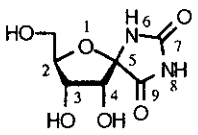
ONE-STEP SYNTHESIS OF (–)-5-*EPI*-HYDANTOCIDIN‡

Noriyuki Nakajima, Masayuki Kirihara, Miyoko Matsumoto, Masaru Hashimoto, Tadashi Katoh, and Shiro Terashima*

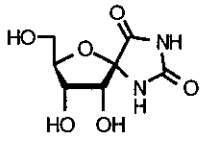
Sagami Chemical Research Center
Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Abstract- *One-step synthesis of (–)-5-epi-hydantocidin was achieved by heating a mixture of* D-*isoascorbic acid and urea without solvent. Studies on N,O-spiroketal formation and epimerization between (+)-hydantocidin and (–)-5-epi-hydantocidin were also carried out to explore some mechanistic aspects of the obtained results.*

(+)-Hydantocidin (**1**), isolated from the fermentation broth of *Streptomyces hygroscopicus* SANK 63584 in 1991, is exceptionally intriguing as a new generation of herbicide because of its promising profile of herbicidal and plant growth regulatory activities with no toxicity against microorganisms and animals. The unique structure carrying a spirohydantoin nucleus at the anomeric position of D-ribofuranose constitutes the first naturally occurring spironucleoside.[1,2] It is also reported that its spiro isomer, (–)-5-*epi*-hydantocidin (**2**), displays herbicidal activity being approximately 60% of that for **1**.[3] Due to its significant herbicidal activity and unique structure, considerable synthetic efforts have so far been devoted to the synthesis of **1**[4] and its analogs.[5-7]



(+)-hydantocidin (**1**)

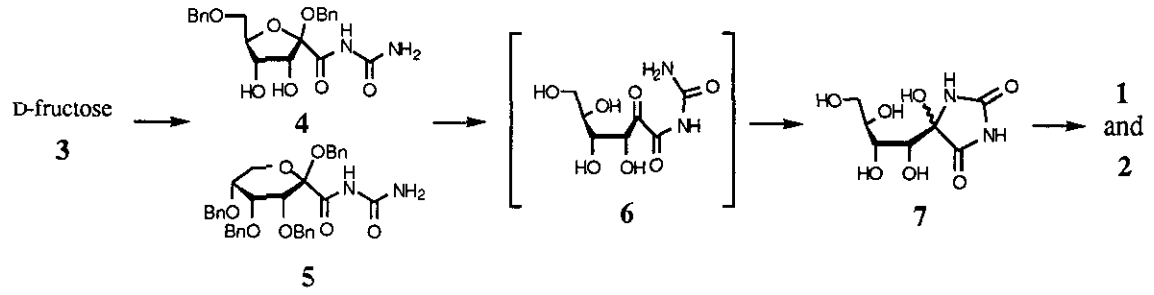


(–)-5-*epi*-hydantocidin (**2**)

We have recently reported a novel synthetic route to **1** and **2** pictured in **Scheme 1**.[8] This was designed based on the speculated biosynthetic process that might occur through the open-chain precursor (**6**) or its equivalent such as **7.** The synthesis was realized by preparing the D-psicose derivatives (**4** and **5**) from D-fructose (**3**) and subsequently employing the intramolecular *N,O*-spiroketal formation of **7** to **1** and **2** as a key step. The 5-hydroxyhydantoin derivative (**7**) being equivalent to **6** was obtained from either **4** or **5** by way of **6**.

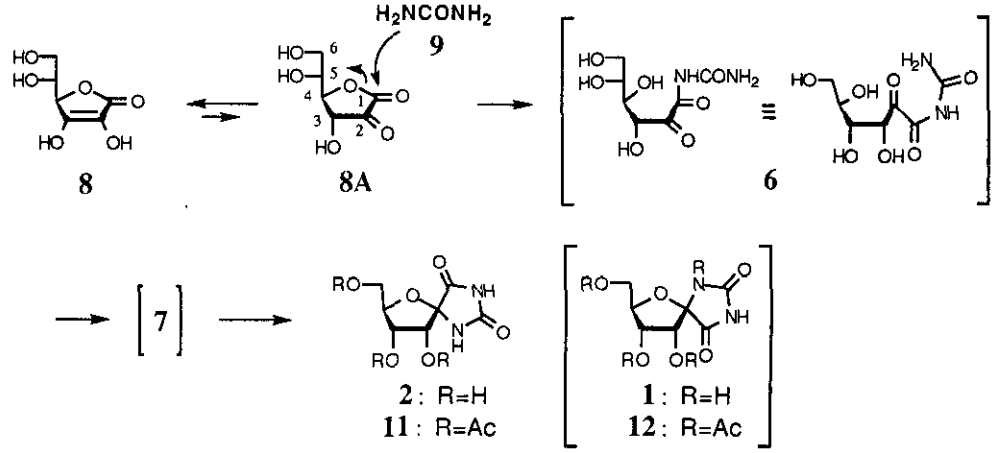
‡ This paper is dedicated to the memory of Professor Emeritus Yoshio Ban.

Scheme 1



This communication described an alternative and more direct preparation method of **2** which also features the intramolecular *N,O*-spiroketal formation. Thus, we have now found that **2** can be simply prepared *in one-step* starting from two readily available simple building blocks, D-isoascorbic acid (**8**) and urea (**9**) as shown in **Scheme 2**. The typical experimental procedure is as follows. A stirred mixture of **8** (3.0 g, 17 mmol) and **9** (0.84 g, 14 mmol) was heated at 130°C for 3.5 h[9] without any solvent. When the reaction was performed using a solvent such as water, *N,N*-dimethylformamide(DMF), or dimethyl sulfoxide (DMSO) under various conditions,[10] none of **1** and/or **2** was detected in the reaction mixture by hplc analysis.[11] The resulting dark brown caramel was subjected to column chromatography on YMC•GEL ODS-AQ 120-S50 (50 g) using water as an eluant. The eluates containing **2** were collected and concentrated *in vacuo* to yield a 1.17 g of the semi-purified product mixture involving **2** as a pale yellow caramel.[12] After acetylation (Ac_2O-Py, DMAP), this mixture could be readily separated by column chromatography on silica gel (20 g, hexane/EtOAc = 3/1), providing an 8.4 mg (0.17 %) of triacetate (**11**)[13] as a colorless caramel, $[\alpha]_D^{20}$ +105° (c = 0.89, $CHCl_3$) [an authentic sample of **11**,[14] $[\alpha]_D^{20}$ +103° (c = 0.92, $CHCl_3$)]. Treatment of the reaction mixture with Dowex 50W-X8 in $^nPrOH/H_2O$ = 2/1 for 2 h at 45°C prior to the first purification slightly increased the isolated yield of **11** to 0.21%. All the spectral data (ir, ^{1}H-nmr, ms) collected for **11** were identical with those of the authentic sample.[14]

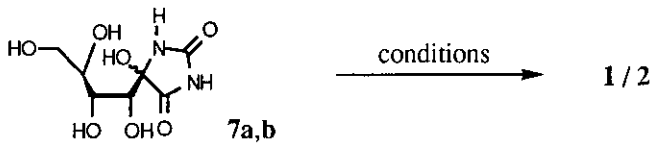
Scheme 2



Contrary to our expectation, no trace amount of tetraacetate (**12**)[15] which may be derived from **1** could be isolated by the one-step synthesis. Unsuccessful isolation of **1** completely differs from the previous results affording a mixture of **1** and **2** (30 : 70, see **Table 1**, entry 1).[8] The most plausible mechanism for this remarkable one-step synthesis is shown in **Scheme 2**. Thus, nucleophilic addition of **9** to the reactive C_1 carbonyl group in **8A** being one of the four possible tautomers of **8**,[16] prompts cleavage of the lactone ring, leading to **6**. Subsequent intramolecular *N,O*-spiroketal formation of **7** produced from **6** in the reaction mixture gives rise to **2**.

With an aim to explore the reason why **12** obtainable from **1** could not be isolated from the one-step synthesis, studies on the *N,O*-spiroketal formation were carried out under three different conditions (A, B and C) employing **7a** (major) and **7b** (minor) as shown in **Table 1**. These epimers (**7a,b**) were prepared according to our previous method[8] and cleanly separated by hplc (TOSOH TSK-gel, ODS-80TS, H_2O).[17] The absolute stereochemistries of **7a,b** could not be determined by their spectral data. A 2 : 1 mixture of **7a,b** had been found to give a 30 : 70[11] mixture of **1** and **2** when treated with Dowex 50W-X8 in ^{n}PrOH/H_2O = 2/1 at 45°C (condition A) for 3.5 h (entry 1).[8] However, treatment of the same mixture of **7a,b** at 130°C (condition B) for 3.5 h (73 % conversion) provided a mixture of **1** and **2** in a ratio of 12 : 88 (entry 2). By heating the mixture of **7a,b** in the presence of D-isoascorbic acid (1 equiv.) (condition C) for 3.5 h, a 14 : 86 ratio of **1** to **2** was also obtained with increased conversion (93 %)(entry 3).

Table 1. *N,O*-Spiroketal formation of **7** to **1** and **2**.



7a,b

entry	substrate	conditions[a]	reaction time, h	conversion, %	**1** : **2**[b]
1	**7** (**7a**/**7b** = 2/1)	A	3.5	100	30 : 70[8]
2	**7** (**7a**/**7b** = 2/1)	B	3.5	73	12 : 88
3	**7** (**7a**/**7b** = 2/1)	C	3.5	93	14 : 86
4	**7a**	A	0.5	47	49 : 51
5	**7a**	A	12.5	100	38 : 62
6	**7a**	B	3.5	85	10 : 90
7	**7a**	C	3.5	91	15 : 85
8	**7b**	A	0.5	95	8 : 92
9	**7b**	A	2.0	100	9 : 91
10	**7b**	B	3.5	62	13 : 87
11	**7b**	C	3.5	94	8 : 92

a) Condition A: Dowex 50W-X8 in ^{n}PrOH/H_2O = 2/1 at 45°C. Condition B: heating at 130°C without solvent. Condition C: heating at 130°C in the presence of D-isoascorbic acid (1 equiv.) without solvent. b) Determined by hplc analysis.[11]

On the other hand, treatment of **7a** under the condition A for 30 min (47 % conversion) afforded a mixture of **1** and **2** in a ratio of 49 : 51 and the ratio changed to 38 : 62 after 12.5 h (100 % conversion)(entries 4 and 5). When **7b** was treated under the same conditions, the ratio of **1** to **2** was found to be 8 : 92 after 30 min (95 % conversion) and no further change of the ratio was observed after 2h (100 % conversion)(entries 8 and 9). Under the condition B, **7a** formed **2** more dominantly with 10 : 90 selectivity and **7b** also provided **2** with 13 : 87 selectivity (entries 6 and 10). In the presence of D-isoascorbic acid (condition C), the reaction proceeded more smoothly and the conversion yields increased up to over 90 % with the selectivity similar to that obtained under the condition B (entries 7 and 11). These observations suggest that the *N,O*-spiroketal formations of **7a** and **7b** may take place through different reaction mechanisms between the conditions A and B, C. Thus, under the condition A, **7a** provided a 1 : 1 mixture of **1** and **2**, whereas **7b** gave **2** with high selectivity. On the other hand, the conditions B and C under which the *N,O*-spiroketal formation was examined at 130°C resulted in the formation of thermodynamically more stable product (**2**) with high selectivity from the both starting materials (**7a** and **7b**).

Table 2. Equilibrium between **1** and **2** under acidic conditions.

1 **2**

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

a) Condition A: Dowex 50W-X8 in ^{n}PrOH/H_2O = 2/1 at 45°C. Condition B: heating at 130°C without solvent. Condition C: heating at 130°C in the presence of D-isoascorbic acid (1 equiv.) without solvent. b) Determined by hplc analysis.[11]

Moreover, it was found that **1** and **2** possessing an *N,O*-spiroketal functionality can readily epimerize under the same acidic conditions as employed for the *N,O*-spiroketal formation. The results summarized in **Table 2** show that **1** and **2** are readily epimerized by treating with Dowex 50W-X8 at 45°C (condition

A)(entries 1, 2, 6 and 7). The half time value ($t_{1/2}$) of epimerization of **1** to **2** and the equilibrium ratio of **1** to **2** were estimated as ca. 6 h and ca. 1 : 10 in favor of **2**, respectively.[18] Although **1** and **2** underwent no epimerization by simple heating (condition B)(entries 3 and 8), the epimerization of **1** readily took place in the presence of D-isoascorbic acid (1 equiv.)(condition C), giving **2** in 49 : 51 ratio after 3 h and no further change of the ratio was observed after 6 h (entries 4 and 5). 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 9 and 10). On the basis of these observations, no isolation of **12** obtainable from **1** in the one-step synthesis might be explained by the very low yield (less than 0.02 %) of **1** induced by the *N,O*-spiroketal formation selectively producing **2** and/or the rapid epimerization of **1** to **2** in the presence of a large excess amount of D-isoascorbic acid.

In summary, we have succeeded in exploring a novel one-step synthesis of **2** starting with D-isoascorbic acid and urea. Further studies for improving the chemical yield are being examined in our laboratories and will be reported in due course.

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9. The reaction performed at 100° for 3.5 h or at 130°C for 2 h gave no trace amount of **2**. The yields of **11** 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).
10. Uses of additives such as Molecular Sieves, $MgSO_4$, *p*-TsOH, H_2SO_4, DBU, DMAP gave no trace amount of **2**.
11. The ratio of **1** and **2** was monitored by hplc system (TOSOH HLC-803) [ODS column (Asahi Chemical Industry, Asahipack® HIKARISIL-C18, i.d. 6x150mm), development with water (0.5 ml/min), and measurement of uv 210 nm absorbance]. ^{t}R-**1**, 11.2 min; ^{t}R-**2**, 9.8 min.
12. All attempts to directly separate **2** from this mixture met with failure.
13. Data for **11**. Ir (neat, cm^{-1}): 3250 (m), 3080 (w), 2950 (w), 1795 (m), 1740 (s), 1420 (m), 1370 (s), 1230 (s), 1100 (m), 1040 (m), 945 (w), 900 (w), 760 (w), 635 (w). ^{1}H-Nmr (400 MHz, $CDCl_3$): 8.14 (1H, br s, >NH), 6.69 (1H, br s, >NH), 5.54 (1H, dd, *J* = 2.7, 5.0, H-3), 5.44 (1H, d, *J* = 5.0, H-4), 4.42-4.46 (2H, m, H-2, H-1), 4.11 (1H, dd, *J* =5.9, 13.5, H-1), 2.16 (3H, s, OAc), 2.15 (3H, s, OAc), 2.12 (3H, s, NAc). ^{13}C-Nmr (100 MHz, $CDCl_3$): 170.7, 170.3, 169.5 (x2), 155.5, 91.2, 80.3, 72.2, 71.5, 62.8, 20.7, 20.5, 20.2. Ms (m/z, 15 eV): 345 (M^++1, 3.5), 303 (1), 302 (9), 271 (6), 242 (4), 224 (3), 214 (6), 211 (6), 187 (17), 170 (52), 128 (63), 68 (24), 43 (100). HRms (m/z): calcd for $C_{13}H_{17}N_2O_9$ 345.0932; found: 345.0932.
14. An authentic sample of **2** was acetylated with Ac_2O-Py containing DMAP (3 mol%) for 60 min at room temperature, giving **11** and the tetraaetate of **2** in 52 % and 46 % yield, respectively, after purification by column chromatography on silica gel.
15. When **1** was treated with Ac_2O-Py in the presence of DMAP (10 mol%) at room temperature for 60 min, **12** was obtained in 89 % yield more selectively than **11**.
16. T. C. Crawford and S. A. Crawford, *Adv. Carbohydr. Chem. Biochem.*, 1980, **37**, 79.
17. Data for **7a**: Tlc R_f 0.28 (SiO_2, MeCN/H_2O, 9/1). ^{1}H-Nmr (400MHz, D_2O): 4.15 (1H, d, *J* = 5.3, H-1'), 3.96 (1H, ddd, *J* = 3.0, 5.2, 6.3, H-3'), 3.91 (1H, dd, *J* = 5.3, 6.3, H-2'), 3.80 (1H, dd, *J* = 3.0, 12.0, H-4'), 3.65 (1H, dd, *J* = 5.2, 12.0, H-4'). ^{13}C-Nmr (100MHz, D_2O): 178.9, 161.0, 90.6, 75.7, 74.8, 72.8, 65.1. Ms (*m/z*, CI): 237 (MH^+), 219 (MH^+-18).
Data for **7b**: Tlc R_f 0.21 (SiO_2, MeCN/H_2O, 9/1). ^{1}H-Nmr (400MHz, D_2O): 4.03 (1H, d, *J* = 9.7, H-1'), 3.90 (1H, ddd, *J* = 3.2, 4.0, 4.5, H-3'), 3.77 (1H, dd, *J* = 3.2, 12.0, H-4'), 3.71 (1H, dd, *J* = 4.0, 9.7, H-2'), 3.66 (1H, dd, *J* = 4.5, 12.0, H-4'). ^{13}C-Nmr (100MHz, D_2O): 178.5, 161.0, 88.9, 76.0, 75.4, 74.2, 64.5. Ms (*m/z*, CI): 237 (MH^+), 219 (MH^+-18).
18. Similar but different equilibrium ratio of **1** to **2** (80 % TFA, *ca.* 1 : 4) had been reported by Fleet *et al.*[5]

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