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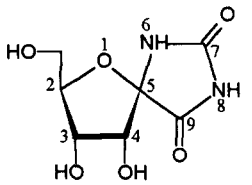
A Straightforward Route to Hydantocidin Analogues with Pyranose Ring Structure

Erzsébet Ősz[a], Erzsébet Sós[a], László Somsák[a]*, László Szilágyi[a]*, Zoltán Dinya[b]

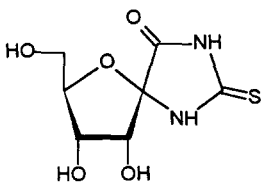
[a]*Department of Organic Chemistry and* [b]*Research Group for Antibiotics of the Hungarian Academy of Sciences, Lajos Kossuth University, H-4010 Debrecen, Hungary*

Abstract: Partial hydrolysis of the nitrile moiety in acetylated 1-bromo-glycopyranosyl cyanides **1** and **9** mediated by $TiCl_4$ gave *C*-(1-bromo-1-deoxy-glycopyranosyl)formamides **2** and **10** whose reaction either with AgOCN, AgSCN or KSCN in nitromethane resulted in the formation of glycopyranosylidene-spiro-hydantoins **3**, **11** and **15** and -thiohydantoins **7** and **16**. Zemplén-deacetylation gave the pyranoid *epi*-hydantocidin analogues **4** and **12**, and thiohydantocidin analogues **8** and **17**, respectively.

In the quest of useful chemical syntheses for and biologically active surrogates and mimics of (+)-hydantocidin, a natural product with potent herbicidal activity,[1] a number of synthetic approaches have been reported recently.[2]



(+)-hydantocidin

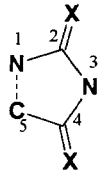


5-*epi*-thiohydantocidin

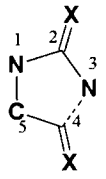
Modifications at either of the spiro-fused rings of the natural product were shown to lead to derivatives with significant biological activity.[2q] A spirohydantoin in which the furanose ring had been replaced by a glucopyranose moiety proved to be a potent inhibitor of glycogen phosphorylase.[2j] It was furthermore shown that replacement of the C-7 carbonyl group by a thiocarbonyl group can be effected without loss of the herbicidal activity.[2q] Moreover, the efficiency of 5-*epi*-thiohydantocidin was found to be superior to that of 5-

epi-hydantocidin.[2q]

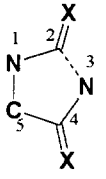
On the basis of these preliminaries we set out to synthesize hydantocidin analogues incorporating modifications in the carbohydrate part as well as in the hydantoin ring of the parent molecule. From the wealth of ring closing reactions to obtain hydantoins[3] methods **A**-**E** (bonds formed in the ring closing step of the syntheses are shown in dotted lines) were used to construct glycosylidene-spirohydantoin derivatives. In general, the preparation of precursors suitable for these cyclizations required 8-10 synthetic steps from an easily available starting material and even more from the appropriate free sugar. Furthermore, since C-5 of the hydantoin ring is the anomeric carbon of the sugar moiety, anomerization may, and frequently does, occur during these multistep processes with the result of diminishing the stereochemical efficiency of the syntheses.



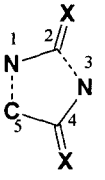
A[2b]



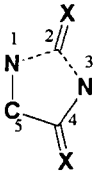
B[2d,f-l]



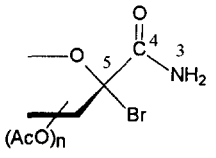
C[2m]



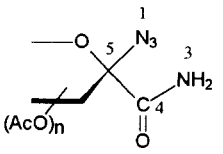
D[2e]



E[2c,q]



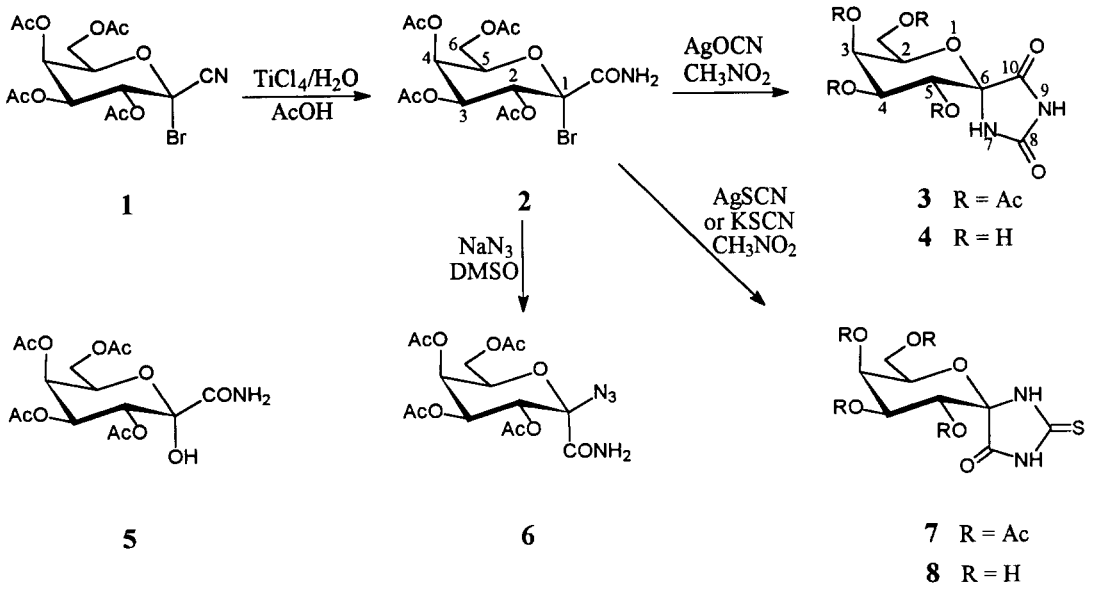
I

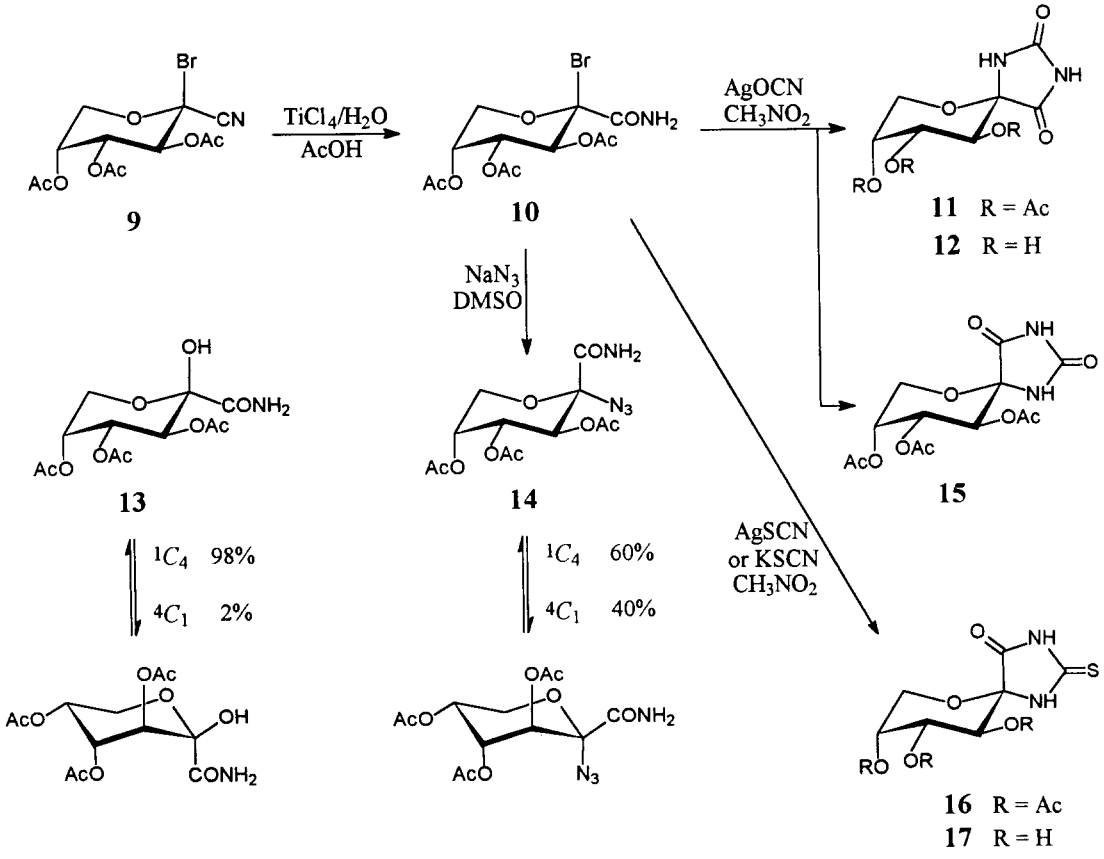


II

Obviously, synthetic routes with less preparative steps and without anomerization would improve the accessibility of (+)-hydantocidin and its analogues. Recently we have reported on the preparation, in a few simple synthetic steps, of anomerically bifunctional pyranoid monosaccharide derivatives **I**[4] and **II**[5] suitable for the formation of spiro-annulated hydantoins following ring closures **D** and **E**, respectively (parts of the hydantoin ring already present in **I** and **II** are numbered). Here we disclose our investigations on the use of these compounds for the synthesis of glycopyranosylidene-spiro-hydantoins and their thio analogues.

Compounds of type **I** were previously obtained in moderate yields by radical-mediated bromination[6] of the corresponding anhydro glyconamide derivatives of either furanoid[2e] or pyranoid[4] structures. We have found that $TiCl_4$ promoted addition[7] of water to the nitrile moiety of either the *(1R)*-1-bromo-D-galactopyranosyl cyanide[8] **1** or the D-*arabino* analogue **9**[8] proceeds smoothly at room temperature and furnishes the


TiCl4/H2O
AcOH
AgOCN
CH3NO2
AgSCN
or KSCN
CH3NO2
NaN3
DMSO
1
2
3 R = Ac
4 R = H
5
6
7 R = Ac
8 R = H


TiCl4/H2O
AcOH
AgOCN
CH3NO2
AgSCN
or KSCN
CH3NO2
NaN3
DMSO
9
10
11 R = Ac
12 R = H
13
14
15
16 R = Ac
17 R = H
1C4 98%
4C1 2%
1C4 60%
4C1 40%

corresponding formamides **2** and **10** in good yields.[9] The crude products are, in general, sufficiently pure for further transformations without purification. The C-1 configurations are retained in both cases as ascertained[4,5,8] by the values of the $^{1}H,^{13}C$ coupling constants $^{3}J_{H\text{-}2,CO(NH2)}$ (~ 1 and 1.4 Hz, respectively, for **2** and **10**).

Compound **2** was converted to the known azido-formamide[5] **6** by treatment with sodium azide in dimethyl sulfoxide. In a similar reaction **14** could be readily obtained from **10**. These derivatives were prepared to serve as starting materials for ring closure into hydantoins via the aza-Wittig protocol[2c,q] (route **E**). The azide **6** failed, however, to react when treated with tri-*n*-butyl-phosphine in the presence of carbon disulfide[2q] for 8 hr. Similar reaction of **6** with carbon dioxide[2c] gave a complicated mixture of at least four products (tlc). The ^{13}C NMR spectrum of the mixture did not, however, reveal the presence of the hydantoin ring. Compound **14** showed an interesting conformational behaviour: the high ratio of the $^{4}C_{1}$ conformer[10] with more unfavourable 1,3-*diaxial* interactions than in the $^{1}C_{4}$ conformer can be explained by the normal and the reverse anomeric effects exerted by the azido[11] and the carboxamido[12] substituents, respectively.

Next, we have attempted to effect hydantoin ring closure by route **D**. We have found that nucleophilic displacement of the bromide in **2** or **10** with cyanate[2e] or thiocyanate ions proceeded smoothly and the corresponding hydantoins **3** and **11** and thiohydantoins **7** and **16**, respectively, could be obtained in one step and in good yields. Silver cyanate for **3** and **11**, and silver thiocyanate as well as potassium thiocyanate for **7** and **16** in dry nitromethane were found to be suitable reagents, the latter requiring, however, shorter reaction times. No intermediates could be detected by tlc in these transformations. Using other solvents gave less satisfactory results: in acetone no reaction took place, in dimethyl sulphoxide decomposition occurred, while in acetonitrile the reaction was more sluggish with concomitant formation of more byproducts. Potassium cyanate brought about no reaction with **2** or **10** in nitromethane even after prolonged (21, 29 h) reaction times. Contrary to observations with analogous furanoid compounds,[2e] **3** and **7** were the only spirohydantoin derivatives detectable by ^{1}H-NMR in reactions of **2**. Reaction of **10** with cyanate gave **11** as the main product (40%) together with a minor isomer **15** (10%). On the other hand, **16** was the sole product (^{1}H-NMR) in the reaction of **10** with thiocyanate. As unavoidable byproducts, hydroxy-formamides **5** and **13** were detected and/or isolated in each reaction. The formation of these compounds was evidently due to the water content of the solvent, despite careful purification and drying, resulting in hydrolysis of the starting bromo-formamides **2** and **10**.

Spirohydantoins **3**, **7**, **11** and **16** could be smoothly deprotected using NaOMe catalyzed deacetylation to furnish the pyranose hydantocidin mimics **4**, **8**, **12** and **17**, respectively.

Ring closure reactions proceeded with inversion of configuration resulting in the formation of spirothiohydantoin derivatives **7** and **16** and the minor spirohydantoin **15**, while retention of the configuration was observed at the anomeric carbon in the case of spirohydantoin derivatives **3** and **11** and by-products **5** and **13**. The structures of these products could be unequivocally established from the presence of the ^{1}H- and ^{13}C-resonances in their NMR spectra expected for the hydantoin as well as for the thiohydantoin ring[13] and

corroborated by long-range $^{13}C/NH$ correlations in the HMBC spectra. The conformations of the pyranose rings ($^4C_1$ for **3** and **7**; $^1C_4$ for **11**, **15** and **16**) are evident from the vicinal ^1H-^1H coupling constants (Experimental). Hence, the C-6 configurations could be deduced by relying on the $^3J_{H\text{-}5,C\text{-}10}$ values [4,5,8] (2.4 Hz in **3**, 5.8 Hz in **7**, 2.5 Hz in **11**, 6.1 Hz in **15** and 5.9 Hz in **16**). As a result, the absolute configuration of C-6 is *S* for **7** and **11** and *R* for **3**, **15** and **16**. The anomeric configurations of **5** and **13** were similarly deduced from the $^3J_{H\text{-}2,CO(NH2)}$ couplings (2.6 Hz in **5** and ~ 1 Hz in **13**). It is interesting to note that anomeric forms other than indicated above could not be detected in the ^1H NMR spectra of **5** and **13** and that **13** exists almost exclusively in the $^1C_4$ conformation.[10] These observations can be regarded as manifestations of normal and reverse anomeric effects of the hydroxy[14] and carboxamido[12] groups, respectively. These effects act synergistically in **5** and **13** thereby preventing anomerization and conformational equilibration.

Table. Selected ^1H NMR chemical shifts[a] for the spiro(thio)hydantoins

Compound	Configuration at C-6[b]	δ(H-5) ppm	δ(H-4) ppm	δ(H-2*ax*) ppm
7	(*S*), *trans*	5.49	5.78	4.89
8	(*S*), *trans*	3.96	4.31	4.55
15	(*R*), *trans*	5.44	5.74	4.49
16	(*R*), *trans*	5.51	5.78	4.58
17	(*R*), *trans*	3.98	4.32	4.45
3	(*R*), *cis*	5.70	5.36	4.22
4	(*R*), *cis*	4.14	3.90-3.70	3.90-3.70
11	(*S*), *cis*	5.75	5.35	4.06
12	(*S*), *cis*	4.12	3.75	3.94

[a]In $CDCl_3$ solutions for the acetylated derivatives **3**, **7**, **11**, **15** and **16** and in D_2O for the deacetylated derivatives **4**, **8**, **12** and **17**. [b]*Cis* and *trans* indicate the orientation of bonds C5-H5 and C6-C10 each to other.

^1H chemical shifts of the hydantoin derivatives display a regular pattern depending on the configuration of the spiro carbon (C-6). Specifically, the values for H-4 and H-2*ax* are shifted downfield by 0.2-0.7 ppm in the isomers in which the C5-H5 and the C6-C10 bonds are in *trans* orientation (**7**, **8**, **15**, **16**, **17**) as compared to those in which these bonds are in *cis* orientation (**3**, **4**, **11**, **12**) and the opposite holds for the H-5 chemical shifts in these isomers (see Table). This effect is likely to be attributed to the shielding anisotropy contribution

arising from the C-10 carbonyl group which occupies a fixed spatial orientation with respect to the pyranose ring in these derivatives. On the contrary, no regularity could be observed in the chemical shifts of the ring protons for derivatives where this carbonyl group can rotate and thereby average the effects of the shielding anisotropy (cf. **2, 5, 10, 13**).

It is remarkable that, contrasted with the moderate stereoselectivity seen in the reaction of *C*-(1-bromo-1-deoxy-β-D-ribofuranosyl)formamide with silver cyanate,[2e] analogous ring closures with the pyranoid precursors proved to be highly stereoselective in most cases. Furthermore, the stereoselectivity with cyanate was opposite to that observed with thiocyanate. Although our experimental data are at present insufficient for rationalizing these observations in a satisfactory manner, we speculate that different mechanisms are operating in the substitution steps. Since with cyanate the transformation took place only in the presence of silver ion, a C-1 carbocationic intermediate must appear along the reaction pathway. In these species participation of the C-2 acetoxy group usually directs the attack of the nucleophile to generate a product with 1,2-*trans* stereochemistry. This well known neighbouring group effect is clearly not observable in reactions of **2** and **10** with cyanate. Therefore, *axial* attack of the nucleophile may be preponderant because of stereoelectronic reasons[15] and/or least motion effects.[16] Remote group participation by the C-4 acetoxy substituent may also act similarly.[17] In the case of thiocyanates the presence of silver ion was not a prerequisite for the reactions to occur; this indicates the higher nucleophilicity of this anion. Therefore, S_N2 displacement of the bromine with inversion of configuration may be the dominant route in reactions of **2** and **10** with thiocyanate.

In summary, we have developed an efficient general procedure for the synthesis of hydantocidin analogues, modified in both the carbohydrate and the hydantoin rings, which is significantly shorter (6 synthetic steps from a free sugar to the deprotected spirohydantoin) and preparatively simpler than those described thus far in the literature. Tests of the biological activity are in progress.

EXPERIMENTAL

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at room temperature. IR spectra were recorded with a Perkin-Elmer 16 PC FT-IR instrument. NMR spectra were recorded with Bruker WP 200 SY (200/50 MHz for $^1H/^{13}C$) or Avance DRX 500 (500/125 MHz) spectrometers. Chemical shifts are referenced to Me_4Si (^1H) or to the residual solvent signals (^{13}C). ^{13}C assignments were based on HMQC and HMBC spectra recorded at 500/125 MHz. Fast-atom bombardment (FAB) mass spectra were obtained using a 7070MS mass spectrometer (VG Analytical, Ltd., Manchester, UK) operated at 4 kV accelerating potencial with a resolving power of 1000 (10% valley definition) and a scan rate of 30 s/decade from m/z 100 to m/z 600 in this low-resolution mode. High resolution mass measurements were carried out by peak matching procedure at a resolving power of 8000. The accuracy of measured masses is estimated to be better than 10 ppm. In all

experiments N-formyl-2-aminoethanol (NFETA) was used as the matrix.[18] Approximately 2 μl of the matrix and various amounts of a sample solution containing 50 μg of sample per μl of $CHCl_3$ were placed on the stainless steel probe tip. Operating conditions for the FAB gun (ION Tech, Teddington, UK) on the instrument were 8 kV at 1 mA equivalent ion current using xenon as the FAB gas. The samples and the FAB ion source were maintained at room temperature in each experiment. TLC was performed on DC-Alurolle, Kieselgel 60 F_{254} (Merck), and the plates were visualised by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063-0.200 mm) was used. Organic solutions were dried over anhydrous $MgSO_4$ and concentrated in vacuo at 40-50°C (water bath). Nitromethane was distilled from P_4O_{10} directly in the reaction flask.

General procedure A for the preparation of C-(*per*-O-*acetyl-1-bromo-1-deoxy*-D-*glycopyranosyl)formamides* **2** and **10**:– To a suspension of **1** or **9** (2.75 mmol) in glacial acetic acid (3 ml), cooled in an ice bath, were added with stirring titanium tetrachloride (5.5 mmol, 0.6 ml) and water (2.75 mmol, 49.5 μl). After 30 min the ice bath was removed and the mixture stirred for 15 h (in the case of **2**) or for 2.5 days (in the case of **10**) at room temperature. Then the solution was poured with continuous stirring into a mixture of ice and water (16 ml) and the crude product was extracted with chloroform. The combined chloroform extracts were washed with cold saturated $NaHCO_3$ solution and water, dried, and the chloroform was evaporated. The crystalline crude products thus obtained were sufficiently pure for further transformations.

General procedure B for the preparation of *per*-O-*acetyl-glycopyranosylidene-spiro-hydantoins* **3**, **11** and **15**, and *thiohydantoins* **7** and **16**: To a solution of **2** (0.44 mmol) or **10** (0.52 mmol) in dry nitromethane (8 ml) were added molecular sieves and freshly prepared dry silver cyanate or thiocyanate, or potassium thiocyanate (4 equivalents). The reaction mixture was stirred at 80°C for 3-4 h (silver cyanate, potassium thiocyanate) or 15 h (silver thiocyanate). After filtration the reaction mixture was evaporated under reduced pressure and the residue separated by column chromatography using ethyl acetate-hexane (2:1) as eluent.

General procedure C for *glycopyranosylidene-spiro-hydantoins* **4** and **12**, and *thiohydantoins* **8** and **17**: To a solution of **3**, **7** or **11**, **16** (0.3 mmol) in dry methanol (~5 ml) were added about 10 drops of a 1M methanolic sodium methoxide solution and the mixtures were stirred at room temperature until disappearance of the starting material (tlc, eluent: chloroform-methanol 1:1). After neutralisation with Dowex 50W(H^+) and filtration, the solvent was removed to furnish the title compounds.

C-*(2,3,4,6-tetra*-O-*acetyl-1-bromo-1-deoxy-β-D-galactopyranosyl)formamide(3,4,5,7-tetra*-O-*acetyl-2-bromo-2-deoxy-α-D*-galacto-*hept-2-ulopyranosonamide)* **2**: Prepared from **1** according to general procedure **A**. Yield 90% for crude **2** (77% after recrystallisation from ethanol); mp 167-169°C; $[\alpha]_D$ +145 (c 1.06, $CHCl_3$). Lit[4] mp 164-167°C; $[\alpha]_D$ +138 (c 2.3, $CHCl_3$). Characteristic spectral data are identical with the reported values.[4]

(2R,3S,4S,5R,6R)*-3,4,5-triacetoxy-2-acetoxymethyl-7,9-diaza-1-oxa-spiro[4,5]decane-8,10-dione* **3**: Prepared from **2** according to general procedure **B**. Amorphous powder, yield 54%; $[\alpha]_D$ +40 (c 2.93, $CHCl_3$);

^{1}H-NMR ($CDCl_3$) δ 9.2 (1H, s, H-9), 8.4 (1H, s, H-7), 5.7 (1H, d, J=11.0 Hz, H-5), 5.44 (1H, d, J=3.5 Hz, H-3), 5.36 (1H, dd, J=11.0, 3.5 Hz, H-4), 4.22 (1H, t, J=6.5 Hz, H-2), 4.14 (1H, dd, J=11.5, 6.5 Hz, CH_2), 4.08 (1H, dd, J=11.5, 6.5 Hz, CH_2); ^{13}C-NMR ($CDCl_3$) δ 167.8 (C-10, $^3J_{H\text{-}5,C\text{-}10}$=2.4 Hz), 156.7 (C-8), 87.9 (C-6), 70.8 (C-2), 68.9 (C-4), 67.5 (C-3), 65.5 (C-5), 61.7 (CH_2). High resolution MS: Calcd. for $C_{16}H_{21}N_2O_{11}$ $[M+H]^+$ 417.1145. Found 417.1152, Δ (mmu) 0.7. Fragment ions: m/z 388 (M−CO), 374 (M+H−CONH).

(2R,3R,4S,5R,6R)-3,4,5-trihydroxy-2-hydroxymethyl-7,9-diaza-1-oxa-spiro[4,5]decane-8,10-dione **4**: Prepared from **3** according to general procedure **C**. Amorphous product, yield 80%; $[\alpha]_D$ +43 (c 1.82, CH_3OH); ^{1}H-NMR (D_2O) δ 4.14 (1H, d, J=10.5 Hz, H-5), 4.05 (1H, d, J=3.2 Hz, H-3), 3.9-3.7 (4H, m, H-2, H-4, CH_2); ^{13}C-NMR (CD_3OD) δ 173.9 (C-10, $^3J_{H\text{-}5,C\text{-}10}$=2.9 Hz), 159.4 (C-8), 91.1 (C-6), 76.8, 72.0, 70.7, 68.9 (C-2 to C-5), 62.5 (CH_2). High resolution MS: Calcd. for $C_8H_{13}N_2O_7$ $[M+H]^+$ 249.0723. Found 249.0727, Δ (mmu) 0.4. Fragment ions: m/z 231 (M+H−H_2O), 221 (M+H−CO).

C-*(2,3,4,6-tetra-O-acetyl-1-hydroxy-β-D-galactopyranosyl)formamide (3,4,5,7-tetra-O-acetyl-α-D-galacto-hept-2-ulopyranosonamide)* **5**: Isolated by column chromatography from the reaction of **2** with silver cyanate and silver thiocyanate in 35% and 23% yields, respectively. Syrup; $[\alpha]_D$ +51 (c 4.50, $CHCl_3$); ^{1}H-NMR (C_6D_6) δ 6.13 (1H, s, -OH), 5.78 (1H, dd, J=10.5, 3.0 Hz, H-3), 5.68 (1H, d, J=10.5 Hz, H-2), 5.62 (1H, dd, J=3.0, 1.3 Hz, H-4), 5.32 (1H, brs, NH_2), 4.9 (1H, brs, NH_2), 4.25 (1H, dt, J=6.6, 1.3 Hz, H-5), 4.03 (2H, ~dd, J=6.6 Hz, H-6,6'); ^{13}C-NMR ($CDCl_3$) δ 170.4 ($CONH_2$, $^3J_{H\text{-}2,CO(NH2)}$=2.6 Hz), 94.0 (C-1), 69.0, 68.3, 67.9 (C-2 to C-5), 61.5 (C-6). High resolution MS: Calcd. for $C_{15}H_{22}NO_{11}$ $[M+H]^+$ 392.1193. Found 392.1195, Δ (mmu) 0.2. Fragment ions: m/z 374 (M+H−H_2O), 350 (M+H−CH_2CO), 332 (M+H−H_2O−CH_2CO).

(2R,3S,4S,5R,6S)-3,4,5-triacetoxy-2-acetoxymethyl-7,9-diaza-1-oxa-spiro[4,5]decane-10-one-8-thione **7**: Prepared from **2** according to the general procedure **B**. Yield 67% for the crude **7**; mp 251-252°C (after recrystallisation from ethyl acetate-hexane); $[\alpha]_D$ +22 (c 0.8, CH_3OH); ^{1}H-NMR (DMSO-d_6) δ 12.33 (1H, s, H-9), 10.9 (1H, s, H-7), 5.62 (1H, dd, J=10.6, 3.3 Hz, H-4), 5.47 (1H, dd, J=3.3, 1.2 Hz, H-3), 5.40 (1H, d, J=10.6 Hz, H-5), 4.83 (1H, dt, J=7.0, 1.2 Hz, H-2); ^{13}C-NMR (CD_3OD) δ 185.5 (C-8), 173.1 (C-10, $^3J_{H\text{-}5,C\text{-}10}$=5.8 Hz), 88.6 (C-6), 71.2 (C-2), 69.7 (C-4), 68.8 (C-3), 68.5 (C-5), 62.9 (CH_2). Anal. found: C, 44.42; H, 4.76; N, 6.76; S, 7.55. Calcd. for $C_{16}H_{20}N_2O_{10}S$ (432.41): C, 44.44; H, 4.66; N, 6.48; S, 7.42%.

(2R,3R,4S,5R,6S)-3,4,5-trihydroxy-2-hydroxymethyl-7,9-diaza-1-oxa-spiro[4,5]decane-10-one-8-thione **8**: Prepared from **7** according to the general procedure **C**. Yield 82%; mp 268-269°C; $[\alpha]_D$ +70 (c 1.04, DMSO); ^{1}H-NMR (DMSO-d_6) δ 11.65 (1H, s, H-9), 10.37 (1H, s, H-7); ^{1}H-NMR (D_2O) δ 4.55 (1H, dt, J~5.7, ~1 Hz, H-2), 4.31 (1H, dd, J=10.1, 3.2 Hz, H-4), 4.06 (1H, dd, J=3.2, ~1 Hz, H-3), 3.96 (1H, d, J=10.1 Hz, H-5), 3.73 (2H, ~d, J~5.7 Hz, CH_2); 13C-NMR (DMSO-d_6) δ 183.5 (C-8), 173.6 (C-10, $^3J_{H\text{-}5,C\text{-}10}$=7.0 Hz), 89.4 (C-6), 74.5, 69.6, 68.8, 68.2 (C-2 to C-5), 60.7 (CH_2). High resolution MS: Calcd. for $C_8H_{13}N_2O_6S$

$[M+H]^+$ 265.0490. Found 265.0491, Δ (mmu) 0.1. Fragment ions: m/z 246 ($M-H_2O$), 236 ($M-CO$), 224 ($M-2xH_2O$), 222 ($M-CS$).

C-(2,3,4-tri-O-acetyl-1-bromo-1-deoxy-α-D-arabinopyranosyl)formamide (3,4,5-tri-O-acetyl-2-bromo-2-deoxy-β-D-fructopyranosonamide) **10**: Prepared from **9** according to general procedure **A**. Yield 77% for crude **10** (61% after recrystallisation from dichloromethane-hexane); mp 146-148°C; $[\alpha]_D$ -198 (c 1.02, DMSO); ^{1}H-NMR (acetone-d_6) δ 7.31 (1H, s, NH_2), 6.91 (1H, s, NH_2), 5.42 (1H, ddd, J=3.5, 1.6, 1.1 Hz, H-4), 5.35 (1H, d, J=9.7 Hz, H-2), 5.31 (1H, dd, J=9.7, 3.5 Hz, H-3), 4.37 (1H, dd, J=13.4, 1.1 Hz, H-5'), 4.20 (1H, dd, J=13.4, 1.6 Hz, H-5); ^{13}C-NMR (acetone-d_6) δ 167.5 ($CONH_2$, $^3J_{H\text{-}2,CO(NH2)}$=1.4 Hz), 98.8 (C-1), 70.2, 68.2, 67.7, 67.6 (C-2 to C-5). Anal. found: C, 37.91; H, 4.30; N, 4.18; Br, 19.98. Calcd. for $C_{12}H_{16}NO_8Br$ (382.02): C, 37.73; H, 4.22; N, 3.66; Br, 20.9.

(3R,4R,5S,6S)-3,4,5-triacetoxy-7,9-diaza-1-oxa-spiro[4,5]decane-8,10-dione **11**: Prepared from **10** according to general procedure **B**. Yield 40%; mp 250-252°C; $[\alpha]_D$ -79 (c 1.675, acetone); ^{1}H-NMR (acetone-d_6) δ 9.9 (1H, s, H-9), 8.61 (1H, s ,H-7), 5.76 (1H, d, J=10.6 Hz, H-5), 5.38-5.33 (2H, m, H-3, H-4), 4.1 (1H, d, J=13.5 Hz, H-2), 3.99 (1H, d, J=13.5 Hz, H-2'); ^{13}C-NMR (CD_3OD) δ 171.5 (C-10, $^3J_{H\text{-}5,C\text{-}10}$=2.5 Hz), 158.6 (C-8), 89.4 (C-6), 69.9, 69.9, 67.2 (C-3 to C-5), 65.2 (C.2). High resolution MS: Calcd. for $C_{13}H_{17}N_2O_9$ $[M+H]^+$ 345.0934. Found 345.0942, Δ (mmu) 0.8. Fragment ions: m/z 316 ($M-CO$), 302 ($M+H-CONH$).

(3R,4R,5S,6S)-3,4,5-trihydroxy-7,9-diaza-1-oxa-spiro[4,5]decane-8,10-dione **12**: Prepared from **11** according to general procedure **C**. Yield 64%; mp 221-223°C; $[\alpha]_D$ -103 (c 0.52, CH_3OH-H_2O 1:1); ^{1}H-NMR (D_2O) δ 4.12 (1H, d, J=10.5 Hz, H-5), 4.04 (1H, ddd, J=3.4, 1.6, ~1 Hz, H-3), 3.94 (1H, dd, J=13.4, 1.6 Hz, H-2), 3.8 (1H, dd, J=13.4, ~1 Hz, H-2'), 3.75 (1H, dd, J=10.5, 3.4 Hz, H-4); ^{13}C-NMR (CD_3OD) δ 173.8 (C-10, $^3J_{H\text{-}5,C\text{-}10}$=2.7 Hz), 159.4 (C-8), 91.5 (C-6), 71.4, 70.5, 68.8 (C-3 to C-5), 67.9 (C-2). High resolution MS: Calcd. for $C_7H_{11}N_2O_6$ $[M+H]^+$ 219.0617. Found 219.0620, Δ (mmu) 0.3. Fragment ions: m/z 201 ($M+H-H_2O$), 191 ($M+H-CO$).

C-(2,3,4-tri-O-acetyl-1-hydroxy-α-D-arabinopyranosyl)formamide (3,4,5-tri-O-acetyl-β-D-fructopyranosonamide) **13**: Isolated from the reaction of **10** with silver cyanate and silver thiocyanate in 35% and 12 % yield, respectively. Syrup; $[\alpha]_D$ -67 (c 2.16, $CHCl_3$); ^{1}H-NMR (DMSO-d_6) δ 7.38 (1H, s, NH_2), 7.3 (1H, s, NH_2), 7.05 (1H, s, -OH), 5.31 (1H, d, J=11.1 Hz, H-2), 5.23-5.17 (2H, m, H-3, H-4), 4.15 (1H, dd, J=13.2, ~1 Hz, H-5), 3.7 (1H, dd, J=13.2, 1.3 Hz, H-5'); ^{13}C-NMR (DMSO-d_6) δ 168.5 ($CONH_2$,$^3J_{H\text{-}2,CO(NH2)}$ ~1 Hz), 94.7 (C-1), 68.7, 68.1, 67.7 (C-2 to C-4), 61.3 (C-5). High resolution MS: Calcd. for $C_{12}H_{18}NO_9$ $[M+H]^+$ 320.0981. Found 320.0982, Δ (mmu) 0.1. Fragment ions: m/z 302 ($M+H-H_2O$), 278 ($M+H-CH_2CO$), 270 ($M+H-H_2O-CH_2CO$).

C-(2,3,4-tri-O-acetyl-1-azido-1-deoxy-β-D-arabinopyranosyl)formamide (3,4,5-tri-O-acetyl-2-azido-2-deoxy-α-D-fructopyranosonamide) **14**: A solution of **10** (0.3 g, 0.785 mmoles) in dry dimethyl sulphoxide (1 ml) was added to a solution of sodium azide (0.102 g, 1.57 mmoles) in dry dimethyl sulphoxide (1.6 ml) at

room temperature and the mixture was stirred for 30 min. Then the mixture was diluted with water (10 ml) and extracted with diethyl ether (5x5 ml). After drying and evaporation of the solvent **14** (0.24 g, 89%) was obtained as a pure crystalline raw-product. Recrystallisation from diethyl ether (79% recovery) gave an analytical sample: mp 118-119°C; $[\alpha]_D$ +76 (c 1.05, $CHCl_3$); ν_{N3} 2120 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 7.29 (1H, s, NH_2), 7.05 (1H, s, NH_2), 5.53 (1H, dd, J=5.9, 3.4 Hz, H-3), 5.41 (1H, d, J=5.9 Hz, H-2), 5.23 (1H, dd, J=4.4, 3.4 Hz, H-4), 4.17 (1H, dd, J=11.6, 4.4 Hz, H-5), 4.08 (1H, dd, J=11.6, 7.5 Hz, H-5') ; ^{13}C-NMR ($CDCl_3$) δ 167.92 ($CONH_2$, $^3J_{H\text{-}2,CO(NH2)}$ =1.7 Hz), 88.49 (C-1), 67.82, 66.76, 65.22, 61.72 (C-2 to C-5). Anal. found: C, 41.84; H, 4.81; N, 16.21. Calcd. for $C_{12}H_{16}N_4O_8$ (344.14): C, 41.88; H, 4.68; N, 16.28.

(3R,4R,5S,6R)-3,4,5-triacetoxy-7,9-diaza-1-oxa-spiro[4,5]decane-8,10-dione **15**: Prepared from **10** according to general procedure **B**. Amorphous product, yield 10%; $[\alpha]_D$ -61 (c 1.64, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.44 (1H, s, H-9), 6.23 (1H, s, H-7), 5.74 (1H, dd, J=10.6, 3.4 Hz, H-4), 5.44 (1H, d, J=10.6 Hz, H-5), 5.38 (1H, dd, J=3.4, 2.0 Hz, H-3), 4.49 (1H, dd, J=13.4, 1.2 Hz, H-2), 3.89 (1H, dd, J= 13.4, 2.0 Hz, H-2'); ^{13}C-NMR ($CDCl_3$) δ 169.2 (C.10, $^3J_{H\text{-}5,C\text{-}10}$=6.1 Hz), 155.1 (C-8), 86.5 (C-6), 68.1 (C-3), 68.0 (C-4), 67.6 (C-5), 64.5 (C-2). High resolution MS: Calcd. for $C_{13}H_{17}N_2O_9$ $[M+H]^+$ 345.0934. Found 345.0937, Δ (mmu) 0.3. Fragment ions: m/z 316 (M−CO), 302 (M+H−CONH).

(3R,4R,5S,6R)-3,4,5-triacetoxy-7,9-diaza-1-oxa-spiro[4,5]decane-10-one-8-thione **16**: Prepared from **10** according to general procedure **B**. Yield 75%; mp 244-245°C; $[\alpha]_D$ -20 (c 1.05, CH_3OH); ^{1}H-NMR (DMSO-d_6) δ 12.28 (1H, s, H-9), 10.84 (1H, s, H-7), 5.59 (1H, dd, J=10.6, 3.4 Hz, H-4), 5.38 (1H, d, J=10.6 Hz, H-5), 5.32 (1H, d, J=3.4 Hz, H-3), 4.42 (1H, d, J=13.6 Hz, H-2), 3.90 (1H, dd, J=13.6, 1.6 Hz, H-2'); ^{13}C-NMR (CD_3OD) δ 185.5 (C-8), 173.1 (C-10, $^3J_{H\text{-}5,C\text{-}10}$=5.9 Hz), 88.6 (C-6), 69.8, 69.5, 68.8 (C-3 to C-5),64.9 (C-2). Anal. found: C, 43.63; H, 4.74; N, 8.06; S, 8.92. Calcd. for $C_{13}H_{16}N_2O_8S$ (360.34): C, 43.33; H, 4.48; N, 7.77; S, 8.90.

(3R,4R,5S,6R)-3,4,5-trihydroxy-7,9-diaza-1-oxa-spiro[4,5]decane-10-one-8-thione **17**: Prepared from **16** according to general procedure **C**. Yield 83%; mp 224-225°C; $[\alpha]_D$-88 (c 2.34, DMSO); ^{1}H-NMR (DMSO-d_6) δ 11.65 (1H, s, H-9), 10.36 (1H, s, H-7); ^{1}H-NMR (D_2O) δ 4.45 (1H, dd, J=13.1, 1.2 Hz, H-2), 4.32 (1H, dd, J=10.0, 3.3 Hz, H-4), 4.08 (1H, ~ddd, J=3.3, 2.0, 1.2 Hz, H-3), 3.98 (1H, d, J=10.0 Hz, H-5), 3.9 (1H, dd, J=13.1, 2.0 Hz, H-2'); ^{13}C-NMR (DMSO-d_6) δ 183.6 (C-8), 173.6 (C-10, $^3J_{H\text{-}5,C\text{-}10}$=6.7 Hz), 89.5 (C-6), 69.0, 68.8, 68.2 (C-3 to C-5), 66.1 (C-2). Anal. found: C, 36.28; H, 4.42; N, 11.91; S, 13.70. Calcd. for $C_7H_{10}N_2O_5S$ (234.23): C,35.89; H, 4.30; N,11.96; S, 13.69.

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REFERENCES AND NOTES

1. a) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindo, M.; Honma, T.; Tohjigamori, M.; Haneishi, T. *J. Antibiot.* **1991**, *44*, 293-300; b) Haruyama, H.; Takayama, T.; Kinoshita, T.; Kondo, M.; Nakajima, M.; Haneishi, T. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1637-1640.
2. *Syntheses for (+)-hydantocidin:* a) Mio, S.; Ichinose, R.; Goto, K.; Sugai, S. *Tetrahedron* **1991**, *47*, 2111-2120; b) Matsumoto, M.; Kirihara, M.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 6289-6292; c) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133-2144; d) Chemla, P. *Tetrahedron Lett.* **1993**, *34*, 7391-7394; e) Harrington, P.; Jung, M.E. *Tetrahedron Lett.* **1994**, *35*, 5145-5148; *Hexofuranose analogues*: f) Burton, J.W.; Son, J.C.; Fairbanks, A.J.; Choi, S.S.; Taylor, H.; Watkin, D.J.; Winchester, B.G.; Fleet, G.W.J. *Tetrahedron Lett.* **1993**, *34*, 6119-6122; g) Brandstetter, T.W.; Kim, Y; Son, J.C.; Taylor, H.M.; de Q. Lilley, P.M.; Watkin, D.J.; Johnson, L.N.; Oikonomakos, N.G.; Fleet, G.W.J. *Tetrahedron Lett.* **1995**, *36*, 2149-2152; h) Estevez, J.C.; Smith, M.D.; Lane, A.L.; Crook, S.; Watkin, D.J.; Besra, G.S.; Brennan, P.J.; Nash, R.J.; Fleet, G.W.J. *Tetrahedron: Asymmetry* **1996**, *7*, 387-390; i) Brandstetter, T.W.; de la Fuente C.; Kim, Y.; Johnson, L.N.; Crook, S.; de Q. Lilley, P.M.; Watkin, D.J.; Tsitsanou, K.E.; Zographos, S.E.; Chrysina, E.D.; Oikonomakos, N.G.; Fleet, G.W.J. *Tetrahedron* **1996**, *52*, 10721-10736; *Hexopyranose analogues:* j) Bichard, C.J.F.; Mitchell, E.P.; Wormald, M.R.; Watson, K.A.; Johnson, L.N.; Zographos, S.E.; Koutra, D.D.; Oikonomakos, N.G.; Fleet, G.W.J. *Tetrahedron Lett.* **1995**, *36*, 2145-2148; k) Brandstetter, T.W.; Wormald, M.R.; Dwek, R.A.; Butters, T.D.; Platt, F.M.; Tsitsanou, K.E.; Zographos, S.E.; Oikonomakos, N.G.; Fleet, G.W.J. *Tetrahedron: Asymmetry* **1996**, *7*, 157-170; l) Estevez, J.C.; Smith, M.D.; Wormald, M.R.; Besra, G.S.; Brennan, P.J.; Nash, R.J.; Fleet, G.W.J. *Tetrahedron: Asymmetry* **1996**, *7*, 391-394; *Tetrofuranose analogues:* m) Hanessian, S.; Sancéau, J.-Y.; Chemla, P. *Tetrahedron* **1995**, *51*, 6669-6678; *Carbocyclic analogues:* n) Sano, H.; Sugai, S. *Tetrahedron* **1995**, *51*, 4635-4646; o) Sano, H.; Sugai, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1143-1150; *Modifications in the hydantoin ring:* p) Lamberth, C.; Blarer, S. *Synth. Commun.* **1996**, *26*, 75-81; *Thiohydantoin derivatives:* q) Sano, H.; Mio, S.; Kitagawa, J.; Shindou, M.; Honma, T.; Sugai, S. *Tetrahedron* **1995**, *51*, 12563-12572 and references cited therein; *For stereoisomers see:* ref. 2. in 2q.
3. López, C.A.; Trigo, G.G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177-228.
4. Kiss, L.; Somsák, L. *Carbohydr. Res.* **1996**, *291*, 43-52.
5. Somsák, L.; Sós, E.; Györgydeák, Z.; Praly, J.-P.; Descotes, G. *Tetrahedron* **1996**, *52*, 9121-9136.
6. Somsák, L.; Ferrier, R.J. *Adv. Carbohydr. Chem. Biochem.* **1991**, *49*, 37-92.

7. BeMiller, J.N.; Yadav, M.P.; Kalabokis, V.N.; Myers, R.W. *Carbohydr. Res.* **1990**, *200*, 111-126.
8. Somsák, L.; Batta, G.; Farkas, I. *Carbohydr. Res.* **1983**, *124*, 43-51.
9. Somsák, L.; Györgydeák, Z.; Eperjesi, I.; Sós, E.; Praly, J.-P. *8th Eur. Carbohydr. Symp.* Sevilla, Spain, 2-7 July 1995, A-144.
10. The conformer ratio was calculated by using $J_{4a,5a}$=11.6 Hz and $J_{4c,5c}$=1.5 Hz as limiting values for the $^4C_1$ and $^1C_4$ conformations, respectively taken from Durette, P.L.; Horton, D. *Carbohydr. Res.* **1971**, *18*, 389-401.
11. Paulsen, H.; Györgydeák, Z.; Friedmann, M. *Chem. Ber.*, **1974**, *107*, 1590-1613.
12. Chmielewski, M.; BeMiller, J.N.; Cerretti, D.P. *J. Org. Chem.* **1981**, *46*, 3903-3908.
13. Corral, R.A.; Orazi, O.O. *Spectrochim.Acta* **1965**, *21*, 2119-2123; Sobczyk, K.; Siemion, I.Z. *Pol. J. Chem.* **1980**, *54*, 1833-1840; Suzuki, T.; Tomioka, T.; Tuzimura, K. *Can. J. Biochem.* **1977**, *55*, 521-527.
14. Tvaroška, I.; Bleha,T. *Adv. Carbohyd. Chem. Biochem.* **1989**, *47*, 45-123.
15. Deslongchamp, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, **1983**, pp.40-41.
16. Sinnott, M.L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113-204.
17. Kovács, L. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1015-1019 and references therein.
18. Tip, L.; Versluis, C.; Dallinga, J.W.; Heezma, W. *Anal. Chim. Acta* **1990**, *241*, 219.

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