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Stereoselective Bromination of β-Ribofuranosyl Amide. Enantioselective Synthesis of (+)-Hydantocidin

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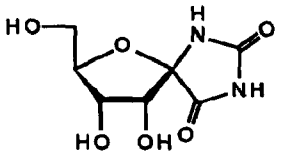
Summary: The synthesis of hydantocidin, a potent herbicidal natural product, is highlighted by a stereoselective bromination of β-D-ribofuranosyl amide to give only the α-bromo β-amide and subsequent spirocyclization about the anomeric position with silver cyanate to form the hydantoin moiety.

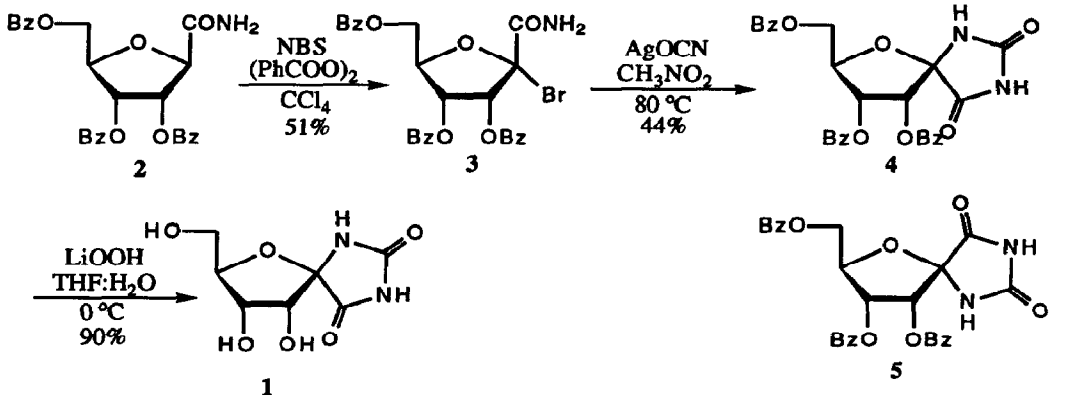
Hydantocidin (**1**) is a potent non-selective herbicidal natural product produced from *Streptomyces hygroscopicus* which was isolated by fermentation from a soil sample collected in Japan.[1] The unusual structure containing a hydantoin ring spiro-annulated at the anomeric position of β-D-ribofuranose as well as the potential commercial utility[2] of **1** prompted us to develop a total synthesis. Although **1** has been prepared previously, none of these approaches are economically feasible in terms of overall yield, the number of required synthetic transformations, or stereochemical selectivity.[3] Unlike the prior routes, we chose to begin with an intact ribofuranose where the C-2, C-3, and C-4 positions possess the required configuration and the anomeric C-1 position can potentially be stereochemically controlled. In particular, we envisioned that the α-bromide **3** would be an ideal intermediate to react with silver cyanate in order to form the desired spirocycle. Reported herein is the successful application of this approach for the preparation of (+)-hydantocidin (**1**).



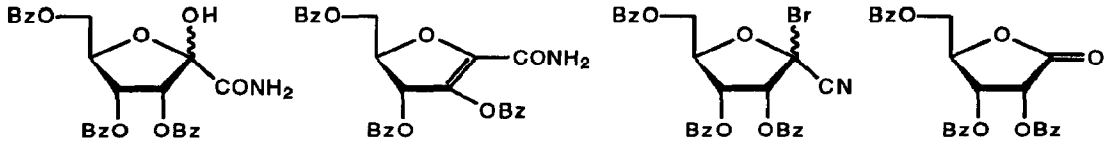
1

Hydration of the readily available 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[4] with manganese(IV) oxide-CH_2Cl_2 was an efficient protocol[5] for preparing the β-amide **2** in 95% yield (41% recovered nitrile). Extended reaction times led to an increased yield of **2** (82%, 12 d) but lower recovery of the starting nitrile. Free radical bromination[6] by refluxing a mixture of **2** and NBS with benzoyl peroxide initiation in carbon tetrachloride led to the formation of **3** (51% yield) as a single stereoisomer tentatively assigned as the α-bromo-β-amide depicted.[7] Confirmation of this structural assignment was based on the following experiments. Treatment of **3** with tributyltin hydride and 2,2'-azobis(2-methyl-propionitrile) initiation[8] furnished the β-amide **2** as well as a minor amount of the anti-elimination product (**7**, see below). Furthermore, a positive heteronuclear nOe was observed between the β-$\underline{C}ONH_2$ and the upfield H-5. These results strongly suggest that the anomeric radical of ribo-

furanosyl amide is attacked at the α-position with retention of configuration, an observation consistent with glucosyl radicals.[9] Precedent for such an observation is provided by Ferrier who has pioneered photobromination[10] on the related six-membered cyclic glycuronic acid derivatives which preferentially take place to give α-adducts at C-5.[11] This represents the first known example of stereoselective intermolecular anomeric radical trapping from the alpha face of a ribofuranose system. While pyranosyl radicals are well documented to give a high diastereoselectivity for axial bond formation,[12] furanosyl radicals have previously been shown to provide anomeric mixtures.[13]



Spirocyclization of **3** was effected with freshly prepared silver cyanate[14] (4 equiv) at 80 °C in anhydrous nitromethane.[15] A 2:1 mixture of bicycles **4** and **5** were obtained, respectively, in 46% yield. The mixture was separated by careful flash column chromatography and the minor isomer **5** subjected to camphorsulfonic acid (0.05 N in methanol, 1 equiv) at 70 °C which established a 6:1 equilibrium mixture of **4** and **5**, presumably facilitated by anchimeric assistance of the 2α-benzoate group, accompanied by a minor amount (<10%) of C-5 saponification.[16] In this way an overall yield of 44% of **4** from **3** was obtained. Interestingly, two unavoidable by-products were isolated from the formation of both **3** and **4**, namely, the corresponding hydroxyamide **6** and unsaturated amide **7** which reflects the lability of the anomeric bromide. It was also found that treatment of 1-bromo-D-furanosyl cyanide **8** (prepared in 73% yield as described in ref. 7) with silver cyanate cleanly formed the ribonolactone **9** which was confirmed by independent synthesis. Similar observations to these from the reaction of 1-bromo-D-glycosyl



6 **7** **8** **9**

cyanides with mercuric acetate have been reported.[17] Deprotection of pure **4** with lithium peroxide[18] (5 equiv) in tetrahydrofuran-water (5:1) at 0 °C produced a 90% yield of **1**.[19] (+)-Hydantocidin (**1**) thus obtained was identical in all respects to the natural product as shown by ^{1}H NMR, ^{13}C NMR, uncorrected mp 178-180 °C (lit.[1a] mp 187-189 °C), and $[\alpha]_D^{25}$ +28.5° (lit.[1a] $[\alpha]_D^{25}$ +28.8°).[20]

We have described a simple and efficient five step synthesis of (+)-hydantocidin (**1**) in 19% overall yield (based on unrecovered starting material) from commercially available reagents (the overall yield is 17% with no recovery of starting nitrile **2**).[21,22] During these studies it was found that β-ribofuranosyl amide is stereoselectively brominated with retention of configuration (**2**→**3**). This finding has implications for a variety of glycosidation

reactions and further experiments with other ribofuranoses bearing large anomeric groups, particularly C-nucleosides, are in progress. The mechanism of action of 1 has yet to be determined and on-going enzymology studies may lead to the identification of a novel herbicidal target site. We also believe that this methodology should be applicable to carbohydrate based derivatives of hydantocidin with expected herbicidal activity. This proposal is currently being tested.

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(7) The regioselectivity, unlike the stereoselectivity, observed upon bromination of 2 can possibly be understood in terms of the capto-dative effect. However, bromination of the corresponding nitrile under identical conditions gave rise to a 1:1 mixture of bromoglycosyl cyanides **8**. For a review of the capto-dative effect, see: Viehe, H.; Janousek, Z.; Merényi, R. *Acc. Chem. Res.* **1985**, *18*, 148. Capto-dative stabilization has been invoked for radical-mediated brominations at ring positions of carbohydrates, consider: Somsák, L.; Ferrier, R. *Adv. Carbohydr. Chem. Biochem.* **1991**, *49*, 37.

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(19) Deprotection of **4** with 1% sodium hydroxide-methanol at 80 °C caused spiroisomerization to produce an 88% yield of **1** and its diastereomer (2:1).

(20) All synthetic compounds afforded satisfactory ^{1}H NMR, ^{13}C NMR, MS, and IR spectroscopic data.

(21) The nitrile **2** is prepared in quantitative yield from commercially available tri-*O*-benzoyl D-ribofuranose acetate, which is itself prepared from D-ribose in two steps and 71.3% overall yield (Ness, R. K.; Diehl, H. W.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 763) or in one operation in 56-57% yield (Recondo, E. F.; Rinderknecht, H. *Helv. Chim. Acta* **1959**, *42*, 1171; Kissman, H. M.; Pidacks, C.; Baker, B. R. *J. Am. Chem. Soc.* **1955**, *77*, 18).

(22) After the submission of our manuscript, a publication appeared (ref. 3d) describing a clever synthesis of **1** which compares well in terms of length and efficiency (12 steps and 7% overall yield from D-fructose) with ours [7 steps and 13.5% overall yield or (6 steps and 11% overall yield) from D-ribose].

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