400 MHz) 8.82 (1 H, br s, NH), 8.00 (1 H, br s, NH), 7.36-7.21 (20 H, m, HC(Ar)), 5.19 (1 H, br s, NH), 4.95 (1 H, d, *J* = 11.4, CH_2Ph), 4.77 (1 H, d, *J* = 12.5, CH_2Ph), 4.73 (1 H, d, *J* = 12.5, CH_2Ph), 4.66 (1 H, d, *J* = 11.4, CH_2Ph), 4.46 (1 H, d, *J* = 11.2, CH_2Ph), 4.38 (1 H, d, *J* = 11.2, CH_2Ph), 4.17 (1 H, dd, *J* = 1.0, 2.8, HC(3)), 4.10 (1 H, dd, *J* = 2.4, 12.3, HC(6)), 3.89 (1 H, dd, *J* = 2.8, 3.3, HC(4)), 3.76 (1 H, dddd, *J* = 1.0, 2.2, 2.4, 3.3, HC(5)), 3.69 (1 H, dd, *J* = 2.2, 12.3, HC(6)); ^{13}C-NMR (100 MHz) 169.3 (C(1)), 152.6 (urea), 138.5, 138.1, 137.8, 136.4, 128.39, 128.36, 128.2, 128.1, 127.94, 127.85, 127.7, 127.64, 127.57, 127.4, 100.9 (C(2)), 76.1 (C(3)), 75.6 (CH_2Ph), 74.8 (CH_2Ph), 72.2 (CH_2Ph), 71.9 (C(5)), 71.2 (CH_2Ph), 65.6 (CH_2Ph), 64.1 (C(6)); IR (neat) 3450 (m), 3380 (w), 3100 (m), 3050 (m), 2950 (w), 2900 (m), 1780 (w), 1735 (s), 1600 (m), 1530 (m), 1515 (m), 1480 (m), 1390 (m), 1250 (m), 1160 (s), 1135 (s), 1080 (s), 1055 (m), 1020 (s), 940 (m), 770 (s), 720 (s), 695 (s), 675 (m); MS (15 eV) 599 (M^+1, 0.1), 598(M^+, 0.1), 509 (M^+-urea, 0.2), 505 (M^+-Bn, 2), 462 (0.5), 397 (0.8), 354 (0.6), 311 (0.6), 371 (1.4), 181 (15), 91 (100); HRMS. Calcd for $C_{28}H_{29}NO_7$ (505.1973): Found: 505.1990.

Mixture of 1-Allophanoyl-1-dehydro-D-ribofuranose (22) and 1-Allophanoyl-1-dehydro-D-ribopyranose (23)

a) Preparation from **17**: A mixture of **17** (1.0 g, 2.4 mmol) and 10 % Pd-C (100 mg) in EtOH (20 mL) was stirred under hydrogen atmosphere (3 atm) for 10 h at room temperature. After filtration, the filtrate was concentrated *in vacuo* to afford a *ca.* 1 : 1 mixture of **22** and **23** as a pale yellow solid (544 mg, 96 %): IR (KBr) 3560 (m), 3470 (s), 2950 (m), 2560 (w), 2450 (w), 1720 (m), 1680 (s), 1590 (m), 1520 (w), 1400 (m), 1280 (w), 1225 (w), 1110 (m), 1075 (m), 1030 (m), 995 (w), 880 (w), 845 (w), 795(m), 770 (m), 720 (m); ^{13}C-NMR (D_2O, 100 MHz) **22**α: 174.0 (C(1)), 157.8 (urea), 103.5 (C(2)), 87.2 (C(5)), 76.3 (C(3)), 72.9 (C(4)), 63.6 (C(6)); **22**β: 174.6 (C(1)), 157.8 (urea), 106.8 (C(2)), 86.7 (C(5)), 79.0 (C(3)), 73.0 (C(4)), 64.9 (C(6)); **23**α: 174.7 (C(1)), 157.8 (urea), 99.8 (C(2)), 73.5 (C(3)), 71.1 (C(4)), 67.7 (C(5)), 67.4 (C(6)); **23**β: 173.6 (C(1)), 157.8 (urea), 99.1 (C(2)), 74.0 (C(3)), 70.4 (C(4)), 68.0 (C(5)), 61.4 (C(6)).

b) Preparation from **21**: The same treatments of **21** (111 mg, 0.19 mmol) as described in a) gave a ca. 1 : 1 mixture of **22** and **23** as a pale yellow solid (38 mg, 87 %) after concentration of the filtrate. The ^{13}C-NMR spectrum of this sample was identical with that described in a).

(5*RS*, 1'*S*, 2'*R*, 3'*R*)-5-(1', 2', 3', 4'-tetrahydrobutyl)-5-hydroxyhydantoin (24a,b)

A solution of a ca. 1 : 1 mixture of **22** and **23** (60 mg, 0.25 mmol) in H_2O (1 mL) were stirred at 70°C for 1.5 h. Concentration of the mixture *in vacuo* afforded a *ca.* 2 : 1 mixture of **24a,b** (60 mg, 100 %) as a colorless oil. The mixture of **24a,b** (60 mg) was subjected to HPLC system [TOSOH HLC-803, ODS column (TOSOH TSK-gel, ODS-80TS, i.d. 21.5 x 300mm), H_2O (1.0 ml/min), and measurement of UV 210 nm absorbance] to afford **24b** as a colorless viscous oil (minor, 14.5 mg, 24 %) from the first fraction and **24a** as a colorless viscous oil (major, 29.8 mg, 50 %) from the second fraction. The absolute stereochemistries of **24a,b** could not be determined by the following spectral data. **24a**: TLC R*f* 0.21 (SiO_2, MeCN/H_2O, 9/1). ^{1}H-NMR (D_2O, 400 MHz) 4.03 (0.35 H, d, *J* = 9.7, HC(1')), 3.90 (0.35 H, ddd, *J* = 3.2, 4.0, 4.5, HC(3')), 3.77 (0.35 H, dd, *J* = 3.2, 12.0, HC(4')), 3.71 (0.35 H, dd, *J* = 4.0, 9.7, HC(2')), 3.66 (0.35H, dd, *J* = 4.5, 12.0, HC(4')). ^{13}C-NMR (D_2O, 100 MHz) 178.5 (C(4)), 161.0 (C(2)), 88.9 (C(5)), 76.0 (C(1')), 75.4 (C(2')), 74.2 (C(3')), 64.5 (C(4')). Ms (*m/z*, CI): 237 (MH^+), 219 (MH^+-18). **24b**: TLC R*f* 0.28 (SiO_2, MeCN/H_2O, 9/1). ^{1}H-NMR (D_2O, 400 MHz) 4.15 (0.65 H, d, *J* = 5.3, HC(1')), 3.95 (0.65 H, ddd, *J* = 3.0, 5.2, 6.3, HC(3')), 3.91 (0.65 H, dd, *J* = 5.3, 6.3, HC(2')), 3.80 (0.65 H, d, *J* = 3.0, 12.0, HC(4')), 3.65 (0.65 H, dd, *J* = 5.2, 12.0, HC(4')). ^{13}C-NMR (D_2O, 100 MHz) 178.9 (C(4)), 161.0 (C(2)), 90.6 (C(5)), 75.7 (C(1')), 74.8 (C(2')), 72.8 (C(3')), 65.1 (C(4')). Ms (*m/z*, CI): 237 (MH^+), 219 (MH^+-18).

(+)-Hydantocidin (1) and (-)-5-*epi*-hydantocidin (2)

Table 1, run 13: Dowex® 50W-X8 (H^+ form, 5.0 g) was added to a solution of a *ca.* 2 : 1 mixture of **24a,b** (130 mg, 0.85 mmol) in ^{n}PrOH/H_2O (2/1) (12 mL). The suspension was stirred for 3.5 h at 40-50°C, and the Dowex® resin was filtered off. Concentration of the filtrate *in vacuo* gave a 30 : 70 mixture of **1** and **2** as a pale yellow oil (108 mg, 90 %). HPLC analysis [H_2O, 0.5 mL/min]. ^{t}R-**2**, 9.85 min (69.8%); ^{t}R-**1**, 11.27 min (30.2%). The mixture of **1** and **2** (108 mg) was subjected to HPLC system [TOSOH HLC-803, ODS column (TOSOH TSK-gel, ODS-80TS, i.d. 21.5 x 300mm), H_2O (1.0 ml/min), and measurement of UV 210 nm absorbance] to afford **2** as a colorless viscous oil (63.4 mg, 59%) from the first fraction and **1** as a colorless solid (28.8 mg, 27 %) from the second fraction.

1: An analytical sample was obtained as colorless prisms by recrystallization from acetone/H_2O: mp 184-185°C [lit.,[1] mp. 187-189°C (acetone)]; $[\alpha]_D^{20}$ = +30.2° (c = 0.61, H_2O) [lit.,[1] $[\alpha]_D^{25}$ +28.8° (c=1.04, H_2O)]; ^{1}H-NMR (D_2O, 400 MHz) 4.34 (1 H, d, *J* = 5.8, HC(4)), 4.28 (1 H, ddd, *J* = 3.2, 4.0, 4.5, HC(2)), 4.16 (1 H, dd, *J* = 4.8, 5.8, HC(3)), 3.72 (1 H, dd, *J* = 3.2, 12.7, HC(1)), 3.62 (1 H, dd, *J* = 4.5, 12.6, HC(1)); (CD_3OD, 400 MHz) 4.24 (1 H, d, *J* = 6.1, HC(4)), 4.22 (1 H, ddd, *J* = 2.2, 3.7, 3.9, HC(2)), 4.04 (1 H, dd, *J* = 2.2, 6.1, HC(3)), 3.64 (1 H, dd, *J* = 3.7, 12.2, HC(1)), 3.61 (1 H, dd, *J* = 3.9, 12.2, HC(1)); IR (KBr) 3600-2800 (s), 1775 (s), 1735 (s), 1705 (s), 1400 (m), 1320 (m), 1240 (w), 1175 (w), 1140 (m), 1055 (m), 1000 (w), 975 (w), 905 (w), 760 (w); MS (SIMS); 219 (MH^+, 12), 185 (6), 148 (4.5), 129 (14), 115 (24), 93 (88), 75 (60), 61 (36), 57 (91), 45 (100).

These spectral data were identical with those reported.[1] Anal. Calcd for $C_7H_{10}N_2O_6$ (218.17): C, 38.54; H, 4.62; N, 12.84. Found: C, 38.54; H, 4.53; N, 12.67.

2: $[\alpha]_D^{24}$ = -10.8° (c = 0.61, MeOH) [lit.,[7b] $[\alpha]_D^{25}$ -11.0° (c = 3.0, MeOH)]; ^{1}H-NMR (D_2O, 400 MHz) 4.26 (1 H, d, *J* = 4.9, HC(4)), 4.17 (1 H, dd, *J* = 3.3, 4.9, HC(3)), 4.09 (1 H, ddd, *J* = 3.3, 4.3, 5.2, HC(2)), 3.66 (1 H, dd, *J* = 4.3, 12.1, HC(1)), 3.60 (1 H, dd, *J* = 5.2, 12.1, HC(1)); IR (neat) 3350 (s), 1780 (s), 1730 (s), 1400 (m), 1320 (m), 1270 (w), 1220 (m), 1140 (m), 1100 (m), 1030 (m), 925 (w), 880 (w), 825 (w); MS (SIMS); 221 (M^++3, 7), 220 (M^++2, 7), 219 (MH^+, 55), 185 (17), 148 (13.5), 129 (30), 93 (100), 75 (58), 57 (63), 45 (59). These spectral data were identical with those reported.[7b]

2α, 3, 4-Tri-*O*-acetyl-6-*N*-acetylhydantocidin (26)

a) Preparation of **26** in the presence of DMAP: 4-Dimethylaminopyridine (0.40 mg, 2.6 μmol) was added to a solution of **1** (5.6 mg, 26 μmol) in Ac_2O-pyridine (2/1) (0.2 mL). After stirring for 1 h at room temperature, the mixture was partitioned between EtOAc (10 mL) and 0.5 N aqueous HCl solution (10 mL). The separated aqueous layer was further extracted with EtOAc (3 x 10 mL) The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), then filtered. Concentration of the filtrate *in vacuo* followed by purification by preparative TLC (hexane/EtOAc, 2/3) afforded **26** as a colorless oil (8.8 mg, 89 %): $[\alpha]_D^{20}$ = +98.4° (c = 1.18, $CHCl_3$); TLC *Rf* 0.26 (hexane/EtOAc, 1/1); ^{1}H-NMR (400 MHz) 7.49 (1 H, br s, HN), 5.69 (1 H, d, *J* = 7.2, HC(4)), 5.46 (1 H, dd, *J* = 7.2, 8.6, HC(3)), 4.62 (1 H, ddd, *J* = 2.7, 5.9, 8.6, HC(2)), 4.58 (1 H, dd, *J* = 2.7, 12.4, HC(1)), 4.17 (1 H, dd, *J* = 5.9, 12.4, HC(1)), 2.57 (3 H, s, NAc), 2.14 (3 H, s, OAc), 2.10 (3 H, s, OAc), 2.06 (3 H, s, OAc); ^{13}C-NMR (100 MHz) 171.2, 170.8, 169.7, 169.0 (C(6)), 151.2 (NCON), 94.1 (C(5)), 81.3 (C(2)), 73.8 (C(4)), 69.5 (C(3)), 62.2 (C(1)), 25.8 (NAc), 20.7 (OAc), 20.5 (OAc), 20.3 (OAc); IR (neat) 3250 (m), 1815 (m), 1770 (s), 1760 (s), 1750 (s), 1740 (s), 1730 (s), 1380 (s), 1310 (s), 1240 (s), 1185 (m), 1110 (s), 1050 (s), 935 (m), 760 (s); MS (15 eV) 387 (MH^+, 2.7), 344 (MH^+-Ac, 2.3), 313 (1), 302 (6), 267 (1), 266 (8), 224 (73), 170 (100), 128 (80), 68 (25), 43 (86); HRMS. Calcd for $C_{15}H_{19}N_2O_{10}$ (387.1037): Found: 387.1058.

b) Preparation of **26** in the absence of DMAP: A solution of **1** (5.8 mg, 27 μmol) in Ac_2O-pyridine (2/1) (0.5 mL) was stirred at room temperature for 10 min. Treatments of the reaction mixture in the same manner as described in a) gave **26** as a colorless oil (8.1 mg, 79 %) after purification by silica gel column chromatography (hexane/EtOAc, 1/1). The ^{1}H-NMR spectrum of this sample was identical with that described in a).

2α, 3, 4-Tri-*O*-acetyl-6-*N*-acetyl-5-*epi*-hydantocidin (27) and 2α, 3, 4-Tri-*O*-acetyl-5-*epi*-hydantocidin (28)

a) Preparation of **27**: 4-Dimethylaminopyridine (0.65 mg, 5.3 μmol) was added to a solution of **2** (11.6 mg, 53 μmol) in Ac_2O-pyridine (2/1) (0.5 mL). After stirring for 12 h at room temperature. The mixture was worked up in the same manner as described for the preparation of **26** from **1**, affording **27** as a colorless oil (18.8 mg, 90 %) after purification by preparative TLC (hexane/EtOAc): $[\alpha]_D^{20}$ = +103° (c = 0.92, $CHCl_3$); TLC *Rf* 0.26 (hexane/EtOAc, 1/1); ^{1}H-NMR (400 MHz) 7.58 (1 H, br s, HN), 5.44 (1 H, d, *J* = 8.6, HC(4)), 5.33 (1 H, dd, *J* = 6.8, 8.6, HC(3)), 4.97 (1 H, ddd, *J* = 2.7, 4.1, 6.8, HC(2)), 4.67 (1 H, dd, *J* = 2.7, 12.4, HC(1)), 4.05 (1 H, dd, *J* = 4.1, 12.4, HC(1)), 2.54 (3 H, s, NAc), 2.16 (3 H, s, OAc), 2.14 (3 H, s, OAc), 2.05 (3 H, s, OAc); ^{13}C-NMR (100 MHz) 171.0, 170.0, 168.6, 166.2 (C(6)), 151.9 (NCON), 94.8 (C(5)), 83.6 (C(2)), 72.7 (C(4)), 70.7 (C(3)), 62.4 (C(1)), 25.7 (NAc), 20.8 (OAc), 20.4 (OAc), 20.0 (OAc); IR (neat) 3600 (w), 3200 (w), 2750 (w), 1815 (m), 1770 (s), 1760 (s), 1740 (s), 1725 (s), 1375 (s), 1310 (m), 1230 (s), 1190 (m), 1125 (m), 1090 (m), 1055 (m), 1005 (m), 990 (m), 760 (s); MS (15 eV) 387 (MH^+, 4.8), 345 (1.4), 344 (MH^+-Ac, 2.4), 313 (3.4), 302 (4.2), 266 (6), 224 (46), 170 (80), 128 (53), 68 (20), 43 (100); HRMS. Calcd for $C_{15}H_{19}N_2O_{10}$ (387.1037): Found: 387.1022.

b) Preparation of **27** and **28**: 4-Dimethylaminopyridine (0.25 mg, 2.0 μmol) was added to a solution of **2** (14.0 mg, 64 μmol) in Ac_2O-pyridine (2/1) (0.5 mL), and the mixture was stirred for 1 h at room temperature. The same treatments of the mixture as described for the preparation of **26** from **1** gave **27** as a colorless oil (11.4 mg, 46 %) from the first fraction and **28** as a colorless oil (11.5 mg, 52 %) from the second fraction after silica gel column chromatography (hexane/EtOAc, 1/1). The ^{1}H-NMR spectrum of **27** was identical with that described in a). **28**: TLC *Rf* 0.12 (hexane/EtOAc, 1/1); ^{1}H-NMR (400 MHz) 5.79 (br s, 1 H, NH), 5.51 (1 H, dd, *J* = 2.5, 5.0, HC(3)), 5.45 (1 H, d, *J* = 5.0, HC(4)), 4..45 (1 H, dd, *J* = 4.3, 11.7, HC(1)), 4..42 (1 H, ddd, *J* = 2.5, 3.8, 4.2, HC(2)), 4.10 (1 H, dd, *J* = 3.8, 11.7, HC(1)), 2.160 (3 H, s, OAc), 2.157 (3 H, s, OAc), 2.12 (3 H, s, OAc); ^{13}C-NMR (100 MHz) 171.0, 170.3, 169.5, 166.2 (C(6)), 155.5 (NCON), 91.2 (C(5)), 80.3 (C(2)), 72.2 (C(4)), 71.5 (C(3)), 62.8 (C(1)), 20.7 (OAc), 20.5 (OAc), 20.2 (OAc); IR (neat) 3250 (w), 3080 (w), 2950 (w), 1795 (m), 1420 (m), 1370 (s), 1230 (s), 1100 (m), 1040 (m), 945 (w), 900 (w), 760 (w), 720 (w), 635 (w); MS (15 eV) 345 (MH^+, 3.5), 313 (3.4), 303 (1.3), 302 (9), 271 (6), 224 (3), 214 (6), 211 (6), 187 (17), 170 (52), 128 (63), 68 (24), 43 (100); HRMS. Calcd for $C_{13}H_{17}N_2O_9$ (345.0932): Found: 345.0932.

One-step synthesis of (-)-5-*epi*-hydantocidin (2)

A stirred mixture of **6** (3.0 g, 17 mmol) and urea (0.84 g, 14 mmol) was heated at 130°C for 3.5 h without any solvent. The resulting dark brown caramel was dissolved in ^{n}PrOH/H_2O = 2/1 (9 ml) and Dowex 50W-X8 (H^+ form, 5.0 g) was added to the dark drown solution. After heating at 45°C for 1.5 h, Dowex resin was filtered off. Concentration of the filtrate *in vacuo* gave a brown caramel. HPLC analysis of this caramel showed more than 25 peaks, among which one peak obviously corresponds to **2**. However, the peak corresponding to **1** was not identified. The brown caramel was purified by ODS column chromatography [YMC•GEL ODS-AQ 120-S50, (50 g), H_2O]. The fractions containing **2** was collected and concentrated *in vacuo* to yield semi-purified **2** as a pale yellow caramel (0.58 g). The fractions which showed the peak corresponding to **1** by HPLC analysis were not obtained. The pale yellow caramel (0.58 g) was dissolved in Ac_2O-pyridine (2/1) (6 mL) containing DMAP (32.4 mg, 0.27 mmol). After stirring for 1h at room temperature, the mixture was partitioned between EtOAc (50 mL) and 1 M aqueous HCl

solution (50 mL). The separated aqueous phase was further extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), filtered, then concentrated *in vacuo* . The residue was purification by silica gel column chromatography (hexane/EtOAc, 1/1) to afford **28** as a colorless oil (10.2 mg, 0.21 %). The ^{1}H-NMR and ^{13}C-NMR spectra of this sample were identical with those of the authentic sample prepared from **2**.

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17. In the preliminary experiments, it was found that the protecting group of anomeric position was very important for efficient preparation of the mixture of **22** and **23**. Thus, the methyl glycosides obtainable from **9** and **11** in essentially the same manner as for **17** and **21** took place no hydrolysis of the methyl glycoside groups even by refluxing under acidic conditions (TsOH/acetone, $HClO_4$/acetone, Dowex® 50W-X8/MeOH-H_2O).
18. The ratio of **1** to **2** was monitored by HPLC system [TOSOH HLC-803, ODS column (Asahi Chemical Industry, Asahipack® HIKARISIL-C18, i.d. 6x150mm), H_2O (0.5 ml/min) and measurement of UV 210 nm absorbance]. ^{t}R-**1**, 11.3 min; ^{t}R-**2**, 9.9 min.
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