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Novel spirohydantoins of D-allose and D-ribose derived from glyco-α-aminonitriles

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Abstract—The synthesis of 3-spirohydantoin derivatives of D-allose and D-ribose is reported. The key step is the stereoselective conversion of glyco-α-aminonitriles from ulose derivatives of D-glucose and D-xylose using titanium(IV) isopropoxide as a mild and efficient catalyst. Cyclisation of the glyco-α-aminonitriles give the target spirohydantoins.

The herbicidal properties of the natural hydantocidin **1** have stimulated considerable interest in the synthesis of **1** itself and of a wide range of its analogues (Fig. 1).[1–4] Sano reported the synthesis of the carbocyclic derivative **2** of (+)-hydantocidin and the 5-*epi*-carbocyclic analogue **3**.[5] The authors described two routes to spirohydantoins: (1) the Bucherer–Bergs synthesis which gives thermodynamically controlled spiro products; (2) the conversion of an α-aminonitrile into a hydantoin with chlorosulfonylisocyanide followed by acid catalysed hydrolysis. The synthesis of the α-aminonitrile intermediate was performed by treatment of the parent ketone with potassium cyanide and ammonium chloride in MeOH–H_2O. This reaction afforded the epimeric mixture of α-aminonitriles **4** and **5** and the cyanohydrin **6** (Fig. 1). Herbicidal activity was found not to be affected when the D-furanose ring oxygen atom of the natural product was replaced with a methylene unit. Fleet used various α-aminolactones as key intermediates for the synthesis of epimeric spirohydantoins of D-mannofuranose and D-glucopyranose derivatives which are potent glycogen phosphorylase inhibitors.[6]

The target compounds were synthesised from D-glucose and D-mannose derivatives by oxidative ring contraction, resulting from nucleophilic attack of methanol at the lactone carbonyl, followed by migration of the ring oxygen atom to the carbon of the imine intermediate. Reaction of α-aminoesters, located at non-anomeric sites of the sugar, with phenylisocyanates afforded the corresponding ureas, which were converted into the corresponding spirohydantoins under basic conditions.[1,7,8]

Otherwise, carbohydrate spirohydantoins are potential precursors of α-amino acids by basic or enzymatic hydrolysis of the hydantoin ring.[9]

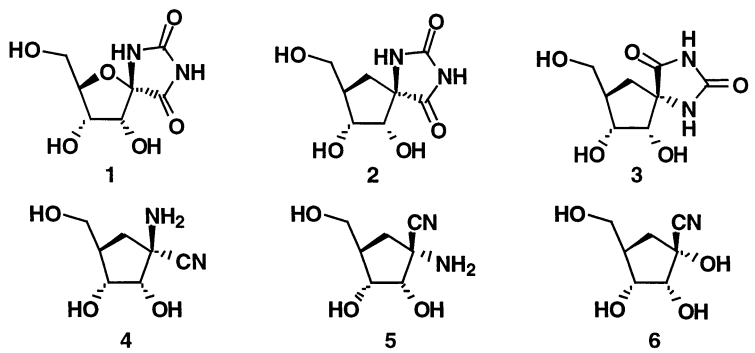

Figure 1.

Keywords: glyco-α-aminontriles; hydantocidin; spirohydantoin.

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We report here the stereoselective synthesis of new 3-spirohydantoins from D-glucose and D-xylose derivatives by a simple and efficient route. The spirohydantoins were synthesised by first converting D-glucose into the ulose **7** by acetonation followed by oxidation (Scheme 1). Attempts to form the spiro ring directly using the conditions reported by Sano[5] (KCN, $(NH_4)_2CO_3$, MeOH–H_2O, 70°C) were unsuccessful and the cyanohydrin **8** was obtained as the exclusive product. Therefore we turned our attention to an alternative route to spirohydantions via α-aminonitrile intermediates. We previously demonstrated that the synthesis of such intermediates from various uloses derivatives was unsuccessful using classical Strecker synthesis conditions. In contrast, we showed that modifying the reaction by using titanium(IV) isopropoxide as a mild Lewis acid catalyst,[10] the glyco-α-aminonitriles **10** could be readily obtained in 80% yield.

Various routes were used to obtain the target compound **14** from **10** via the α-carboxamidoisocyanate intermediate **13**.

Reaction of **10** with both carbon dioxide (MeOH; 75 atm; 85°C; 20 h) and ammonium carbonate (MeOH–H_2O 1/1; 70°C; 4 h) gave the spiro derivative **14** in 80% yield.

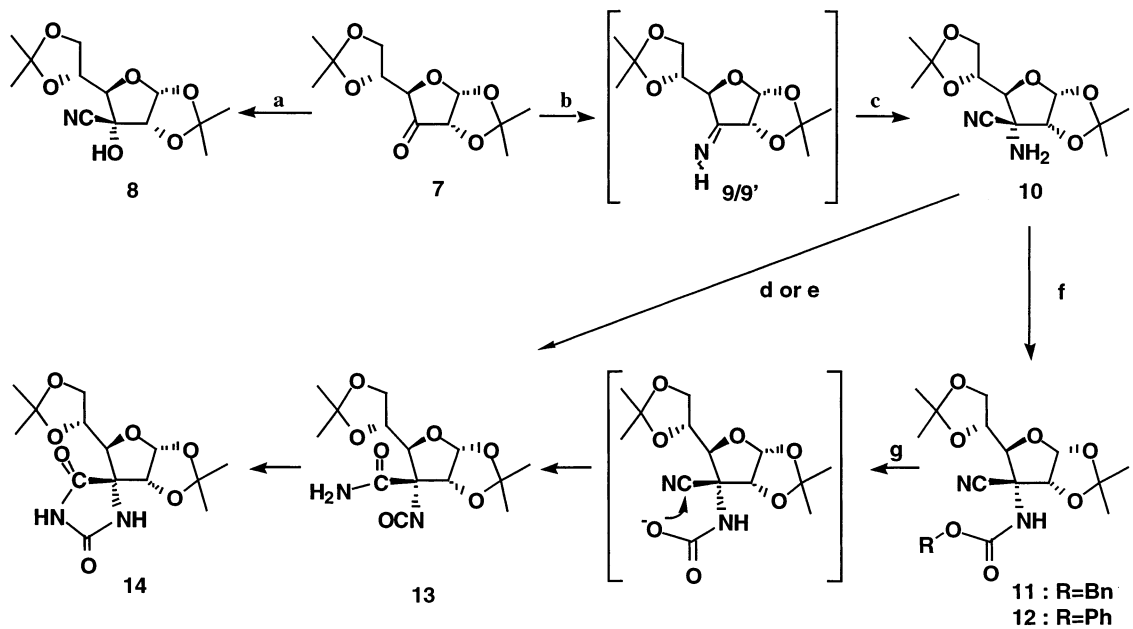
An alternative strategy involving cyclisation and cleavage also proved successful. The amino group of the glyco-α-aminonitrile **10** was activated to the isocyanate **13** following formation of either of the carbamoyl esters **11** or **12** followed by basic hydrolysis. The carbamoyl esters **11** and **12** were obtained by condensation of benzyl and phenyl chloroformate, respectively, with the 3-NH_2 of **10**. It is of note that the classical esterification conditions commonly used in carbohydrate chemistry (toluene–TEA) were unsuccessful. In contrast, carbamoylation was readily achieved using BnOC(O)Cl and PhOC(O)Cl in acetone–H_2O and K_2CO_3 yielding **11** and **12** in 44 and 45% yields, respectively.

The spirohydantoin ring formation was achieved using a *one-pot* procedure that consisted of the formation of the α-carboxamidoisocyanate intermediate **13** which underwent intramolecular cyclisation in basic conditions. Treatment of the benzyloxycarbonyl derivative **11** with NaOH in H_2O–1,4-dioxane at 80°C for 2 h gave a black mixture and the desired spirohydantoin **14** in low yield (20%). The darkness of the reaction mixture may be due to the decarboxylation of the carbamoyl ester to give the initial tertiary α-aminonitrile **10** which is known to be unstable under strong basic conditions. In contrast, **14** was obtained efficiently under the same conditions from the phenyloxycarbonyl derivative **12** in 80% yield.[11]

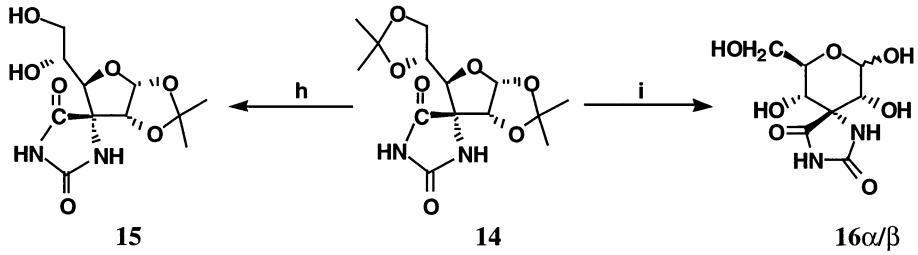
Deprotection of the acetonide group in **14** was achieved with aqueous HCl at room temperature for 1 h to give **15** in 52% yield after 1 h. Alternatively, **14** was treated with aqueous trifluoroacetic acid for 1 h to give **16** in 97% yield (Scheme 2).[12]

Using a similar strategy, spiro ring formation to give **19** (Fig. 2) was achieved directly from the D-ribose α-aminonitrile derivative **17** with CO_2 in 86% yield. Also, **19** was obtained from the phenyloxycarbonyl derivative **18** (83% from **17**) under basic conditions in 85% yield. Treatment of **19** with aqueous trifluoroacetic acid gave **20** in quantitative yield.

In conclusion, we have reported a simple and efficient strategy for the stereoselective synthesis of spirohydantoin at non-anomeric sites of sugars from monosaccha-



Scheme 1. (a) $(NH_4)_2CO_3$, KCN, MeOH; (b) Ti(O*i*Pr)$_4$, NH_3–MeOH; (c) TMSiCN; (d) CO_2 75 atm. MeOH; (e) $(NH_4)_2CO_3$, MeOH–H_2O; (f) ROC(O)Cl, K_2CO_3, acetone–H_2O; (g) NaOH, H_2O–1,4-dioxane.



Scheme 2. (h) Aqueous HCl (1N); (i) CF_3COOH–H_2O, 9/1.

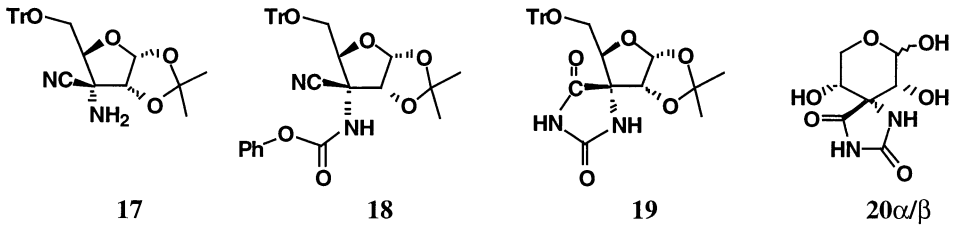


Figure 2.

rides. α-Aminonitriles are employed as key intermediates, titanium(IV) isopropoxide is used as a catalyst and finally a *one-pot* spiroring formation is effected under basic conditions. Also, partial and total deacetalisation of the spiro derivatives could be achieved by acid catalysed hydrolysis.

The compounds synthesised in this programme are being evaluated for their herbicidal activities and glycogen phosphorylase inhibition. Also, it is of note that spirohydantoin carbohydrates have the potential to provide a convenient access to α,α-disubstituted glyco-α-aminoacids. Studies in this direction and the synthesis of thio compounds are in progress.

Acknowledgements

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11. *Procedure for the preparation (3R) 3,3-(1,3-diazaspiro-2,4-dioxo)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**14**)*: A solution of the phenylcarbamate derivative **16** (450 mg, 1.11 mmol) and NaOH (0.13 g, 3.33 mmol) in 25 mL of 1,4-dioxane/water (1:1) was stirred at 80°C for 1 h. Then the mixture was neutralised with acetic acid and extracted with ether. The organic layer was dried and evaporated. The residue was purified by silica gel chromatography (hexane/EtOAc 1:1) to afford the spirohydantoin **14** (290 mg, 80%) as a solid. Mp 232–236°C; $[\alpha]_D^{25}$ +56 (*c* 0.76, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.77 (s, 1H, NH), 6.16 (s, 1H, NH), 5.91 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.55 (d, 1H, H-2), 4.17 (m, 1H, $J_{4,5}$ 9.0 Hz, H-5), 4.06 (dd, 1H, $J_{5,6a}$ 3.5 Hz, H-6a), 3.96 (dd, 1H, $J_{5,6b}$ 3.5 Hz, H-6b), 3.96 (d, 1H, H-4), 1.54 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$) δ 172.1 (C=O), 156.2 (C=O), 113.6 (CH_3CCH_3), 109.9 (CH_3CCH_3), 104.8 (C-1), 81.5 (C-2), 79.6 (C-4), 74.1 (C-5), 71.2 (C-3), 67.9 (C-6), 26.8 (CH_3), 26.6 (CH_3), 26.4 (CH_3), 24.8 (CH_3).
12. *Selected spectroscopic values*: Complex **15**: ^1H NMR (CD_3OD) δ 5.89 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.87 (s, 4H, NH, OH), 4.60 (d, 1H, H-2), 4.18 (m, 1H, $J_{4,5}$ 9.0 Hz, H-4), 3.72 (m, 2H, $J_{5,6a}$ 5.5 Hz, H-5, H-6b), 3.54 (dd, 1H, $J_{6a,6b}$ 11.5 Hz, H-6a), 1.57 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C (CD_3OD) δ 174.8 (1C, C=O), 158.2 (1C, C=O), 113.4 (1C, CH_3CCH_3), 105.1 (1C, C-1), 82.4 (1C, C-2), 77.8 (1C, C-4), 72.0 (1C, C-3), 71.7 (1C, C-5), 64.3 (1C, C-6), 26.1 (1C, CH_3), 25.7 (1C, CH_3). Complex **16α**: ^1H

NMR (C_5D_5N) δ 12.62 (s, 1H, NH), 8.23 (s, 1H, NH), 5.84 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.82 (d, 1H, H-4), 4.75 (m, 1H, $J_{4,5}$ 10.5 Hz, H-5), 4.66 (d, 1H, H-2), 4.40 (dd, 2H, $J_{5,6a}=J_{5,6b}$ 5.0 Hz, H-6a, H-6b), ^{13}C NMR ($CDCl_3$) δ 178.0 (C=O), 160.6 (C=O), 93.7 (C-1), 74.4 (C-2), 73.4 (C-3), 70.0 (C-5), 68.4 (C-4), 62.7 (C-6). Complex **16β**: ^{1}H NMR (C_5D_5N) δ 12.62 (s, 1H, NH), 8.23 (s, 1H, NH), 5.76 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1), 4.88 (d, 1H, H-4), 4.68 (d, 1H, H-2), 4.59 (m, 1H, $J_{4,5}$ 10.0 Hz, H-5), 4.50 (dd, 2H, $J_{5,6a}=J_{5,6b}$ 2.0 Hz, H-6a, H-6b), ^{13}C NMR ($CDCl_3$) δ 178.2 (C=O), 161.0 (C=O), 97.2 (C-1), 78.1 (C-2), 73.5 (C-3), 70.8 (C-5), 69.3 (C-4), 63.0 (C-6).