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A Novel Biogenetic Type Synthesis of (+)-Hydantocidin

Miyoko Matsumoto, Masayuki Kirihara, Toshiharu Yoshino, Tadashi Katoh, Shiro Terashima*

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

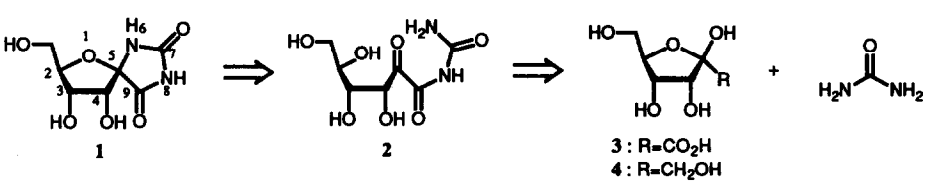
Key words: biogenetic type synthesis, hydantocidin, 5-epi-hydantocidin, herbicide, benzylglycocide formation, intramolecular N, O-spiroketal formation, D-psicose, D-fructose, urea

Abstract: *The title synthesis was accomplished by featuring the proposed biosynthetic pathway. The synthesis commenced with the D-psicose derivative readily obtainable from D-fructose and employed intramolecular N, O-spiroketal formation of the open-chain N-acylurea derivative as a key step.*

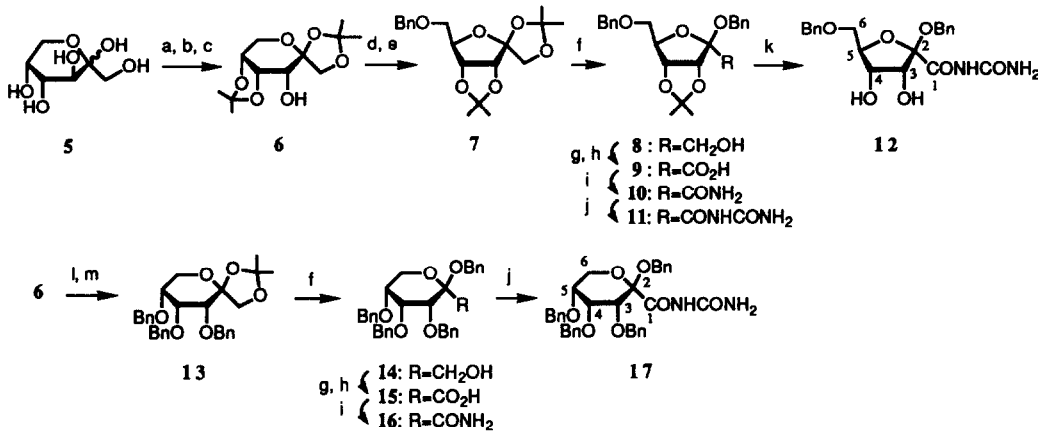
Hydantocidin **1**, isolated from the culture broth of *Streptomyces Hygroscopicus* SANK 63584 in 1991, exhibits prominent herbicidal and plant growth regulatory activity with no toxicity against microorganisms, fishes, and animals.[1] The stereostructure of **1** except its absolute configuration was first elucidated by extensive spectroscopic studies to have a unique spirohydantoin nucleus at the anomeric position of D-ribofuranose with contiguous four asymmetric carbons.[2] The absolute configuration of **1** depicted below was subsequently confirmed by the total synthesis of (+)-**1** by Mio *et al.*.[3] This unique structure has never been found in the field of nucleoside antibiotics.[4] Taking into account its remarkable herbicidal activity and intriguing structure, we embarked on the total synthesis of **1** by employing a novel synthetic strategy.[5, 6, 7]

Considering the plausible biosynthetic pathway, our synthetic plan for **1** was designed as shown in **Scheme 1**.[8] Thus, the *N,O*-spiroketal moiety of **1** can be disconnected retrosynthetically to give the open-chain *N*-acylurea **2**. Removal of the urea unit in **2** leads back to the carboxylic acid **3** accessible from D-psicose **4**. The key step in this approach is envisioned to be the intramolecular *N,O*-spiroketal formation of **2** to furnish **1**, wherein the stereochemistry at the C5 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 **2**. In this communication, we wish to report a simple and efficient synthesis of **1** based on this novel synthetic strategy, demonstrating viability of the proposed biosynthetic pathway.

Scheme 1



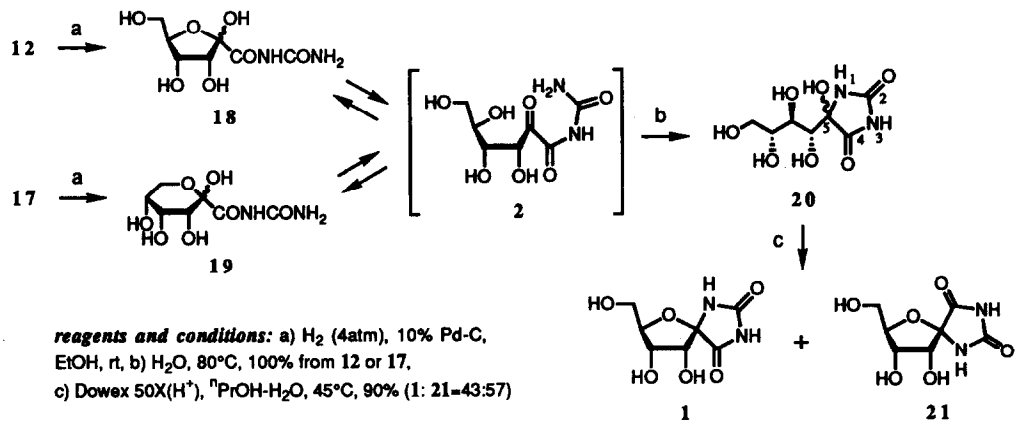
Scheme 2



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 **8**, 71% for **14** or MsOH, BnOH, rt, 66% for **8**, 41% for **14** g) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N h) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-butene, ^tBuOH-H_2O, rt i) $ClCO_2{}^iPr$, Et_3N, THF, 0°C; NH_3(gas), rt, 92% for **10** from **8**, 85% for **16** from **14** j) $(COCl)_2$, $Cl(CH_2)_2Cl$, 80°C; NH_3(gas), rt, 89% for **11**, 70% for **17** k) HCl, ^iPrOH, 90°C, 99% l) p-TsOH, MeOH, rt, 86% m) BnCl, KOH, 130°C, 100%

As shown in **Scheme 2**, the key substrates **12** and **17** being synthetically equivalent to **2** were prepared starting from inexpensive D-fructose **5**. Thus, **5** was first converted to 6-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-D-psicofuranose **7** in 38% overall yield according to the reported methods[3b, 9] with several improvements in the reaction conditions. The critical benzylglycoside formation of **7** turned out to be effected in a site-, chemo-, and stereoselective manner by employing benzyl alcohol in the presence of trifluoromethanesulfonic acid or methanesulfonic acid at ambient temperature, furnishing the desired benzylglycoside **8**, $[\alpha]_D^{20}$-30.0°(c=1.55, CHCl3), in 74% and 66% yields, respectively. The stereochemical issue with respect to the anomeric center in **8** was corroborated unambiguously by its conversion to the oxetane derivative.[10] Swern oxidation of **8** followed by sodium chlorite oxidation of the resulting aldehyde provided the carboxylic acid **9**. For introducing a urea unit required for hydantoin ring formation, direct access to the *N*-acylurea **11** from **9** was first examined. All attempts to directly acylate urea with the activated carboxylic acid derivatives obtainable from **9** met with failure, presumably due to both low nucleophilicity of urea and steric hindrance of the carbonyl group in **9**. However, success was eventually realized by following stepwise reaction sequence. Thus, the mixed acid anhydride derived from **9** was allowed to react with gaseous ammonia, yielding the amide **10**, mp 145-146°C, $[\alpha]_D^{20}$ -37.4°(c=1.23, CHCl3). The reactive *N*-acylisocyanate *in situ* generated by treating **10** with oxalyl chloride was subjected to the reaction with gaseous ammonia, giving rise to **11**, $[\alpha]_D^{20}$-68.1°(c=1.06, CHCl3), in 82 % overall yield from **8**. Acidic hydrolysis of the acetonide moiety in **11** afforded the key D-psicofuranose derivative **12**, $[\alpha]_D^{20}$-40.7°(c=0.67, CHCl3-MeOH=1:1v/v), in a quantitative yield. Next, preparation of another key D-psicopyranose derivative **17** was attempted starting from **6**. Thus, acidic hydrolysis of the acetonide moiety in **6** followed by complete benzylation of the resulting triol provided the tribenzyl ether **13**, $[\alpha]_D^{20}$+1.0°(c=7.78, CHCl3). By employing the reaction sequence similar to that described for the preparation

Scheme 3



of **11** from **7**, **13** was converted to **17**, $[\alpha]_D^{20}$-20.0°(c=1.99, $CHCl_3$), *via* **14**, $[\alpha]_D^{20}$-80.2°(c=1.34, $CHCl_3$), **15**, and **16**, $[\alpha]_D^{20}$-5.25°(c=1.10, $CHCl_3$).

With the key intermediates **12** and **17** possessing the requisite carbon frameworks and functional groups with correct stereochemistries at the C2, C3, and C4 positions (hydantocidin numbering) in hand, we next focused our attention to the crucial intramolecular *N,O*-spiroketal formation of **2** which should be generated *in situ* by removal of the protective groups. As shown in **Scheme 3**, complete debenzylation of **12** furnished an equilibrium mixture of the furanose and the pyranose derivatives **18** and **19** in a quantitative yield. Structural assignments of **18** and **19** were achieved by the ^{13}C-NMR spectrum of the mixture. After experiments, this mixture was found to be isomerized by simple thermal treatment to the hydantoin **20** as an inseparable epimeric mixture. Additionally, **17** could be also converted to **20** in a similar manner to that described above *via* the equilibrium mixture of **18** and **19**. These observations can be explained as follows. Thus, **18** and **19** initially produced from **12** and **17**, respectively, promptly take place tautomerism through **2**, producing the equilibrium mixture of **18** and **19**. Subsequent hydantoin ring formation gradually occurs from **2** which intervenes between **18** and **19**, ultimately yielding thermodinamically most stable **20**. The final intramolecular *N,O*-spiroketal formation was best effected by exposure of **20** to Dowex 50X(H^+) in ^{n}PrOH-H_2O(2:1v/v) at 45°C, giving rise to **1**, mp 186-189°C[lit.[1] mp 187-189°C] and $[\alpha]_D^{25}$+30.2°(c=0.61, H_2O)[lit.[1] $[\alpha]_D^{20}$+28.8° (c= 1.04, H_2O)], along with 5-*epi*-hydantocidin **21**, $[\alpha]_D^{20}$-10.8°(c=0.61, MeOH)[lit.[5b] $[\alpha]_D^{20}$-11.0°(c=0.30, MeOH)], in a ratio of 43:57 in 90% yield.[11, 12, 13, 14] The latter C5 epimer **21** has been reported to exhibit herbicidal activity being almost 60% of that of **1**.[15] The spectroscopic properties (IR, ^{1}H-NMR, MS) of both **1** and **21** were identical with those of authentic samples.

In summary, we have succeeded in developing a novel synthetic scheme to **1** based on the proposed biosynthetic pathway. The explored synthetic scheme which is obviously more efficient than those previously reported,[3] may be applicable to an industrial scale preparation of **1** and **21** due to operational simplicity and uses of inexpensive and less toxic reagents. Since it is implied that enzymatic conversion of **2** to **1** *in vivo* might proceed in a more highly stereoselective manner, further studies to improve stereoselectivity in the intramolecular *N,O*-spiroketal formation are in progress.

Acknowledgement

We are grateful to Drs. S. Mio and S. Sugai, Agricultural Chemicals Research Laboratories, Sankyo Co. Ltd., for providing us with IR and ^{1}H-NMR spectra of both **1** and **21**.

References and Notes

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7. For the structure-activity relationship of **1**: a) Mio, S., Sano, H., Shindo, M., Honma, T., Sugai, S., *Agric. Biol. Chem.*, **1991**, *55*, 1105-1109. b) Mio, S., Sugai, S., *Annu. Rep. Sankyo Res. Lab.*, **1991**, *43*, 133-139.
8. No obvious biosynthetic pathway has *hitherto* been proposed for **1**.
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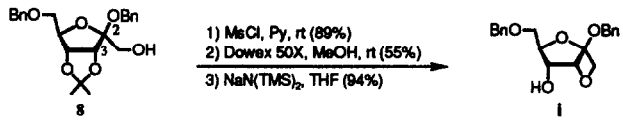
10. As shown in the following scheme , sequential mesylation of **8**, removal of the acetonide group, and oxetane ring formation produced **i**. Based on this chemical transformation, the C2 hydroxymethyl and the C3 hydroxy groups in **8** were assigned to have *cis* configuration.[3b]



11. Quite recently, Fleet *et al.* reported that unnatural **21** is thermodynamically more stable than natural **1** and the ratio of **21** to **1** in the mixture equilibrated under protic acidic conditions is approximately 4:1.[6]
12. Direct cyclization of the equilibrium mixture of **18** and **19** resulted in a poor yield of the mixture of **1** and **21**.
13. If the cyclization was performed in other alcoholic media such as MeOH, EtOH, ^{i}PrOH, ^{n}BuOH, or ^{t}BuOH under the same conditions as for in ^{n}PrOH , an epimeric mixture of **1** and **21** was obtained in a ratio of 19:81~34:66. Full details of our observations on the cyclization of **20** will be reported separately.
14. ^{1}H-NMR or ^{13}C-NMR spectra of the key intermediates are as follows:

    12: ^{1}H-NMR(400MHz, CD_3OD) δ 3.57(1H, dd, J=10.8, 5.9Hz, H-6), 3.80(1H, dd, J=10.8, 2.3Hz, H-6), 4.09(1H, d, J=4.2Hz, H-3), 4.25(1H, d, J=10.8Hz, -C<u>H</u>$_2$Ph), 4.32(1H, dd, J=8.3, 4.2Hz, H-4), 4.38(1H, ddd, J=8.3, 5.9, 2.3Hz, H-5), 4.53-4.63(3H, m, -C<u>H</u>$_2$Ph), 7.19-7.38(10H, m, Ar-H).

    17: ^{1}H-NMR(400MHz, $CDCl_3$) δ 3.69(1H, dd, J=12.3, 2.2Hz, H-6), 3.74-3.78(1H, m, H-5), 3.89(1H, t, J=3.1Hz, H-4), 4.10(1H, dd, J=12.3, 2.4Hz, H-6), 4.17(1H, dd, J=2.8, 1.0Hz, H-3), 4.38(1H, d, J=11.2Hz, -C<u>H</u>$_2$Ph), 4.46(1H, d, J=11.2Hz, -C<u>H</u>$_2$Ph), 4.59(2H, s, -C<u>H</u>$_2$Ph), 4.66(1H, d, J=11.4Hz, -C<u>H</u>$_2$Ph), 4.73(1H, d, J=12.5Hz, -C<u>H</u>$_2$Ph), 4.77(1H, d, J=12.5Hz, -C<u>H</u>$_2$Ph), 4.95(1H, d, J=11.4Hz, -C<u>H</u>$_2$Ph), 5.19(1H, brs, >NH), 7.21-7.36(20H, m, Ar-H), 8.00(1H, brs, >NH), 8.82(1H, brs, >NH).

    20: ^{13}C-NMR(100MHz, D_2O) δ major: 178.9(C-2), 161.0(C-4), 90.6(C-5), 75.7, 74.8, 72.8, 65.1(C-4'). minor: 178.5(C-2), 161.0(C-4), 88.9(C-5), 76.0, 75.4, 74.2, 64.5(C-4').
15. Private communication from Dr. S. Mio, Agricultural Chemicals Research Laboratories, Sankyo Co. Ltd..

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