Tetrahedron Letters, Vol. 34, No. 20, pp. 3327-3330, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis of 1-*epi*Hydantocidin from D-Ribose

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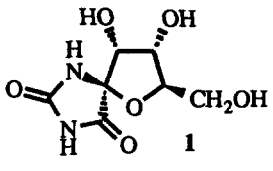
Abstract: A key step in a short synthesis of 1-*epi*hydantocidin (2) is the unanticipated transformation of azidolactones (8) and (10) to a bicyclic amine (12) induced by tetra-*n*-propyl-ammonium perruthenate in the presence of morpholine-N-oxide. The structure of (12) was established by X-ray crystallographic analysis.

The isolation of hydantocidin (1) from the fermentation broth of *Streptomyces hygroscopicus* SANK 63584 provided the first example of a spirohydantoin nucleus at the anomeric position of a sugar.[1]



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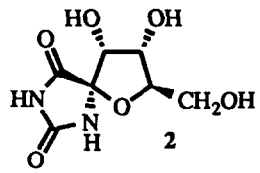
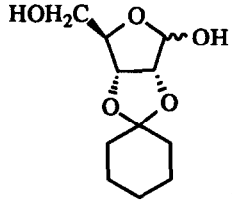


2

Because of the potent herbicidal and plant growth regulatory activity of the natural product (1),[2] considerable interest has been shown in the synthesis of hydantocidin itself[3] and of its stereoisomers by aldol,[4] dihydroxylation[5] and other procedures.[6] Various deoxyhydantocidins have also been described.[7] As yet, no proposal has been made for the mode of action of hydantocidin. This paper reports a short synthesis of 1-*epi*hydantocidin (2) in which the key step is the transformation of the azidolactones (8) and (10) to the bicyclic amine (12) by tetra-*n*-propyl-ammonium perruthenate (TPAP) in the presence of morpholine-N-oxide.



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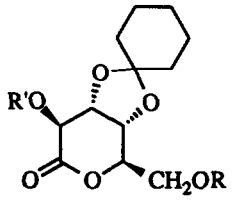
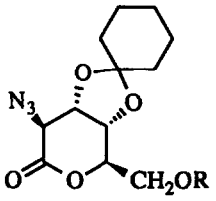
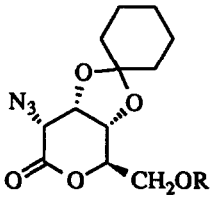


4 R = R' = H
5 R = *t*-BuMe$_2$Si; R'= H
6 R = *t*-BuMe$_2$Si; R'=SO$_2$CF$_3$



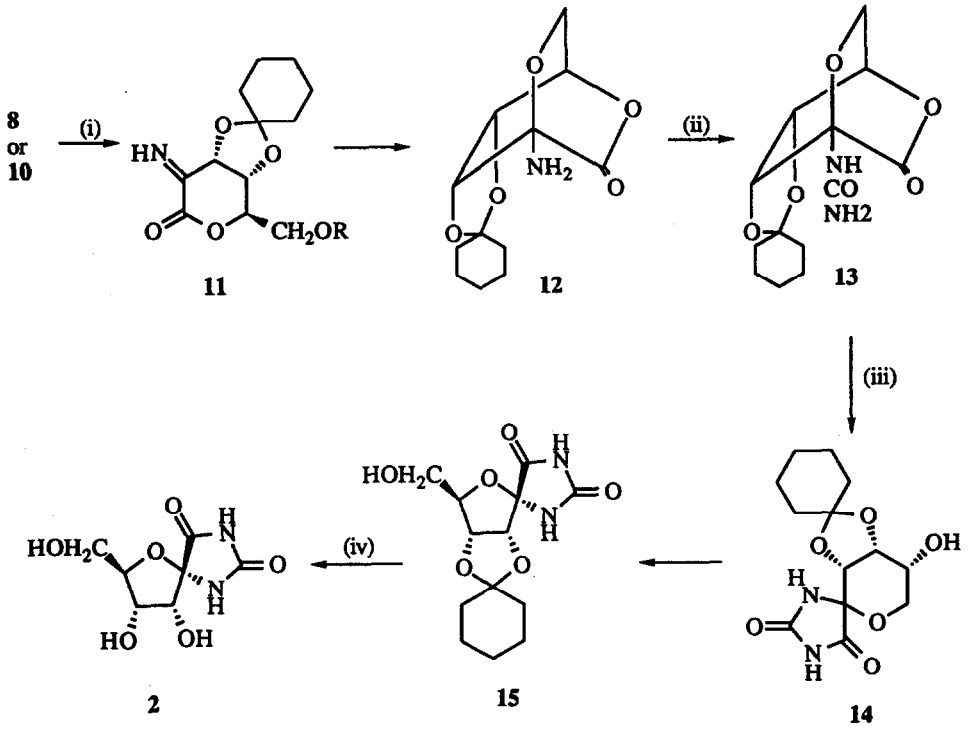
7 R = *t*-BuMe$_2$Si
8 R = H



9 R = *t*-BuMe$_2$Si
10 R = H

In a project directed to the synthesis of very highly substituted cyclopentane α-amino acids, the azido lactones (8) and (10) were prepared from D-ribose.[8] Treatment of cyclohexylidene ribose (3)[9] with sodium cyanide under conditions described for the Kiliani synthesis for isopropylidene ribose[10] resulted in the formation[11,12] of the crystalline *altrono*-δ-lactone (4), m.p. 119-120 °C, $[\alpha]_D^{20}$ +80.4 (*c*, 1.02 in EtOH). The primary hydroxyl group in (4) was protected as the silyl ether (5), m.p. 74-75°C, $[\alpha]_D^{20}$ +71.3 (*c*, 1.02 in $CHCl_3$), by reaction with *tert*-butyldimethylsilyl chloride in dimethylformamide in the presence of imidazole [92% yield]. The remaining secondary hydroxyl group was esterified with triflic anhydride in dichloromethane in the presence of pyridine to afford the triflate (6), m.p. 76-78°C, $[\alpha]_D^{20}$ +19.1 (*c*, 1.1 in $CHCl_3$), which is a

stable crystalline solid,[13] in quantitative yield. Reaction of the triflate (6) with sodium azide in dimethylformamide for 10 min gave a mixture of the *altrono*azidolactone (7), m.p. 67-68°C, $[\alpha]_D^{20}$ +18.2 (*c*, 1.06 in $CHCl_3$), in 50% yield, and the *allono*azidolactone (9), m.p. 160-162°C, $[\alpha]_D^{20}$ -77.2 (*c*, 1.08 in $CHCl_3$) in 25% yield. The epimerisation of protected α-azides of δ-lactones by sodium azide under these conditions is precedented.[14] Attempts to remove the silyl ether protecting groups in (7) and (9) by fluoride caused substantial decomposition, probably by base catalysed pathways. However, the silyl ethers group in (7) could be selectively removed by treatment with aqueous acetic acid at 60°C to give the *altrono*azide (8)[15] in 76% yield, together with a trace of the *allonoazide* (10). In contrast, treatment of (9) with aqueous acetic acid at 60°C afforded the *allonoazide* (10)[16] in only 47% yield, accompanied by 28% of (8); thus, even aqueous acetic acid can cause significant epimerisation of some α-azidolactones.[17]



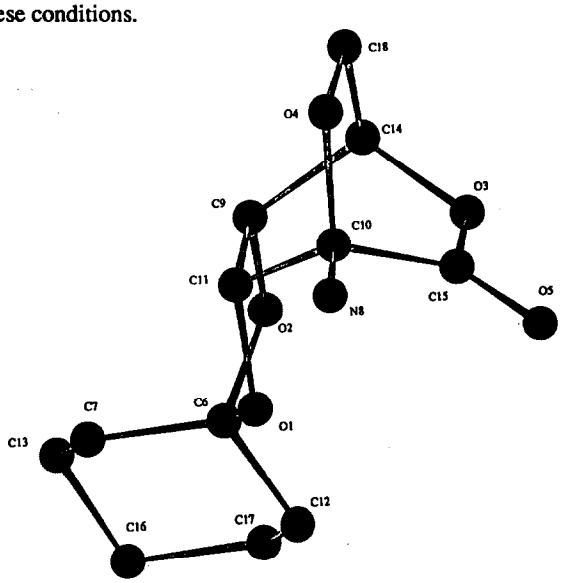
Scheme: (i) TPAP, morpholine-N-oxide in MeCN, room temp, 1 h (ii) KCNO in AcOH, 60°C, 1.5 h (iii) *tert*-BuOK in THF, room temp, 10 min (iv) aq. CF_3COOH, room temp, 2 h

A large number of attempts was made to oxidise the azidoalcohols (8) and (10) to the corresponding aldehydes for a project in which the objective was to make very highly substituted cyclopentanes by intramolecular aldol condensations.[18] Most oxidising agents had little effect on either of the azidoalcohols but reaction of the *altrono*azide (8) with tetra-*n*-propylammonium perruthenate (TPAP) in the presence of morpholine-N-oxide gave a single product (12) in 63% yield; similar treatment of the *allono*azide gave (12) in 61% yield. TPAP is an excellent, selective and versatile oxidant for the oxidation of alcohols to the corresponding carbonyl compounds[19] but in this case there has been no oxidation of the alcohol. The reagent has induced the azide (8) to undergo disproportionation to an intermediate imine (11) [Scheme] and nitrogen,

followed by the intramolecular trapping of (11) by the primary hydroxyl group to give the bicyclic amine (12);[20] the structure of the bridgehead amine (12) was established by single crystal X-ray structural analysis.[21]

The amine (12) has the correct functionality at C-1 for subsequent elaboration for a synthesis of a spirohydantoin at the anomeric position of ribose. Thus, treatment of (12) with potassium cyanate in acetic acid afforded the urea (13), m.p. 258-262°C (decomp, MeOH), $[\alpha]_D^{20}$ -46.9 (*c*, 0.7 in MeOH), which with potassium *tert*-butoxide in tetrahydrofuran gave the protected *epi*hydantocidin (15)[22] in an overall yield of 61% over the two steps. Deprotonation of the urea followed by intramolecular attack at the lactone carbonyl may give a spirohydantoin of a pyranose (14); however, all attempts to isolate (14) were unsuccessful so that, under the reaction conditions, the base must induce further ring opening and closing to give the more stable furan derivative (15). The cyclohexylidene group in (15) was removed by treatment with trifluoroacetic acid:water [3:2] to give 1-*epi*hydantocidin (2)[23] in 98% yield, with infrared, ^1H and ^{13}C NMR spectra consistent with those provided by Dr. S Mio of Sankyo Agricultural Research Laboratories and Dr. S Mirza of CIBA GEIGY.

1-*epi*Hydantocidin (2) is more thermodynamically stable than the natural product (1). Treatment of an authentic sample of hydantocidin [generously provided by Dr Mirza] with 40% aqueous trifluoroacetic acid for 16 h at room temperature gave a mixture of the two epimers in a ratio, as indicated by NMR, of approximately 2.2:1 of the unnatural (2) to hydantocidin (1); after 32 h, the ratio had changed to 4.0:1. When (2) was treated under the same conditions, after 16 h the ratio of (2) to (1) was approximately 10:1 and after 32 h, about 4.5:1. Thus, although the spirohydantoin survives such treatment with acid, the stereochemistry at the anomeric position equilibrates under these conditions.



X-ray Crystal structure of (4R,7S,8R)-1-Amino-7,8-*O*-cyclohexylidene-7,8-dihydroxy-2,5-dioxabicyclo[2.2.2]octan-6-one (12)

Most azides which are not α- to a lactone carbonyl function are not significantly affected by TPAP; the scope and limitations of the TPAP-induced reaction with α-azidolactones and of other reagents that may accomplish the type of transformation reported in this paper are currently under investigation. Synthetic hydantoins have a long history as chemotherapeutic agents for the treatment of diseases as diverse as epilepsy

and AIDS.[24] The chemistry described in this paper, if it works generally, may provide access to novel spirohydantoins at the anomeric position of pyranose and furanose sugars which may have interesting biological properties.

Acknowledgements: We are very grateful to Dr. S. Mirza of CIBA GEIGY Basle for spectra and for an authentic sample of hydantocidin, and also to Dr S. Mio of Sankyo Agricultural Research Laboratories for spectra. This work has been supported by an SERC graduate studentship [to AJF].

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11. Spectrocopic and microanalytical data consistent with the proposed structure have been obtained for all new compounds reported.
12. The overall yield of (4) from D-ribose is 20% and is significantly higher and easier to isolate than is the case for the altronolactone from the Kiliani ascension of isopropylidene ribose.
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14. Fleet, G. W. J., Bruce, I., Girdhar, A., Haraldsson, M., Peach, J. M., Watkin, D. J., *Tetrahedron*, 1990, **46**, 19.
15. Data for *altrono*azidolactone (8): m.p. 97-99°C, $[\alpha]_D^{20}$ +28.9 (*c*, 1.01 in $CHCl_3$), ν_{max} (KBr) 2119 (N_3), 1762 (C=O) cm^{-1} ; δ_H ($CDCl_3$) 1.43-1.78 (10H, m, cyclohexylidene), 3.87 (1H, dd, H-6, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 12.8 Hz), 4.06 (1H, dd, H-6', $J_{5,6'}$ 2.6 Hz), 4.21 (1H, ddd, H-5, $J_{4,5}$ 9.4 Hz),4.30-4.32 (2H, m, H-2, H-3), 4.42 (1H, m, H-4); δ_C ($CDCl_3$) 23.3, 23.7, 24.7, 33.9, 36.6 (5 x t, cyclohexylidene), 61.3 (t, C-6), 62.3 (d, C-2), 69.9, 75.2, 78.8 (3 x d, C-3, C-4, C-5), 113.8 (s, cyclohexylidene), 167.5 (s, C-1).
16. Data for *allono*azidolactone (10): m.p. 110-112°C, $[\alpha]_D^{20}$ -68.8 (*c*, 1.03 in EtOH). ν_{max} (KBr) 3438 (OH), 2116 (N_3), 1757 (C=O) cm^{-1} ; δ_H (d_6 acetone) 1.40-1.77 (10H, m, cyclohexylidene), 3.94 (2H, br, d, H-6, H-6', J 4.0 Hz), 4.58 (1H, t, H-5, J 4.1 Hz), 4.67 (1H, d, H-4, $J_{3,4}$ 4.1 Hz), 4.79 (1H, d, $J_{2,3}$ 7.3 Hz), 4.97 (1H,dd, H-3); δ_C (d_6 acetone) 23.3, 23.6, 24.6, 33.4, 35.9 (5 x t, cyclohexylidene), 58.3 (d, C-2), 62.3 (t, C-6), 73.5, 76.1, 82.8 (3 x d, C-3, C-4, C-5), 110.4 (s, cyclohexylidene), 167.2 (s, C-1).
17. The assignments of the stereochemistries of the azidolactones (8) and (10) at C-2 are given on the basis of n.O.e. experiments.
18. Fairbanks, A. J., Elliott, R. P., Hui, A. H., Smith, C., Storer, R. C., Fleet, G. W. J., in preparation.
19. Griffith, W. P., Ley, S. V., *Aldrichimica Acta*, 23, 13 (1990).
20. Data for bicyclic amine (12): m.p. 161-163 °C, $[\alpha]_D^{20}$ -54.2 (*c*, 1.1 in $CHCl_3$), δ_H ($CDCl_3$) 1.36-1.67 (10H, m, cyclohexylidene), 3.89 (1H, d, H-6, $J_{6,6'}$ 10.6 Hz), 4.09 (1H, dd, H-6', $J_{5,6'}$ 2.8 Hz), 4.38 (1H, d, H-3, $J_{3,4}$ 7.6 Hz), 4.49 (1H, dd, H-4, $J_{4,5}$ 2.1 Hz), 4.82 (1H, t, H-5); δ_C ($CDCl_3$) 23.4, 23.6, 24.8, 34.0, 35.3 (5 x t, cyclohexylidene), 63.7 (t, C-6), 73.2, 74.2, 77.1 (3 x d, C-3, C-4, C-5), 83.7 (s, C-2), 112.1 (s, cyclohexylidene), 169.2 (s, C-1).
21. The atomic coordinates for (12) are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW; the crystallographic numbering system differs from that used elsewhere in the text. Any request should be accompanied by the full literature citation for this paper.
22. Data for cyclohexylidene *epi*hydantocidin (15): a white foam, $[\alpha]_D^{20}$ -59.4 (*c*, 1.18 in $CHCl_3$); ν_{max} (film) 3369 (br, OH, NH), 1791, 1735 (hydantoin) cm^{-1} ; δ_H ($CDCl_3$) 1.41-1.78 (10H, m, cyclohexylidene), 3.67 (1H, dd, H-6, $J_{5,6}$ 2.8 Hz, $J_{6,6'}$ 13.0 Hz), 3.87 (1H, dd, H-6', $J_{5,6'}$ 1.6 Hz), 4.50 (1H, br s), 4.90 (1H, d, J 5.9 Hz), 5.02 (1H, d), 5.92 (1H, br s, NH), 8.14 (1H, br s, NH); δ_C ($CDCl_3$) 23.4, 23.8, 24.7, 33.5, 35.9 (5 x t, cyclohexylidene), 63.7 (t, C-6), 80.7, 81.9, 85.2 (3 x d, C-3, C-4, C-5), 94.3 (s, C-2), 115.0 (s, cyclohexylidene),155.4, 175.4 (2 x s, hydantoin)
23. Data for *epi*hydantocidin (2): a white amorphous solid, $[\alpha]_D^{20}$ -7.0 (*c*, 0.52 in MeOH)[Lit: ref 5 above gives white amorphous solid, $[\alpha]_D^{20}$ -11.0 (*c*, 0.30 in MeOH)]; ν_{max} (film) 3333 (br, OH, NH), 1783, 1736 (hydantoin) cm^{-1} ; δ_H (CD_3OD) 3.59 (1H, dd, H-6, $J_{5,6}$ 5.2 Hz, $J_{6,6'}$ 12.1 Hz), 3.66 (1H, dd, H-6', $J_{5,6'}$ 4.3 Hz), 4.09 (1H, ddd, H-5, $J_{4,5}$ 3.2 Hz), 4.17 (1H, dd, H-4, $J_{3,4}$ 4.9 Hz), 4.25 (1H, d, H-3); δ_C (CD_3OD) 63.6 (t, C-6), 73.1, 74.3, 87.1 (3 x d, C-3, C-4, C-5), 94.4 (s, C-2),158.2, 175.7 (2 x s, hydantoin).
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(Received in UK 1 March 1993)