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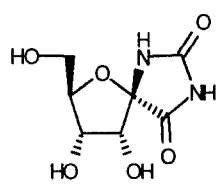
Stereoselective Synthesis of (+)-Hydantocidin

Philippe Chemla

Plant Protection Division, Ciba-Geigy Ltd., CH-4002 Basel, Switzerland

Abstract: The naturally occurring spironucleoside (+)-hydantocidin **1** was synthesized from 1,2:3,4-di-*O*-isopropylidene-D-psicofuranose using a new oxygen-bridged intramolecular Vorbrüggen coupling of the N-hydroxyurea **5** in presence of a catalytic amount of trimethylsilyltriflate.

(+)-Hydantocidin **1** is a natural spironucleoside which has been isolated from the fermentation broth of *Streptomyces hygroscopicus* SANK 63584,[1] Tu-2474[2] and A1491,[3] that exhibits an interesting profile of herbicidal and plant growth regulatory activities. Its unique structure provides the first example of a nucleoside with a spirohydantoin nucleus attached to a sugar at the anomeric position. Because of this unusual structural feature and hydantocidin's potent biological activity, considerable synthetic work has been invested on the preparation of the parent compound[4] and on various deoxyhydantocidin analogs.[5] Furthermore, studies on structure-activity relationships showed that among the 16 diastereoisomers possible with the 4 contiguous stereogenic centers, only the natural compound was biologically active.[6]



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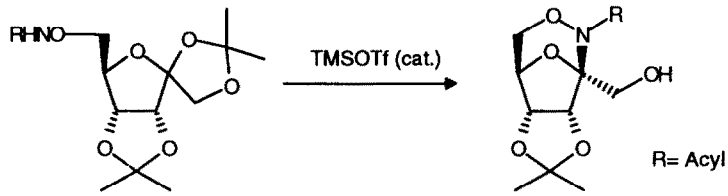
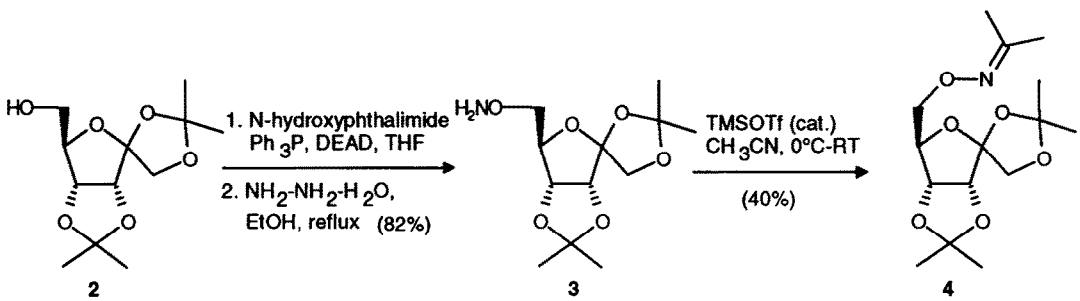
The low fermentation yield prompted us to develop a practical multigram synthesis in order to evaluate in detail the biological activity of (+)-hydantocidin. Studies of the previous syntheses[4] showed that the main challenge is the control of the configuration at the anomeric center. This difficulty is compounded by the fact that the isomer bearing nitrogen in the α-anomeric position is thermodynamically more stable than the β-isomer.[7] This paper reports a short stereocontrolled synthesis of (+)-hydantocidin **1**, based on a new intramolecular oxygen-bridged Vorbrüggen coupling[8] yielding exclusively the N-β-isomer (scheme 1).



Scheme 1

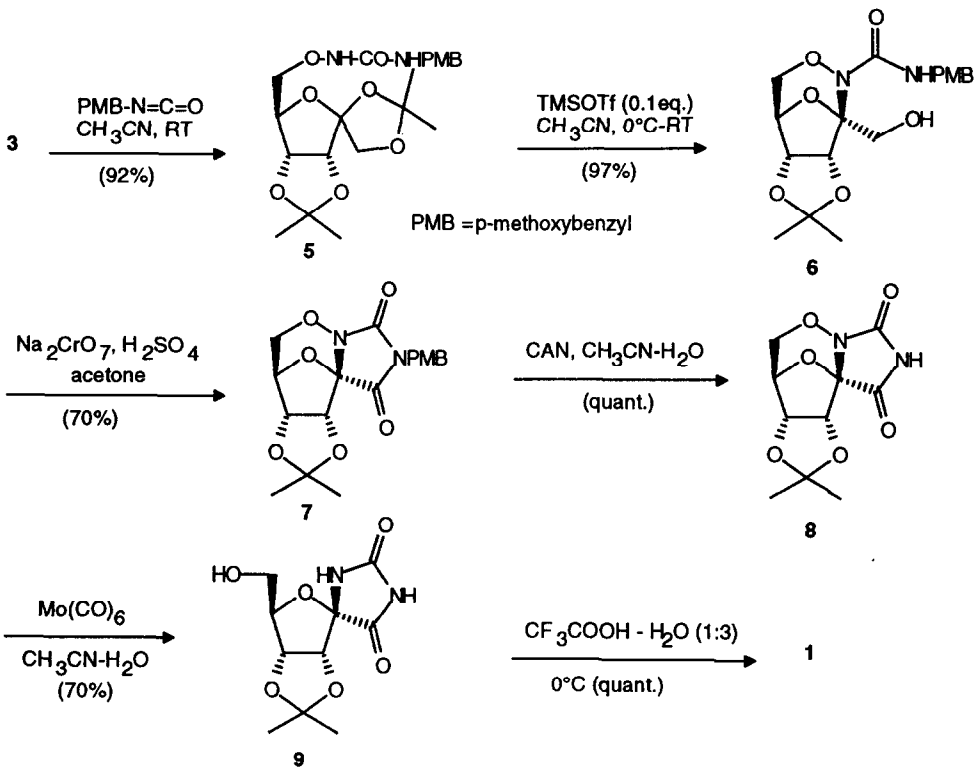
Scheme 2 and 3 show the route followed to our intended target. 1,2:3,4-Di-*O*-isopropylidene-D-psicofuranose **2**, which is readily available on a large scale from D-fructose following Moffat's improved procedure,[9] was chosen to provide the required carbon framework. Conversion of **2** to the corresponding hydroxylamine **3** was effected in a two step sequence by substitution of the 5'-OH by N-hydroxyphthalimide followed by cleavage with hydrazine[10] (82% yield, 2 steps). Initial attempts towards internal cyclization on the free hydroxylamine **3** catalyzed with trimethylsilyltriflate led only to the oxime **4**.[11]



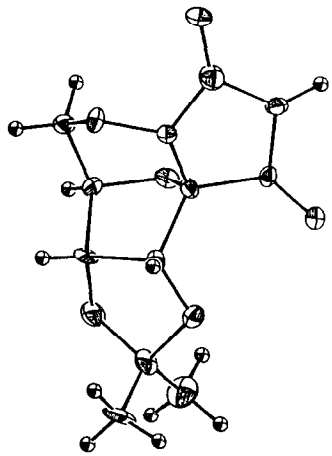
Scheme 2

In order to prevent the intermolecular acetone migration, compound **3** was converted to the *p*-methoxybenzylurea[12] **5** (92% yield). Treatment of the latter at room temperature with a catalytic amount trimethylsilyltriflate led to the isoxazolidine **6** in 97% yield. The configuration at C-1 is thus fixed eliminating any risk of epimerization. In contrast to the usual Hilbert-Johnson[8c] reaction, the attacking nitrogen does not need to be silylated prior to coupling. Compound **6**, when treated with Jones reagent,[13] underwent oxidation and spontaneously cyclized to the tricyclic isoxazolidine hydantocidin **7** which, after treatment with ceric ammonium nitrate (CAN),[14] afforded the crystalline compound **8**,[15] whose structure was confirmed by single crystal X-ray structural analysis.[16] Presumably, because of a deactivation of the N-O bond by the carbamoyl group, the conventional cleavage methods (H_2-Pd/C, H_2-Ra/Ni,[17] Zn/AcOH,[18] Li/NH_3,[19] Al-Hg[20]) failed. However, the organometallic complex $Mo(CO)_6$ [21] proved to be the reducing agent of choice in this case, and the resulting 2',3'-isopropylidene-hydantocidin **9** (70% yield) was subsequently deprotected with trifluoroacetic acid in aqueous solution for two hours in quantitative yield (prolonged reaction times caused epimerization at C-1). The synthetic compound was found to be identical in every respect with the natural product.

By this route, (+)-hydantocidin was obtained in 8 steps with an overall yield of 36% starting from 1,2:3,4-di-*O*-isopropylidene-D-psicofuranose.



Scheme 3



ORTEP representation of [1S,8R,9R,13R]-11,11-dimethyl-6,10,12,14-tetraoxa-3,5-diaza-tetracyclo[6.5.1.$0^{9,13}$.$0^{1,5}$] tetradodecane-2,4-dione **8**

Although another oxygen-bridged intramolecular Vorbrüggen coupling used for the preparation β-2'-deoxyuridine has been reported recently,[22] our method appears to be very flexible, and may provide an

efficient access to other β-N-spironucleosides as well as a large number of nucleosides, if the cyclization could be extended to other sugars. Work in this direction is now in progress in our laboratories.

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