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Spirohydantoins from D-ribose as new potent enzymatic inhibitors

A. Nguyen, P. Villa, G. Ronco and D. Postel

Abstract

Anomeric spirohydantoin derivatives from monosaccharides are known for various biological properties. We describe herein the synthesis of the 3-spirohydantoin derivatives of D-allose and D-ribose. The key step is the stereoselective glyco-α-aminonitrile formation from ulose derivatives of D-glucose and D-xylose using titanium tetra-isopropoxide as a mild and efficient catalyst. Target compounds were synthesized from these intermediates. The glucidic moiety was partially or totally deprotected under acidic conditions. These new heterocyclic monosaccharidic derivatives are potent glycogen phosphorylase inhibitors.

Introduction

The development of new heterocyclic derivatives of monosaccharides is of great value for the discovery of new biologically active compounds. Modification of the parent compound is currently effected either by introduction of an aglycone moiety or by substitution of the pyranose or furanose ring oxygen by a nitrogen or a carbon atom. Modification of the carbohydrate moiety has also been achieved by a spiro ring formation; examples include various analogues (**I**–**III**; Figure 1) of hydantocidin (**IV**) for herbicidal or enzymatic inhibitor action (Chemla 1993; Fairbanks et al 1993; Matsumoto et al 1993; Harrington & Jung 1994; Brandstetter et al 1995).

Different routes have been described in the literature for the synthesis of spirohydantoins. Sano & Sugai (1995) described the Bucherer-Bergs synthesis, which gives thermodynamically controlled spiro products, and also reported the conversion of an α-aminonitrile into a hydantoin with chlorosulfonylisocyanide followed by acid-catalysed hydrolysis. In this work herbicidal activity was found to be not affected when the D-furanose ring oxygen atom of the natural product was replaced with a methylene unit (Sano & Sugai 1995). Fleet and colleagues 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 (Bichard et al 1995; Estevez et al 1995). The target compounds were synthesized from D-glucose and D-mannose derivatives by oxidative ring contraction. Reaction of α-aminoesters, located at non-anonmeric sites of the sugar, with phenylisocyanates afforded the corresponding ureas, which were converted into the corresponding spirohydantoins under basic conditions.

In the course of our ongoing interest in the preparation of novel structures based on glyco-α-aminonitrile derivatives (Postel et al 2000), we describe the synthesis of non-anonmeric spirohydantoins from D-allose and D-ribose (**V**, **VI**) as new potent enzymatic inhibitors.

Laboratoire des Glucides, Université de Picardie, F-80039 Amiens, France

A. Nguyen, P. Villa, G. Ronco, D. Postel

Correspondence: D. Postel, Laboratoire des Glucides, Université de Picardie, F-80039 Amiens, France.

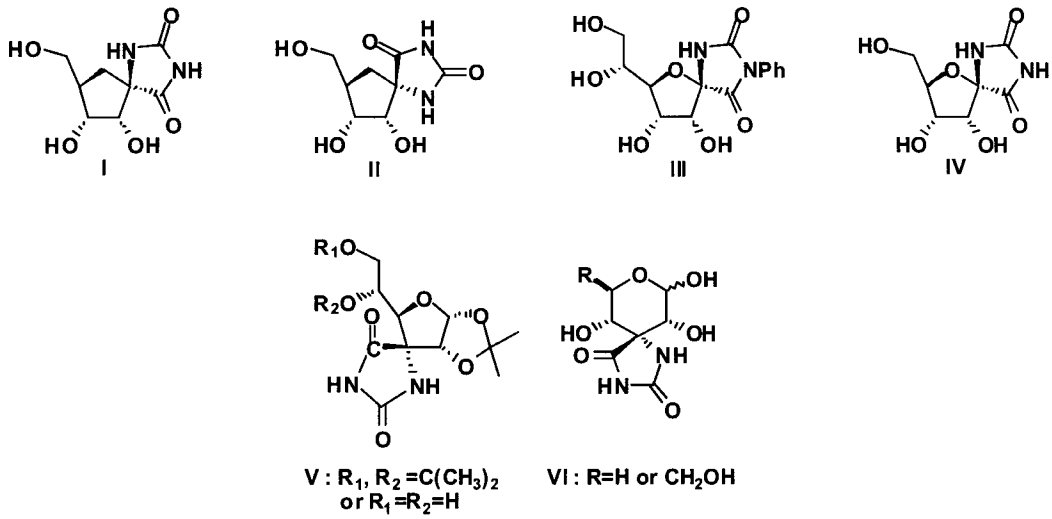

Figure 1 Structure of analogues (**I**–**III**) of hydantocidin (**IV**).

Materials and Methods

Melting points were determined on a digital melting-point apparatus (Electrothermal) and are uncorrected. Optical rotations were recorded at 22°C in $CHCl_3$ or MeOH solutions with a digital polarimeter DIP-370 (JASCO) using a 1-dm cell. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, Me_2SO-d_6 or Me_2CO-d_6 (internal Me_4Si), respectively, at 300.13 MHz and at 75.47 MHz (Bruker Avance-300). TLC was performed on Silica F254 (Merck) and detection by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was effected on Silica Gel 60 (Merck, 230 mesh). Me_2CO, hexane, ether and each industrial grade were supplied by CINAS. Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de Recherche Scientifique (Vernaison, France). Bases and solvents were supplied by ACROS or ALDRICH. MeOH–NH_3 is methanol saturated with ammonia gas at room temperature.

Synthesis

*3-Amino-3-C-cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**3a**)*

A mixture of **1a** (1g , 3.87 mmol) (Figure 2), MeOH–NH_3 (7 N ; 5.4 mL), $Ti(OiPr)_4$ (1.3 g, 4.56 mmol) and dry MeOH (2.4 mL) was stirred at room temperature. After 5 h, TMSiCN (0.37 g; 3.8 mmol) was added and the solution was stirred for 5 h. Water (0.5 mL) and EtOAc (10 mL) were added and the mixture was evaporated under reduced pressure. The residue was purified by silica-gel chromatography (hexane–EtOAc, 4:1) to give **3a** (0.88 g, 80%) as a syrup; $[\alpha]_D^{25}$ +5.2 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 5.84 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.68 (d, 1 H, H-2), 4.29 (m, 1 H, $J_{4,5}$ 8.9 Hz, H-5), 4.10 (dd, 1 H, $J_{5,6a}$ 6.2 Hz, H-6a), 3.92 (dd, 1 H, $J_{5,6b}$ 4.4 Hz, H-6b), 2.02 (s, 2 H, NH_2), 1.49 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.29 (s, 6H, CH_3), ^{13}C NMR ($CDCl_3$) δ 118.6 (CN), 113.7 (CH_3CCH_3), 110.1 (CH_3CCH_3), 103.9 (C-1), 83.3 (C-2), 81.6 (C-4), 75.0 (C-5), 67.6 (C-6), 62.7 (C-3).

*3-Amino-3-C-cyano-3-deoxy-5-O-trityl-1,2-O-isopropylidene-α-D-xylofuranose (**3b**)*

Likewise, 5-*O*-trityl-1,2-*O*-isopropylidene-*erythro*-pentofuranos-3-ulose (**1b**; 1 g , 2.31 mmol) gave, after 2 h, **3b** (1.07 g, 98%) as a solid; mp 163–167°C; $[\alpha]_D^{25}$ −29.3 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.50–7.39 (m, 15 H, H Tr), 5.91 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.70 (d, 1 H, H-2), 3.86 (dd, 1 H, $J_{4,5a}$ 7.3 Hz, H-4), 3.80 (dd, 1 H, $J_{4,5b}$ 5.4 Hz, H-5b), 3.54 (dd, 1 H, $J_{5a,5b}$ 9.7 Hz, H-5a), 2.04 (s, 2 H, NH_2), 1.58 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$) δ 143.3 (3C, C*ipso*), 128.6, 128.1, 127.4 (15 C, Tr), 118.5 (CN), 113.4 (CH_3CCH_3), 103.9 (C-1), 87.9 (C Tr), 83.2 (C-2), 79.9 (C-4), 63.3 (C-5), 62.3 (C-3), 26.5 (CH_3), 26.4 (CH_3).

*N-Phenyloxycarbonyl-3-amino-3-C-cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**4a**)*

Phenyl chloroformate (2.09 g; 13.4 mmol) was added to a stirred mixture of **3a** (3.18 g , 11.2 mmol) and K_2CO_3 (2.32 g; 16.8 mmol) in acetone–H_2O (56 mL; 1:1 v/v) at 0°C. After 5 h the mixture was filtered and evaporated under reduced pressure. The residue was purified by

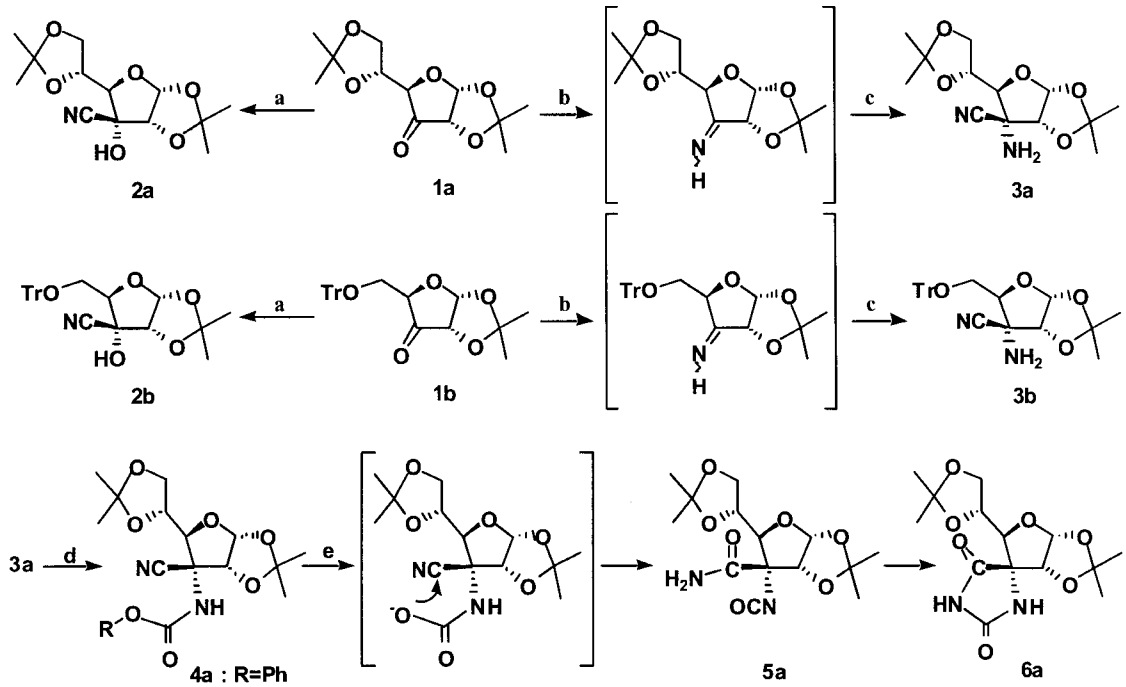

Figure 2 Synthesis of the glyco-α-aminonitriles **3a** and **3b** and the spirohydantoin **6a**. Reagents: a, NH_4Cl, KCN, MeOH; b, $Ti(OiPr)_4$, NH_3–MeOH; c, TMSCN; d, PhOC(O)Cl, K_2CO_3, acetone–H_2O; e, NaOH, H_2O–1,4-dioxane.

silica-gel chromatography (hexane–EtOAc, 4:1) to give **4a** (2.03 g; 45%) as a solid; mp 126–129°C, $[\alpha]_D^{25}$ 24.8 (*c* 1.14, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.35–7.19 (m, 5 H, Ph), 5.98 (s, 1 H, NH), 5.91 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.30 (d, 1 H, H-2), 4.47 (m, 1 H, $J_{4,5}$ 9.1 Hz, H-5), 4.20 (dd, 1 H, $J_{5,6a}$ 6.4 Hz, H-6a), 4.03 (dd, 1 H, $J_{5,6b}$ 4.3 Hz, H-6b), 3.84 (d, 1 H, H-4), 1.55 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$) δ 152.6 (C=O), 150.3 (C *ipso*), 129.3–121.3 (5C, Ph), 115.7 (CN), 114.0 (CH_3CCH_3), 110.7 (CH_3CCH_3), 104.3 (C-1), 82.0 (C-2), 79.2 (C-4), 74.3 (C-5), 67.5 (C-6), 62.4 (C-3), 26.7 (CH_3), 26.5 (2xCH_3), 24.6 (CH_3).

*N-Phenyloxycarbonyl-3-amino-3-C-cyano-3-deoxy-5-O-trityl-1,2-O-isopropylidene-α-D-ribofuranose (**4b**)*

Likewise 3-amino-3-*C*-cyano-3-deoxy-5-*O*-trityl-1,2-*O*-isopropylidene-α-D-ribofuranose (**3b**; 3 g; 6.6 mmol) gave **4b** (3.14 g; 83%) as a solid; mp 196–198°C; $[\alpha]_D^{25}$ −26.9 (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.49–7.31 (m, 20 H, Ph, Tr), 6.19 (s, 1 H, NH), 5.91 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.25 (d, 1 H, H-2), 4.00 (dd, 1 H, $J_{4,5a}$ 4.7 Hz, H-4), 3.87 (dd, 1 H, $J_{4,5b}$ 8.3 Hz, H-5b), 3.76 (dd, 1 H, $J_{5a,5b}$ 10.2 Hz, H-5a), 1.55 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$) δ 152.6 (C=O), 150.5 (C *ipso*), 142.9 (3C, C *ipso*), 129.4–121.3 (20 C, trityl and Ph), 115.6 (CN), 113.8 (CH_3CCH_3), 104.3 (C-1), 88.6 (C *trityl*), 82.1 (C-2), 77.6 (C-4), 62.9 (C-5), 62.0 (C-3), 26.6 (CH_3), 26.4 (CH_3).

*(3R)-3,3-(1,3-diazaspiro-2,4-dioxo)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**6a**)*

A solution of the phenylcarbamate derivative **4a** (450 mg, 1.11 mmol) and NaOH (0.13 g, 3.33 mmol) in 25 mL 1,4-dioxane–water (1:1) was stirred at 80°C for 1 h. Then the mixture was neutralized with acetic acid and extracted with ether. The organic layers were dried, and evaporated. The residue was purified by silica-gel chromatography (hexane–EtOAc, 1:1) to afford the spirohydantoin **6a** (290 mg, 80%) as a solid; mp 232–236°C ; $[\alpha]_D^{25}$ +56.4 (*c* 0.76, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.77 (s, 1 H, NH), 6.16 (s, 1 H, NH), 5.91 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.55 (d, 1 H, H-2), 4.17 (m, 1 H, $J_{4,5}$ 9.1 Hz, H-5), 4.06 (dd, 1 H, $J_{5,6a}$ 3.4 Hz, H-6a), 3.96 (dd, 1 H, $J_{5,6b}$ 3.4 Hz, H-6b), 3.96 (d, 1 H, 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).

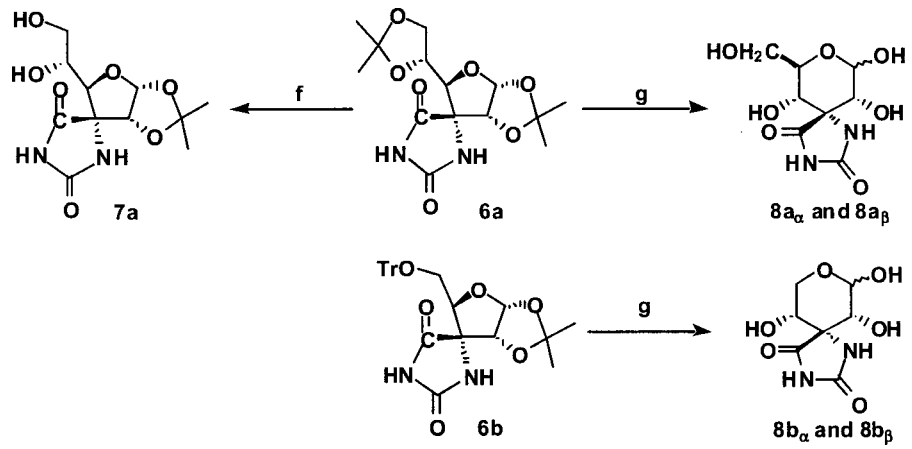

Figure 3 Synthesis of spirohydantoin derivatives **8a** and **8b**. Reagents: f, aqueous HCl (1 N); g, CF_3COOH–H_2O, 9:1.

*(3R)-3,3-(1,3-diazaspiro-2,4-dioxo)-5-O-trityl-1,2-O-isopropylidene-α-D-ribofuranose (**6b**)*

Likewise the phenyl carbamate derivative **4b** (0.30 g; 0.5 mmol) gave **6b** (0.22 g; 85%) as a solid; mp 115–120°C; $[\alpha]_D^{25}$ +10.15 (*c* 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 9.36 (s, 1 H, NH), 7.36–7.19 (m, 15 H, Tr), 6.18 (s, 1 H, NH), 5.88 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.36 (d, 1 H, H-2), 4.17 (dd, 1 H, $J_{4,5b}$ 7.1 Hz, H-4), 3.58 (dd, 1 H, $J_{4,5a}$ 5.2 Hz, H-5a), 3.23 (dd, 1 H, $J_{5a,5b}$ 10.2 Hz, H-5b), 1.52 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$) δ 171.9 (C=O), 156.3 (C=O), 143.2 (3C, C *ipso*), 128.4–127.1 (15 C, trityl), 113.3 (CH_3CCH_3), 104.7 (C-1), 87.4 (C *trityl*), 81.2 (C-2), 77.8 (C-4), 70.7 (C-3), 61.5 (C-5), 26.7 (CH_3), 26.4 (CH_3).

*(3R)-3,3-(1,3-diazaspiro-2,4-dioxo)-1,2-O-isopropylidene-α-D-allofuranose (**7a**)*

A solution of the spirohydantoin **6a** (465 mg, 1.41 mmol) in 23.3 mL of aqueous HCl (1 N) was stirred at 0°C for 1 h. $NaHCO_3$ was added and the solvent co-evaporated with 1,4-dioxane under reduced pressure. The residue was solubilized in THF (tetrahydrofuran), filtered and evaporated to give **7a** (210 mg; 52%) as a solid; mp 228–230°C; $[\alpha]_D^{28} = +72{,}4°$ (*c* 0,2; MeOH); ^{1}H (ppm) (CD_3OD) δ 5.89 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.87 (s, 4 H, NH, OH), 4.60 (d, 1 H, H-2), 4.18 (m, 1 H, $J_{4,5}$ 9.1 Hz, H-4), 3.72 (m, 2H, $J_{5,6a}$ 5.5 Hz, , H-5, H-6b), 3.54 (dd, 1 H, $J_{6a,6b}$ 11.7 Hz, H-6a), 1.57 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C (ppm) (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).

*(3R)-3,3-(1,3-diazaspiro-2,4-dioxo)-D-allopyranose (**8a**$_\alpha$ and **8a**$_\beta$)*

A solution of the spirohydantoin **6a** (360 mg, 1.09 mmol) in 3.3 mL of trifluoroacetic acid–water (9:1) was stirred at room temperature for 1 h. Then the solvent was co-evaporated with toluene. The residue was triturated with ether and filtered to afford the spirohydantoin derivatives **8a**$_\alpha$ and **8a**$_\beta$ (264 mg, 97%) as a solid; mp 230–235°C; $[\alpha]_D^{26}$ 89.0 (c 1.0, MeOH). **8a**$_\alpha$: ^{1}H NMR (C_5D_5N) δ 12.62 (s, 1 H, NH), 8.23 (s, 1 H, NH), 5.84 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.82 (d, 1 H, H-4), 4.75 (m, 1 H, $J_{4,5}$ 10.3 Hz, H-5), 4.66 (d, 1 H, H-2), 4.40 (dd, 2 H, $J_{5,6a} = J_{5,6b}$ 4.9 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). **8a**$_\beta$: ^{1}H NMR (C_5D_5N) δ 12.62 (s, 1 H, NH), 8.23 (s, 1 H, NH), 5.76 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 4.88 (d, 1 H, H-4), 4.68 (d, 1 H, H-2), 4.59 (m, 1 H, $J_{4,5}$ 10.1 Hz, H-5), 4.50 (dd, 2 H, $J_{5,6a} = J_{5,6b}$ 2.1 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).

*(3R)-3,3-(1,3-diazaspiro-2,4-dioxo)-D-ribopyranose (**8b**$_\alpha$ and **8b**$_\beta$)*

Likewise the spirohydantoin **6b** (427 mg, 8.53 mmol) gave **8b**$_\alpha$ and **8b**$_\beta$ (160 mg, 86%) as a solid; mp 227–230°C; $[\alpha]_D^{26}$ 43.7 (c 1.0, MeOH). **8b**$_\alpha$: ^{1}H NMR (C_5D_5N) δ 12.67 (s, 1 H, NH), 8.34 (s, 1 H, NH), 5.77 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.77 (dd, 1 H, H-4), 4.67 (d, 1 H, H-2), 4.54 (dd, 1 H, $J_{4,5a}$ 11.2 Hz, H-5a), 4.07 (dd, 1 H, $J_{4,5b}$ 5.3 Hz, $J_{5a,5b}$ 10.9 Hz, H-5b), ^{13}C NMR ($CDCl_3$) δ 178.0 (C=O), 160.5 (C=O), 93.2 (C-1), 73.4 (C-3), 69.8 (C-2), 68.1 (C-4), 60.1 (C-5). **8b**$_\beta$: ^{1}H NMR (C_5D_5N) δ

12.67 (s, 1 H, NH), 9.85 (s, 1 H, NH), 5.62 (d, 1 H, $J_{1,2}$ 8.25 Hz, H-1), 4.89 (dd, 1 H, H-4), 4.68 (d, 1 H, H-2), 4.43 (dd, 1 H, $J_{4,5a}$ 5.2 Hz, H-5a), 4.26 (dd, 1 H, $J_{4,5b}$ 11.0 Hz, $J_{5a,5b}$ 11.3 Hz, H-5b), ^{13}C NMR ($CDCl_3$) δ 177.8 (C═O), 160.9 (C═O), 97.5 (C-1), 74.2 (C-3), 73.1 (C-2), 68.8 (C-4), 67.1 (C-5).

Results and Discussion

The stereoselective synthesis of non-anonmeric glyco-α-aminonitrile using Strecker synthesis (KCN and NH_4Cl) from the ulose derivatives **1a** and **1b** was unsuccessful and only the corresponding cyanohydrines (**2a** and **2b**) were observed (Figure 2). In contrast, the glyco-α-aminonitriles **3a** and **3b** were readily obtained from the same intermediates, using titanium (IV) isopropoxide as a mild Lewis acid catalyst, MeOH-NH_3 and TMSCN as cyanating agent, in 80% yield from **1a** and **1b**.

Attempts to synthesize the spirohydantoins from **1a** using the conditions reported by Sano & Sugai (1995) (KCN, $(NH_4)_2CO_3$, MeOH–H_2O, 70°C) resulted in the formation of **2a**. We therefore turned our attention to an alternative method via an α-carboxamidoisocyanate intermediate. This route involved preliminary carbamoyl ester synthesis followed by an intramolecular cyclization in basic conditions. The carbamoylation step was readily achieved with PhOC(O)Cl in acetone–H_2O and K_2CO_3 yielding **4a** in 44% yield. Treatment of **4a** with NaOH in H_2O–1,4-dioxane at 80°C for 2 h gave the desired spirohydantoin **6a** in 80% yield.

Deprotection of the acetonide group in **6a** was achieved with aqueous HCl at room temperature (1 h) to give **7a** in 52% yield (Figure 3). Alternatively, **6a** was treated with aqueous trifluoroacetic acid for 1 h to give **8a** in 97% yield. Using a similar strategy, **6b** was obtained from the phenyloxycarbonyl derivative **4b** (83% from **3b**) under basic conditions in 85% yield. Treatment of **6b** with aqueous trifluoroacetic acid gave **8b** in quantitative yield.

In conclusion, the target compounds were easily synthesized from glyco-α-aminonitriles via an isocyanate intermediate. These new spirohydantoin derivatives are being evaluated for their herbicidal activities and glycogen phosphorylase inhibition. Also, it is noteworthy that spirohydantoin carbohydrates have the potential to provide a convenient access to α,α-disubstituted glyco-α-amino acids. Studies in this direction and the synthesis of thio compounds are in progress.

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