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Short and highly stereoselective total synthesis of D-*ribo*-configured ureido sugars

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ABSTRACT

An highly stereoselective, flexible and very short synthetic approach to D-*ribo*-configured ureido monosaccharides of the aldose, aldonic acid and alditol series has been performed starting from the 5-(alditol-1-*C*-yl)-hydantoin intermediates, obtained via aldol-type addition reaction of hydantoin based building blocks to enantiomerically pure aldehydes. A study to assess the stereoselectivity of this reaction has been undertaken and a very high increase of diastereoselectivity was observed depending on the hydantoin protecting group. The imidazolidinone ring elaboration of 5-(alditol-1-*C*-yl)-hydantoin intermediates to give ureido sugar derivatives was studied.

1. Introduction

Because of their relevant biological properties a few naturally occurring carbohydrate-based ureas awakened interest during the eighties with the discovery of antibiotic activity in a family of glycocinnamoylspermidines pseudooligosaccharides **1**[1] incorporating an urea–glycosyl linkage, in CV-1 **2**[2] and in *N*-carbamoylglucosamine SF-1993 **3**[3] uerido monosaccharides (Fig. 1). But only in recent years a renewed interest in ureido sugar derivatives has been observed, and a few sugar ureas with new and interesting biological properties were synthesized. Some azasugar ureas such as **4** or **5** showed glycosidase inhibition activity.[4] Ureido glycuronate derivatives **6** were proposed as novel antibacterial agents because of their ability to inhibit ligases distinguishing between NAD^+ and ATP-dependent ligases,[5a] as antifilarial agents because they are inhibitors of filarial glutathione-*S*-transferases.[5b,c] Furthermore, they also show an α-glycosidase inhibition activity and a mild antitubercular activity.[5d] *N*-Glucopyranosyl ureido derivatives **7** exhibit a strong inhibition activity against glycogen phosphorylase, an important biological target for the treatment of type II diabetes.[6] Hydroxyalkylureas like **8** have shown antifungal activity and have found cosmetic application for treating desquamative conditions of the scalp particularly seborrhoeic dermatitis and dandruff.[7] They are also components of selective inhibitors of platelet-derived growth factor and inhibitors of human ileal bile acid transporter.[8] Ureido-furanosyluronic acid pyrimidine derivative **9** inhibits the synthesis of chitin, a cell wall component of fungi.[9] An ureido-glucose analogue shows *Trypanosoma brucei* hexose transporter inhibition[10] and finally, a new angucycline compound from *Streptomyces* containing an ureido sugar in its structure exhibits antigastrin- and gastric-mucosal protective activity.[11]

In contrast to the increasing interest in biological properties of these sugar mimics, a relatively scarce number of synthetic strategies have been used for the synthesis of ureido sugars. The first approach to carbohydrate-based ureas was the condensation of monosaccharides with ureas.[12] More recent procedures were mainly based on the condensation of sugar-derived isocyanates[1c,4c,13] and isothiocyanates,[14] sugar-derived carbamates[15] or oxazolidinones[4b,16] with amines or aminosugars in order to obtain ureido monosaccharides and pseudodisaccharides, respectively. Other methods involve the condensation of aminosugars with isocyanates,[5d,17] hydrolysis of glycosylcarbodiimides obtained via iminophosphoranes derived from glycosyl azides,[4a,18] and finally modified Curtius rearrangement of sugar carboxylic acids.[19] Although these new interesting procedures have been successful used for the synthesis of ureido mono- and polysaccharides, new highly stereoselective approaches that also replace dangerous reagents are particularly attractive.

Searching for a new versatile and stereoselective procedure for the synthesis of carbohydrate-based ureas, we looked at imidazolidinone derivatives type **A** as suitable intermediates for the synthesis of enantiopure ureido sugars equipped with a variable polyol chain and different stereochemical centres (Scheme 1).[20] In fact, the elaboration of the imidazolidinone ring, via heterocycle ring opening or reduction, could be an easy way to synthesize ureido-aldonic acids (**B**) or ureido-aldoses and -alditols (**C** and **D**), respectively. This approach requires the enantiomerically pure key intermediate **A** that could be synthesized by a stereoselective coupling reaction of enantiopure aldehydo precursors and hydantoin derivatives[21,22] as well as stereoconservative procedures for the non-trivial chemical imidazolidinone ring elaboration.[23] This very short route for the synthesis of carbohydrate-based ureas

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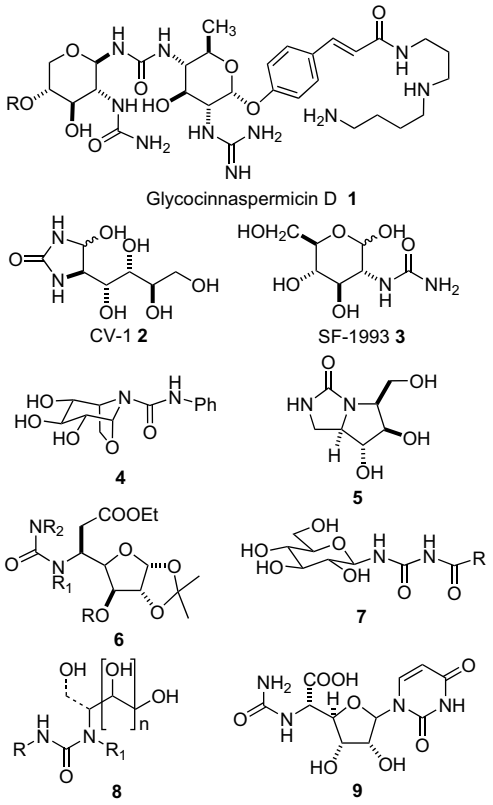


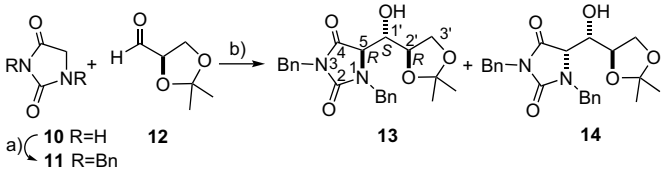
Figure 1. Natural and synthetic ureido sugar derivatives.

is based on two steps only: (a) diastereoselective aldol-type addition and (b) efficient hydantoin ring elaboration, and in principle offers a divergent and flexible approach too. In fact the choice of different starting aldehydo sugars can generate products with $2+n$ carbon chain atoms and different stereochemical variants.

We wish to report here the stereoselective synthesis of D-*ribo*-configured carbohydrate-based ureas, in particular the synthesis of analogues of bioactive compounds **2** and **8**, as the first application of this new flexible synthetic approach to ureido monosaccharide derivatives and the study of protecting group influence both on diastereoselectivity of the aldol-type reaction and on the reactivity of hydantoin intermediates.

2. Results and discussion

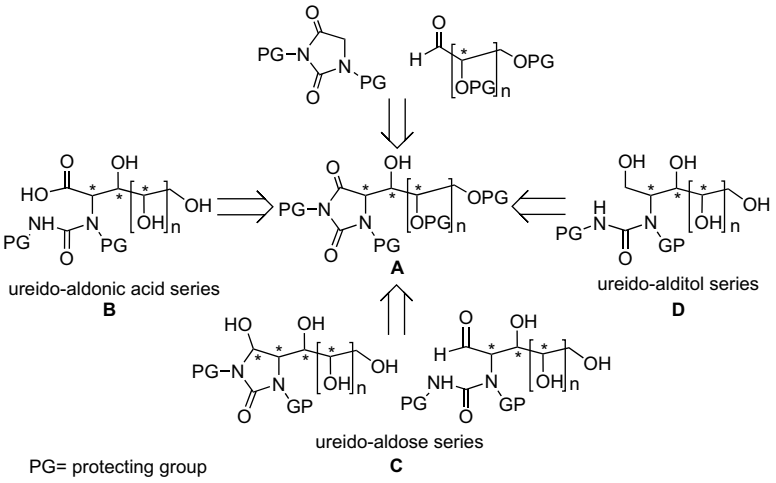
In order to obtain the 5-(alditol-1-*C*-yl)-hydantoin intermediates of type **A**, we previously examined the homologation of enantiopure aldehydo sugars with 1,3-dibenzylhydantoin derivative (DBnHy) **11** prepared by N-protection of commercially available hydantoin **10** under weakly basic conditions (Scheme 2).[21a]



Scheme 2. Synthesis of 5-(alditol-1-*C*-yl)-1,3-dibenzylhydantoins **13** and **14**: (a) BnBr, K_2CO_3, DMF, 85%; (b) LiHMDS, THF, −80 °C, 80:20 isomer ratio **13**/**14**.

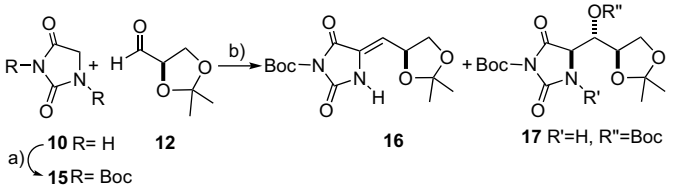
The synthesis of the required D-*ribo*-configured 5-(alditol-1-*C*-yl)-hydantoin intermediate was performed by addition reaction of the enantiopure C-3 aldehydo sugar **12** to DBnHy lithium enolate, derived from the reaction of **11** with 1.2 equiv of LiHMDS in anhydrous THF at −80 °C. D-*ribo*-Configured 5-(alditol-1-*C*-yl)-hydantoin **13** was obtained in good yield and diastereoselectivity with a small amount of its C-5 epimer **14** (80:20 isomer ratio **13**/**14**) (Scheme 2).[24] Purification of compound **13** was achieved at this stage by crystallization of the crude reaction mixture from CH_2Cl_2/hexane (1:3) to give **13** in 45% yield.[25]

Then, we have explored the reactivity of differently protected hydantoin derivatives in the aldol-type addition reaction in order to improve the diastereoselectivity of this reaction, and to find a more easy elaboration of hydantoin ring of the 5-(alditol-1-*C*-yl)-hydantoin intermediates. For this purpose 1,3-di-(*tert*-butoxycarbonyl)hydantoin **15** (DBocHy) was synthesized in high yield (81%) by reaction of hydantoin **10** with Boc_2O in CH_3CN in presence of a catalytic amount of DMAP (Scheme 3). Furthermore, the preparation of 1,3-di-(*tert*-butyldimethylsilyl)hydantoin (DTBSHy) **18** was performed in high yield (84%) by reaction of hydantoin **10** with TBSCl in CH_2Cl_2, Et_3N (Scheme 4). The

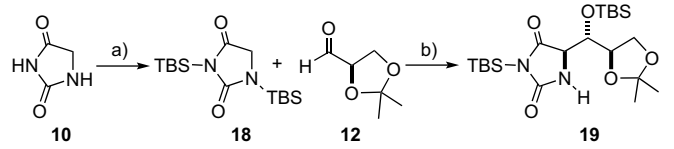


Scheme 1. Retrosynthetic analysis of ureido-alditol, aldose and aldonic acid series.

aldol-type addition reaction to 2,3-*O*-isopropylidene-D-glyceraldehyde **12** was then performed with both hydantoin derivatives **15** and **18**. The addition reaction of the DBocHy lithium enolate derived from the reaction of DBocHy **15** with LiHMDS in anhydrous THF at −80 °C to the aldehyde **12** gave, after quenching with water at −80 °C and workup, a mixture of products that were identified by NMR analysis as the dehydrated **16** and the product **17** (Scheme 3).



Scheme 3. Synthesis of 5-(alditol-1-*C*-yl)-3-Boc-hydantoin **17**: (a) Boc_2O, CH_3CN, DMAP, 81%; (b) LiHMDS 1 M solution, THF, −80 °C, 98%.



Scheme 4. Synthesis of 5-(alditol-1-*C*-yl)-3-TBS-hydantoin **19**: (a) TBSCl, CH_2Cl_2, Et_3N, 84%; (b) LiHMDS 1 M solution, THF, −80 °C, 56%.

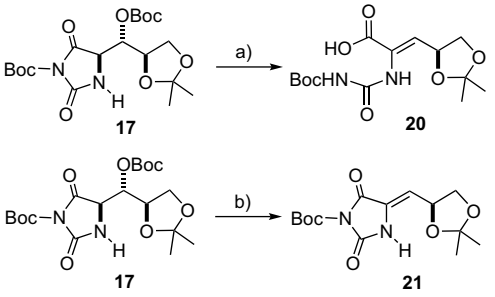
To avoid the dehydration process, we repeated the experiment under the same reaction conditions quenching the reaction at −80 °C with a saturated aqueous solution of NaH_2PO_4 (pH 5–6). We observed, by NMR analysis of the crude mixture, that now only the aldol addition product **17** was obtained without trace of the dehydrated **16** in 98% yield. Interestingly, only one of the four possible diastereomers was formed in the addition step (de>98%). The substitution of the Bn protecting groups by Boc groups generated a dramatic increase of diastereomeric excess from 60% up to >98%, with a significant increase of the reaction yield. The product **17** was obtained by an interesting 1,3-Boc-migration from the N-1 nitrogen to the oxygen on C-1′.[26] This also explained the easy dehydration process in the basic conditions of the workup.

An analogous migration, although of the Bz group (1,3-benzoyl migration), was reported by Seebach et al. for the reaction of enantiopure 1-benzoyl-2-*tert*-butyl-3-methylimidazolidin-4-one lithium enolate with achiral aldehydes.[27] No evidence was reported for Boc group, but interestingly this 1,3-migration was not observed when Bz group was substituted with Cbz group. Furthermore the 1,3-benzoyl migration proceeds with retention of configuration at the LiO-substituted *C*-atom.

The addition reaction of 1,3-di-(*tert*-butyldimethylsilyl)hydantoin **18** to 2,3-*O*-isopropylidene-D-glyceraldehyde was finally investigated (Scheme 4). The aldehyde **12** was added to the DTBSHy lithium enolate obtained by the addition of LiHMDS to **18** in anhydrous THF at −80 °C.

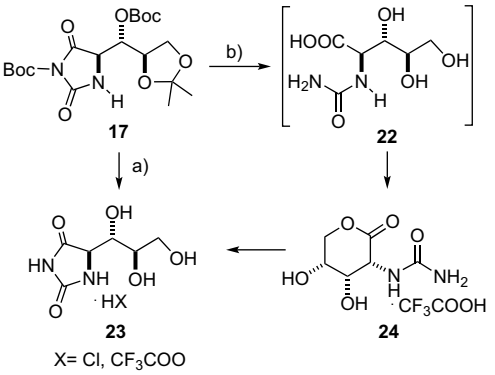
After quenching and aqueous workup we obtained a crude material that was composed by a mixture of starting material **18** (44%) and the aldol addition product **19** (56%). Although the DTBSHy addition reaction to **12** shows a good diastereoselectivity the reaction yield was low.

In order to synthesize the ureido sugar targets of the three series, we have investigated the imidazolidinone ring reactivity of 5-(alditol-1-*C*-yl)-hydantoin intermediates **17** and alternatively of **13** towards basic, acidic and reductive conditions. The reaction of compound **17** in THF with a LiOH aqueous solution at 0 °C to room temperature gave stereoselectively an interesting diastereopure (*Z*) dehydrated ureido acid **20** (Scheme 5). The same reaction performed at −20 °C to 0 °C gave only the dehydrated product **21** indicating that the dehydrating process was the first reaction step eventually followed by hydrolytic ring opening.[28,29]



Scheme 5. Synthesis of ureido aldonic acid dehydrated **20**: (a) LiOH aq, THF, 0 °C to rt, 95%; (b) LiOH aq, THF, −20 °C to 0 °C, 90%.

Acidic conditions were then investigated. By treatment of compound **17** with 37% aqueous HCl at room temperature for 12 h, deprotected hydantoin derivative **23** was quantitatively obtained without trace of aldonic acid **22** (Scheme 6). Unexpectedly, the treatment of compound **17** with neat TFA at room temperature gave, after 12 h, the desired ureido aldonic acid **24** in the lactone form (2-ureido-2-deoxy-D-*ribonic* acid-1,5-lactone) as single diastereomer in quantitative yield. This interesting ureido polyoxamic acid lactone[30] was completely transformed after 24–36 h into the hydantoin derivative **23** by standing at room temperature in methanol or water solution. A methanol solution of lactone **24** at −15 °C was slowly converted into hydantoin **23**. A 1:2 mixture of **24** and **23** was detected by NMR analysis after 4 weeks.

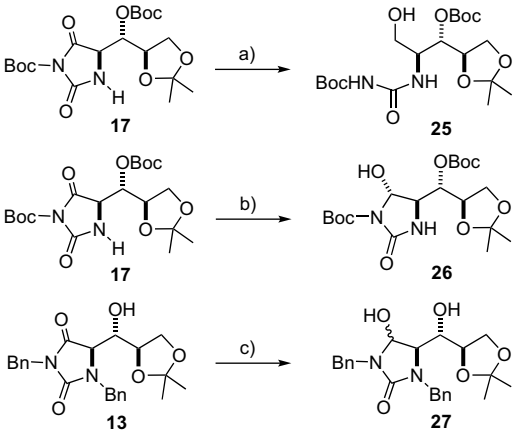


Scheme 6. Synthesis of ureido aldonic acid **24**: (a) HCl 37%, rt, 12 h, quantitative; (b) TFA, rt, 12 h, quantitative.

Starting from the α-carbamoylamino acid intermediate **22** the formation of the α-carbamoylamino-δ-lactone **24** was kinetically favoured in these acidic conditions with respect to a new cyclization to hydantoin.[31] On the contrary, the same reaction with neat TFA performed at room temperature on the benzyl derivative **13** gave the 1,3-dibenzyl polyhydroxylated hydantoin without formation of lactone intermediate.

Reduction of imidazolidinone ring of compounds **17** and **13** was then studied to obtain aldose and alditol ureido sugars by using a series of reductive conditions. Treatment of the derivative **17** with $NaBH_4$ in CH_2Cl_2 and CH_3OH (3 equiv) at room temperature gave

the desired reductive opening of imidazolidinone ring. The D-*ribo*-configured 2-deoxy-2-ureido alditol **25**, analogous to the bioactive compound **8**, was obtained in 94% yield as single diastereomer (Scheme 7). On the contrary, when compound **13** was submitted to the same $NaBH_4$ reductive conditions we obtained a mixture of unidentifiable products.

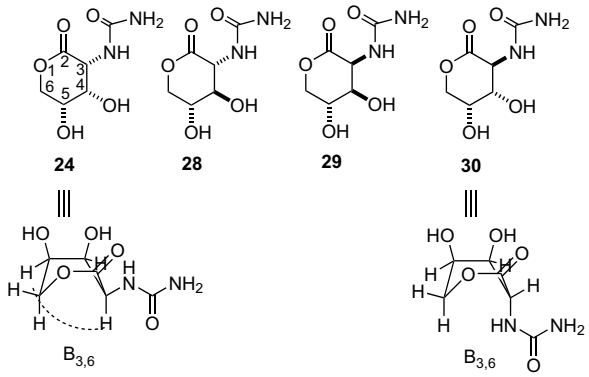


Scheme 7. Synthesis of ureido alditol **25** and ureido aldose **26** and **27**: (a) $NaBH_4$, CH_2Cl_2, MeOH (3 equiv), 85%; (b) Super H® (3 equiv), THF, −18 °C, quantitative; (c) $LiBH_4$, THF, rt, 96%.

The synthesis of ureido aldose derivatives was then investigated starting from compounds **17** and **13**. Addition of a THF solution of Super H® to compound **17** at low temperature (−18 °C) in anhydrous conditions gave the desired D-*ribo*-configured 2-deoxy-2-ureido aldose **26**, analogous of bioactive compound **2**, in quantitative yield without evidence of the ring opened aldose. Interestingly, the reaction was diastersoselective too, furnishing only compound **26** with (*R*)-configuration to C-1 as detected from the coupling constant value (J_{1-2}=2.0 Hz). Alternatively, reduction of compound **13** performed in anhydrous THF with $LiBH_4$ at room temperature gave D-*ribo*-configured 2-deoxy-2-ureido aldose **27** in high yield as a mixture of C-1 epimers. The reduction of compound **17** under the same reaction conditions gave a mixture of not identifiable products.

The protecting group of the hydantoin building block has then a great influence both on the diastereoselectivity of the aldol-type reaction and on the reactivity of the imidazolidinone ring towards basic, acidic and reductive conditions.

The (5*R*,1′*S*) stereochemistry of the two new stereocentres of the preferential 1,3-dibenzyl-imidazolidine-2,4-dione derivative **13** was unambiguously established by single crystal X-ray analysis of **13** on the basis of the known (*R*) configuration of the 2′ carbon atom.[21a] In analogy with the product **13**, we assumed that compound **17** could be derived by the same unlike (*Re* enolate, *Si* aldehyde) approach of the reaction partners in the addition step and that the 1,3-Boc-migration step, observed in the case of DBocHy addition reaction, proceeds with retention of configuration at the C-1′ carbon atom.[27] The same (5*R*,1′*S*) stereochemistry of the two new stereocentres was then tentatively assigned at this stage to compound **17** also on the basis of a similar value of the indicative *J* H(5)–H(1′) coupling constant for **13** and **17**. A confirmation of the stereochemistry previously assigned to **17** was possible at this stage by NMR analysis of the lactone **24**. We started from an analysis of energy-minimized ideal δ-lactone conformations that, respect to the classical boat (B), chair (C), envelope (E), half-chair (H) and skew (S) conformations for nonplanar six-membered rings, considers conformational restrictions due to the strong preference of the C(6)–O(1)–C(2)–C(3) unit to be close to planar (Scheme 8).[33] Energy-minimized ideal conformations $B_{3,6}$, $^4H_5$, E_5, $^2C_5$, $^2S_6$, $^1S_3$ have been examined although many previous studies of the conformation of δ-lactones in solution consider only the half-chair and boat as main types.[33] At first we attempted to distinguish between these conformations on the basis of ^1H NMR coupling constants, the diagnostic parameters being $J_{3,4}$=1.6 Hz, $J_{4,5}$=9.2 Hz, $J_{5,6a}$=2.8 Hz and $J_{5,6b}$=5.6 Hz. Established the stereochemistry of C-5 carbon atom of **24** because derived from the stereochemistry of the C-2 carbon atom of the glyceraldehyde progenitor, the conformations $^4H_5$, E_5 and $^2C_5$ are excluded because they require a not found trans biaxial $J_{5,6}$ coupling constant. We analyzed then the remaining three conformations $B_{3,6}$, $^2S_6$, $^1S_3$ for the possible four diastereomers **24** (3*R*,4*S*,5*R*), **28** (3*R*,4*R*,5*R*), **29** (3*S*,4*R*,5*R*) and **30** (3*S*,4*S*,5*R*) (Scheme 8). On the basis of diagnostic $J_{4,5}$ and $J_{3,4}$ values we excluded the (3*R*,4*R*,5*R*) and (3*S*,4*R*,5*R*) configurations of **28** and **29**. Furthermore, only the $B_{3,6}$ conformation for both **24** and **30** fit with the *J* measured values. The stereochemistry of both diastereomers **24** and **30** derives from the expected Felkin approach of the *Re* or *Si* face of the enolate of **15** to the *Si* face of the isopropylidene protected glyceraldehyde **12** (unlike or like approach).[32] Finally, a diagnostic small positive NOE effect between H-3 and H-5 permits to confirm the previous assigned (2*R*,3*S*,4*R*) configuration of the lactone **24** and then the (5*R*,1′*S*,2′*R*) configuration of **17**.[34]



Scheme 8. Boat conformations of 2-deoxy-2-ureido-D-ribonic acid-1,5-lactone diastereomers **24** and **30**.

3. Conclusion

We have developed the first highly stereoselective total synthesis of biologically important ureido sugar derivatives in only two steps and in very high yield. This method realizes the access to ureido monosaccharides not by a simple modification of preformed sugars, aminosugars or their derivatives but by building the skeleton of carbon atoms of the target molecules and their chirality. This approach offers a divergent, stereoselective and flexible procedure. In fact the simple modification of the protecting groups of hydantoin building block introduces variability in the reactivity of the condensed product **A** and in the stereoselectivity of the aldol-type addition reaction. Furthermore, a different choice of the aldehyde precursors can generate products with 2+*n* carbon atoms chains (2 derived from hydantoin building block and *n* furnished by the aldehyde). Exploiting the reactivity of differently protected 5-(alditol-1-*C*-yl)-hydantoin derivatives, new stereoconservative procedures for chemical imidazolidinone ring elaborations are also performed. As an example of the potentiality of this approach the highly stereoselective synthesis of different D-*ribo*-configured ureido aldose and alditol, analogues of bioactive molecules **2** and **8**, and D-*ribo*-configured aldonic acid have been performed and

further investigations are in progress in our laboratory to extend this approach to the synthesis of other biologically interesting ureido sugar derivatives.

4. Experimental

4.1. General

All organic solvents were dried and freshly distilled before use according to the literature procedures. All moisture sensitive reactions were carried out under a positive nitrogen pressure. For thin layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm) were used. Column chromatography was performed on silica gel (silica gel 60). Melting points are uncorrected. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury (^{1}H 400 MHz, ^{13}C 100 MHz) or Varian XL-300 (^{1}H 300 MHz, ^{13}C 75.4 MHz) spectrometer. Optical rotation were measured with a Perkin–Elmer 341 digital polarimeter using a sodium lamp (λ 589, D-line) and are given in units of 10^{-1} deg cm^2 g^{-1}. 2,3-*O*-Isopropylidene-D-glyceraldehyde **12** was prepared from 1,2-5,6-di-*O*-isopropylidene-D-mannitol (Fluka) by periodate fission and used immediately. The IR spectra were recorded on a Nicolet Avatar 330 FT-IR; ν_{max} is expressed in cm^{-1}.

4.2. 1,3-Dibenzylhydantoin (11)

To a suspension of hydantoin **10** (1 g, 10 mmol) in anhydrous DMF (80 mL), K_2CO_3 (2.76 g, 20 mmol) was added. The suspension was stirred at room temperature for 6 h, then BnBr (2.96 mL, 20 mmol) was added. After a further 19 h, the TLC (CH_2Cl_2/Et_2O 9:1) showed the disappearance of the starting material. Water was added and the solution was extracted with CH_2Cl_2 (3×40 ml). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure, the crude material obtained was purified by flash chromatography on silica gel eluting with CH_2Cl_2/Et_2O 9:1 to afford 2.1 g of compound **11** (DBnHy) in 83% yield. White solid, mp 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.20 (m, 10H, 2×Ph), 4.66 (s, 2H, CH_2Ph), 4.52 (s, 2H, CH_2Ph), 3.68 (s, 2H, H-5). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.4, 156.4, 135.9, 135.2, 128.9, 128.6, 128.5, 128.0, 127.8, 49.0, 46.6, 42.5. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found C, 72.91; H, 5.81; N, 9.89. IR (Nujol, cm^{-1}): 1701 (C=O).

4.3. (5*R*,1′*S*,2′*R*)-5-(1′-Hydroxy-2′,3′-isopropylidenedioxypropyl)-1,3-dibenzyl hydantoin (13)

To a solution of DBnHy **11** (1 g, 3.6 mmol) in anhydrous THF (60 mL), 1 M LiHMDS solution (4.3 mL) was added at −80 °C under nitrogen. The solution was stirred at this temperature for 30 min, then 2,3-*O*-isopropylidene-D-glyceraldehyde **12** (600 mg, 4.61 mmol) was added. The reaction mixture was stirred at −80 °C for 3 h, then was quenched at −80 °C with H_2O (10 mL). The solution was extracted with Et_2O (2×50 mL) and CH_2Cl_2 (2×50 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture containing **13** and **14** in a 80:20 isomer ratio. Enantiopure compound **13** was obtained via crystallization of the crude reaction mixture from CH_2Cl_2/hexane 1:3 (0.650 g, 45%). White solid, mp 182–184 °C, $[\alpha]_D^{20}$ +44 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.22 (m, 10H, 2×Ph), 5.03 (d, *J*=14.8 Hz, 1H, CH_2Ph), 4.69 and 4.64 (AB system, J_{AB}=14.4 Hz, 2H, CH_2Ph), 4.40–4.32 (m, 1H, H-1′), 4.24 (d, *J*=15.2 Hz, 1H, CH_2Ph), 4.09 (d, *J*=1.6 Hz, 1H, H-5), 4.02 (dd, *J*=8.4, 6.4 Hz, 1H, H-3′a), 3.93 (dd, *J*=8.8, 4.4 Hz, 1H, H-3′b), 3.91–3.85 (m, 1H, H-2′), 2.72 (d, *J*=4.8 Hz, 1H, OH), 1.22 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.2, 157.3, 135.8, 135.6, 129.0, 128.6, 128.3, 127.8, 109.7, 74.0, 71.0, 66.8, 61.2, 45.3, 42.6, 26.6, 24.8. Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found C, 67.42; H, 6.42; N, 6.70. IR (Nujol, cm^{-1}): 1709 (C=O), 3453 (OH).

4.4. 1,3-Di-(*tert*-butoxycarbonyl)hydantoin (15)

To a suspension of hydantoin **10** (1 g, 10 mmol) in CH_3CN (30 mL), Boc_2O (4.8 g, 22 mmol) and DMAP (122 mg, 1 mmol) were added at room temperature. The formation of a limpid solution was observed followed by CO_2 evolution. The reaction was monitored by TLC (CH_2Cl_2/AcOEt 9:1). The reaction mixture was stirred for 12 h, then the solvent was evaporated under reduced pressure. The crude reaction mixture was then purified by flash chromatography eluting with CH_2Cl_2/AcOEt 9:1 to give 2.4 g of compound **15** (81% yield) as a white solid, mp 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (s, 2H, H-5), 1.58 (s, 9H, ^{t}Bu), 1.56 (s, 9H, ^{t}Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 148.2, 147.3, 145.0, 86.8, 85.1, 48.2, 27.9, 27.7. Anal. Calcd for $C_{13}H_{20}N_2O_6$: C, 51.99; H, 6.71; N, 9.33. Found C, 51.88; H, 6.76; N, 9.27. IR (Nujol, cm^{-1}): 1733, 1755, 1772, 1827 (C=O).

4.5. (5*R*,1′*S*,2′*R*)-5-(1′-*tert*-Butoxycabonyloxy-2′,3′-isopropylidenedioxypropyl)-3-*tert*-butoxycarbonylhydantoin (17)

To a solution of DBocHy **15** (500 mg, 1.67 mmol) in anhydrous THF (30 mL), 1.67 mL of a 1 M LiHMDS solution in THF was added at −80 °C under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 45 min, then 2,3-*O*-isopropilidene-D-glyceraldehyde **12** (217 mg, 1.67 mmol) was added. The reaction mixture was stirred at −80 °C for 3.5 h, then an NaH_2PO_4 saturated solution was added. The solution was extracted with Et_2O (3×40 mL), the organic layers were dried over Na_2SO_4 and after filtration concentrated under reduced pressure to give 718 mg (98%) of a pale yellow solid that was, by NMR analysis, the pure product **17**, mp 56–59 °C. $[\alpha]_D^{20}$ −25.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (br s, 1H, NH), 4.98 (dd, *J*=4.8, 2.0 Hz, 1H, H-1′), 4.34–4.29 (m, 1H, H-2′), 4.26 (t, *J*=1.6 Hz, 1H, H-5), 4.19 (dd, *J*=9.2, 7.5 Hz, 1H, H-3′a), 3.86 (dd, *J*=9.2, 5.6 Hz, 1H, H-3′b), 1.58 (s, 9H, ^{t}Bu), 1.50 (s, 3H, CH_3), 1.46 (s, 9H, ^{t}Bu), 1.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9.0, 152.5, 152.3, 145.8, 110.6, 85.6, 83.9, 75.2, 73.9, 66.6, 56.5, 27.8, 27.6, 26.4, 24.6. Anal. Calcd for $C_{19}H_{30}N_2O_9$: C, 53.02; H, 7.02; N, 6.51. Found: C, 53.18; H, 7.08; N, 6.43. IR (Nujol, cm^{-1}): 1776 (C=O), 3286 (NH).

4.6. 1,3-Di-(*tert*-butyldimethylsilyl)hydantoin (18)

To a suspension of hydantoin **10** (1 g, 10 mmol) in anhydrous CH_2Cl_2 (40 mL), Et_3N (3.62 mL) and TBSCl (3.92 g, 26 mmol) were added under nitrogen at room temperature. The reaction mixture was stirred for one night and monitored by the TLC (hexane/Et_2O 1:1), further TBSCl (1.8 g, 11.9 mmol) and Et_3N (3 mL) were added. The reaction mixture was stirred for another 3 h, then water was added, and the mixture was extracted with CH_2Cl_2 (3×40 mL). The organic layers were dried over Na_2SO_4 and after filtration concentrated under reduced pressure. The crude reaction mixture (~6 g) was purified by flash chromatography eluting with hexane/Et_2O 1:1 to give 5 g of a mixture of compound **18** containing TBSOH. This material was further purified via flash chromatography eluting with CH_2Cl_2/AcOEt 9:1 to give 2.75 g of product **18** as a white solid in 84% yield, mp 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 2H, H-5), 0.96 (2s, each 9H, 2×^{t}Bu), 0.45 (s, 6H, 2×CH_3), 0.31 (s, 6H, 2×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 163.9, 52.3, 26.4, 26.3, 19.4, 18.8, −4.6, −5.3. Anal. Calcd for $C_{15}H_{32}N_2O_2Si_2$: C, 54.83; H,

9.82; N, 8.53. Found C, 54.78; H, 9.91; N, 8.61. IR (Nujol, cm^{-1}): 1700 (C=O).

4.7. (5*R*,1′*S*,2′*R*)-5-(1′-*tert*-Butyldimethylsilyloxy-2′,3′-isopropylidenedioxypropyl)-3-*tert*-butyldimethyl silylhydantoin (19)

To a solution of **18** (500 mg, 1.52 mmol) in anhydrous THF (30 mL), 1.52 mL of a 1 M LiHMDS solution in THF was added at −80 °C under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 45 min, then 2,3-*O*-isopropilidene-D-glyceraldehyde **12** (197 mg, 1.52 mmol) was added. The reaction mixture was stirred at −80 °C for 3.5 h, then a citric acid solution was added to pH=8. The solution was extracted with Et_2O (3×40 mL), the organic layers were dried over Na_2SO_4 and after filtration concentrated under reduced pressure to give 690 mg of crude product as a pale yellow oil. The crude product was purified by flash chromatography (SiO_2, Hexane/Et_2O 6:4) to give 391 mg (56%) of product **19** as pale yellow foam. $[\alpha]_D^{20}$ −81.4 (*c* 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (br s, 1H, NH), 4.18–4.08 (m, 4H, H-1′, H-2′, H-3′a, H-5), 3.70 (dd, *J*=8.0, 6.0 Hz, 1H, H-3′b), 1.45 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 0.96 (s, 9H, ^{t}BuSi), 0.86 (s, 9H, ^{t}BuSi), 0.46 (s, 3H, CH_3Si), 0.43 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 161.4, 110.0, 78.6, 71.4, 66.7, 60.5, 26.4, 26.3, 25.6, 24.6, 19.0, 18.0, −4.3, −4.5, −4.6, −4.7. Anal. Calcd for $C_{21}H_{42}N_2O_5Si_2$: C, 54.98; H, 9.23; N, 6.11. Found: C, 54.87; H, 9.27; N, 6.15. IR (Nujol, cm^{-1}): 1722 (C=O), 3328 (NH).

4.8. (4*S*,*Z*)-2-(3-(*tert*-Butoxycarbonyl)ureido)-4,5-isopropylidenedioxypent-2-enoic acid (20)

To a solution of **17** (82 mg, 0.19 mmol) in THF (5 mL), 1.9 mL of an aqueous solution of 1 M LiOH was added. The reaction mixture was stirred at room temperature for 1 h, and monitored by TLC (AcOEt/hexane 7:3). The solution was diluted with a solution of NaH_2PO_4 to pH=5–6 and extracted with AcOEt (3×10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (AcOEt/hexanes 2:1) to give **20** as a pale yellow oil (59 mg, 95%). $[\alpha]_D^{20}$ −6.2 (*c* 2.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 6.41 (d, *J*=8.0 Hz, 1H, H-3), 4.86–4.80 (m, 1H, H-4), 4.30 (dd, *J*=8.0, 6.0 Hz, 1H, H-5a), 3.76 (dd, *J*=8.0, 6.8 Hz, 1H, H-5b), 1.55 (s, 9H, ^{t}Bu), 1.44 (s, 3H, CH_3), 1.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 170.6, 155.9, 154.7, 132.0, 130.2, 111.4, 84.3, 75.4, 70.6, 29.2, 27.8, 26.4. Anal. Calcd for $C_{14}H_{22}N_2O_7$: C, 50.90; H, 6.71; N, 8.48. Found: C, 50.86; H, 6.68; N, 8.37. IR (Nujol, cm^{-1}): 1718 (C=O), 3421 (OH, NH).

4.9. (2′*R*,*Z*)-5-(2′,3′-Isopropylidenedioxypropylidene)-3-*tert*-butoxycarbonylhydantoin (21)

To a solution of **17** (20 mg, 0.05 mmol) in anhydrous THF (4 mL), 180 μl of an aqueous solution of 0.5 M LiOH was added at −20 °C, the mixture was stirred at this temperature and monitored by TLC (AcOEt/hexane 7:3) for 4 h but there was only starting material. The temperature was allowed to rise to 0 °C in 7 h and an aqueous solution of NaH_2PO_4 was added to pH=6. The solution was extracted with AcOEt (3×5 mL), the organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **21** (14 mg, 90%) as colourless glass. $[\alpha]_D^{20}$ −7.4 (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1H, NH), 5.80 (d, *J*=3.6 Hz, 1H, H-1′), 4.92–4.84 (m, 1H, H-2′), 4.25 (dd, *J*=8.0, 6.8 Hz, 1H, H-3′a), 3.71 (t, *J*=8.0 Hz, 1H, H-3′b), 1.59 (s, 9H, ^{t}Bu), 1.47 (s,3H, CH_3), 1.43 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 149.4, 146.0, 127.5, 110.9, 109.7, 86.2, 74.1, 69.3, 28.0, 26.3, 25.9. Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.71; H, 6.55; N, 9.01. IR (KBr, cm^{-1}): 1734 (C=O), 3326 (NH).

4.10. (5*R*,1′*S*,2′*R*)-5-(1′,2′,3′-Trihydroxypropyl)hydantoin hydrochloride (23)

To compound **17** (47 mg, 0.11 mmol), 7 mL of 37% aqueous HCl was added. The mixture was stirred for 12 h at room temperature, then HCl was removed under vacuum to give compound **23** as a white solid in quantitative yield, mp 197–199 °C. $[\alpha]_D^{20}$ −28.8 (*c* 1.25, H_2O). ^1H NMR (400 MHz, CD_3OD) δ 4.43 (d, *J*=1.6 Hz, 1H, H-5), 3.93 (dd, *J*=8.8, 1.6 Hz, 1H, H-1′), 3.79 (dd, *J*=10.8, 3.2 Hz, 1H, H-3′a), 3.66–3.54 (m, 2H, H-2′, H-3′b). ^{13}C NMR (100 MHz, CD_3OD) δ 179.1, 161.7, 73.1, 71.0, 64.1, 62.4. Anal. Calcd for $C_6H_{11}ClN_2O_5$: C, 31.80; H, 4.89; N, 12.36. Found: C, 31.64; H, 4.77; N, 12.28. IR (KBr, cm^{-1}): 1653 (C=O), 3447 (OH, NH).

4.11. 2-Deoxy-2-ureido-D-ribonic acid-1,5-lactone trifluoroacetate (24)

To compound **17** (52 mg, 0.12 mmol), 3 mL of TFA was added. The mixture was stirred for 12 h at room temperature, then TFA was removed under vacuum to give compound **24** as a yellow glass in quantitative yield. $[\alpha]_D^{20}$ −17.8 (*c* 0.9, CH_3OH). ^1H NMR (400 MHz, CD_3OD) δ 4.63 (dd, *J*=11.6, 2.8 Hz, 1H, H-5a), 4.47 (dd, *J*=11.6, 5.6 Hz, 1H, H-5b), 4.32 (d, *J*=1.6 Hz, 1H, H-2), 3.92 (dd, *J*=9.2, 1.6 Hz, 1H, H-3), 3.86–3.80 (m, 1H, H-4). ^{13}C NMR (100 MHz, CD_3OD) δ 178.1, 161.8, 71.7, 71.3, 71.1, 62.7. Anal. Calcd for $C_8H_{11}F_3N_2O_7$: C, 31.59; H, 3.65; N, 9.21. Found: C, 31.45; H, 3.50; N, 9.08. IR (KBr, cm^{-1}): 1726, 1793 (C=O), 3293 (OH, NH).

4.12. 2-Deoxy-2-(3-(*tert*-butoxycarbonyl)ureido)-4,5-*O*-isopropylidene-D-ribitol (25)

To a solution of **17** (20 mg, 0.05 mmol) in CH_2Cl_2 anhydrous (2 mL), CH_3OH (6.1 μl, 0.15 mmol) and $NaBH_4$ (1.8 mg, 0.5 mmol) were added. The mixture was stirred at room temperature for 2 h, and a solution of NaH_2PO_4 was added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the organic layers were dried over Na_2SO_4, filtered and the solvent removed under vacuum. The crude mixture was purified by flash chromatography (AcOEt/hexane 1:1) to give 18 mg 85% yield of the product **25** as a colourless oil. $[\alpha]_D^{20}$ +20 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J*=8.4 Hz, 1H, NH), 6.82 (br s, 1H, NH), 4.98 (dd, *J*=7.2, 2.8 Hz, 1H, H-3), 4.37–4.31 (m, 1H, H-2), 4.24 (ddd, *J*=7.6, 6.0, 6.0 Hz, 1H, H-4), 4.04 (dd, *J*=8.8, 6.4 Hz, 1H, H-5a), 3.87 (dd, *J*=8.8, 5.6 Hz, 1H, H-5b), 3.78–3.72 (m, 1H, H-1a), 3.63–3.57 (m, 1H, H-1b), 2.77 (br t, *J*=6.0H, 1H, OH), 1.50 (s, 9H, ^{t}Bu), 1.49 (s, 9H, ^{t}Bu), 1.43 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 153.3, 152.7, 109.8, 83.5, 83.0, 74.7, 74.2, 66.2, 62.3, 52.0, 28.0, 27.6, 26.6, 25.4. Anal. Calcd for $C_{19}H_{34}N_2O_9$: C, 52.52; H, 7.89; N, 6.45. Found: C, 52.63; H, 7.93; N, 6.51. IR (thin film, cm^{-1}): 1695, 1722, 1747 (C=O), 3327 (OH, NH).

4.13. (4*S*,5*R*,1′*S*,2′*R*)-3-*tert*-Butoxycarbonyl-4-hydroxy-5-(1′-*tert*-butoxycabonyloxy-2′,3′-isopropylidenedioxypropyl)-imidazolidin-2-one (26)

To a solution of **17** (100 mg, 0.23 mmol) in 5 mL of anhydrous THF at −18 °C under nitrogen was added dropwise a solution of $LiEt_3BH$ (Super-Hydride®, 0.69 mmol in 5 mL of anhydrous THF). The reaction mixture was stirred for 3 h at −18 °C, then quenched with saturated aqueous NaH_2PO_4 (to pH 5–6) and extracted with ethyl acetate (2×10 mL) and Et_2O (2×10 mL). The organic phases were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give **26** in quantitative yield as a colourless oil.

$[\alpha]_D^{20}$ −18 (*c* 1.03, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (d, *J*=2.0 Hz, 1H, H-4), 4.75 (dd, *J*=6.0, 4.0 Hz, 1H, H-1′), 4.19–4.09 (m, 2H, H-2′, H-3′a), 3.81 (dd, *J*=8.4, 5.6 Hz, 1H, H-3′b), 3.73 (dd, *J*=3.6, 2.0 Hz, 1H, H-5), 1.55 (s, 9H, ^{t}Bu), 1.47 (s, 9H, ^{t}Bu), 1.34 (s, 3H, CH_3), 1.27 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 152.9, 150.8, 110.4, 83.7, 83.6, 80.7, 75.0, 74.8, 66.7, 56.3, 29.1, 27.6, 26.5, 25.0. Anal. Calcd for $C_{19}H_{32}N_2O_9$: C, 52.77; H, 7.46; N, 6.48. Found: C, 52.89; H, 7.40; N, 6.40. IR (thin film, cm^{-1}): 1744, 1773 (C=O), 3327 (OH, NH).

4.14. (*R*)-1,3-Dibenzyl-4-hydroxy-5-((1′*S*,2′*R*)-2′,3′-isopropylidenedioxypropyl) imidazolidin-2-one (27)

To a solution of **13** (100 mg, 0.24 mmol) in anhydrous THF (10 mL), 2 M $LiBH_4$ solution in THF (2.4 mL, 4.8 mmol) was added under nitrogen at room temperature. The reaction mixture was stirred at this temperature for 3 h following the disappearance of the starting material by TLC (CH_2Cl_2/Et_2O 7:3). Water was added and the mixture was extracted with CH_2Cl_2 (3×10 mL) and AcOEt (3×10 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give **27** (87 mg, 96%) as a colourless glass. $[\alpha]_D^{20}$ +12 (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (m, 10H, $PhCH_2$), 5.20 (d, *J*=7.2 Hz, 1H, H-4a), 5.04 (d, *J*=2.8 Hz, 1H, H-4b), 4.92 (d, *J*=15.2 Hz, 1H, CH_2Ph), 4.73–4.22 (m, 3H, CH_2Ph), 4.38–4.33 (m, 1H, H-2′a), 4.34 (d, *J*=15.2 Hz, 1H, CH_2Ph), 4.24–4.18 (m, 3H, CH_2Ph), 4.03 (dd, *J*=8.8, 6.0 Hz, 1H, H-3′a_α), 3.99–3.96 (m, 1H, H-3′a_β), 3.95–3.88 (m, 2H, H-2′b, H-3′b_α), 3.82–3.78 (m, 1H, H-1′a), 3.70–3.64 (m, 2H, H-3′b_β, H-1′b), 3.57 (dd, *J*=7.2, 2.8 Hz, 1H, H-5a), 3.48 (dd, *J*=2.8, 1.6 Hz, 1H, H-5b), 1.27 (s, 3H, CH_3b), 1.24 (s, 3H, CH_3b), 1.21 (s, 3H, CH_3a), 1.13 (s, 3H, CH_3a). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.1, 136.9, 136.5, 128.9, 128.6, 128.3, 128.0, 127.8, 127.5, 109.7, 109.5, 79.6, 77.9, 75.1, 74.1, 70.3, 69.1, 67.7, 66.8, 63.7, 62.7, 46.0, 45.6, 44.6, 43.6, 26.7, 25.0. Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found C, 66.81; H, 6.96; N, 6.71. IR (KBr, cm^{-1}): 1704 (C=O), 3457 (OH).

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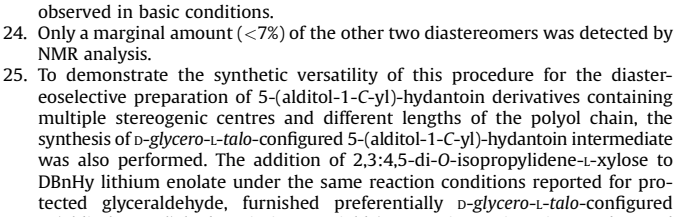
20. Stereoselective and isocyanate-free procedures for the synthesis of ureido sugars are of particular interest because isocyanates are toxic and are usually prepared from a dangerous reagent such as phosgene.
21. A preliminary report on the diastereoselective synthesis of 5-(alditol-1-*C*-yl)-hydantoin intermediates was previously published. (a) Ulgheri, F.; Orrù, G.; Crisma, M.; Spanu, P. *Tetrahedron Lett.* **2004**, *45*, 1047; (b) Spanu, P.; Ulgheri, F. In *Targets in Heterocyclic Systems: Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Springer: 2004; Vol. 8, p 330.
22. A previous example of aldol condensation of hydantoin derivatives with enantiopure C-4 aldehydo sugar for the synthesis of hydantocidin was described although a very low diastereoselectivity of the aldol addition reaction was reported. (a) Mio, S.; Ichinose, R.; Goto, K.; Sugai, S.; Sato, S. *Tetrahedron* **1991**, *47*, 2111; (b) Mio, S.; Shiraishi, M.; Sugai, S.; Haruyama, H.; Sato, S. *Tetrahedron* **1991**, *47*, 2121.
23. Hydantoin derivatives are important precursors of α-amino acids via chemical and enzymatic heterocycle ring opening reactions. The chemical synthesis of enantiomerically pure α-amino acids from 5-monosubstituted hydantoins is difficult because hard conditions are required (high temperature and pressure) in an acid environment while epimerisation of the C-5 stereogenic centre is observed in basic conditions.
24. Only a marginal amount (<7%) of the other two diastereomers was detected by NMR analysis.
25. To demonstrate the synthetic versatility of this procedure for the diastereoselective preparation of 5-(alditol-1-*C*-yl)-hydantoin derivatives containing multiple stereogenic centres and different lengths of the polyol chain, the synthesis of D-*glycero*-L-*talo*-configured 5-(alditol-1-*C*-yl)-hydantoin intermediate was also performed. The addition of 2,3:4,5-di-*O*-isopropylidene-L-xylose to DBnHy lithium enolate under the same reaction conditions reported for protected glyceraldehyde, furnished preferentially D-*glycero*-L-*talo*-configured 5-(alditol-1-*C*-yl)-hydantoin in 70% yield (a 72:28 isomeric ratio was detected by NMR analysis of the crude material), see Ref. 21a.



26. *N*-Boc to *O*-Boc migration is a known although rarely observed rearrangement. (a) Bunch, L.; Norrby, P.-O.; Frydenvang, K.; Krogsgaard-Larsen, P.; Madsen, U. *Org. Lett.* **2001**, *3*, 433; (b) Dieltiens, N.; Stevens, C. V.; Masschelein, K. G. R.; Rammeloo, T. *Tetrahedron* **2005**, *61*, 6749.
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28. For the use of dehydrated hydantoins in the synthesis of hydantocydin derivatives see Ref. 22a and Renard, A.; Kotera, M.; Brochier, M.-C.; Lhomme, J. *Eur. J. Org. Chem.* **2000**, 1831 and references quoted therein.
29. The (*Z*) stereochemistry of the compound **22** was assigned on the basis of the chemical shift of the olefin proton in analogy with the reported data by Mio (Refs. 22 and 28).
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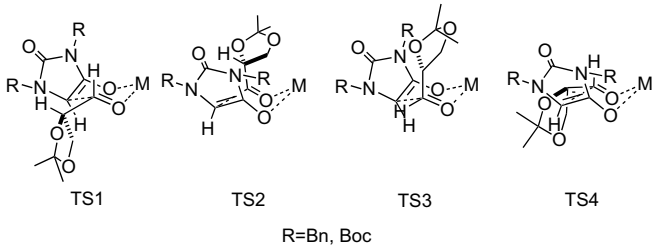
32. The formation of 5,1′-*anti*-1′,2′-*anti* aldol **11** or **19** and 5,1′-*syn*-1′,2′-*anti* aldol **12** results from an unlike (*Re* enolate, *Si* aldehyde) and like (*Si* enolate, *Si* aldehyde) approach, respectively, of the reaction partners in the addition step. In both cases the *Si*-face of aldehyde **10** reacts selectively. In fact aldol reactions between α-chiral aldehydes and E(*O*)-enolates preferentially give the Felkin-type adduct by abiding both the Felkin–Anh rule and the Zimmerman–Traxler model. (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191; (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151; (c) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439; The diastereoselectivity observed can be explained by the preferential formation of the cyclic transition state TS1 over TS2 and both over the more hindered TS3 or TS4. An explanation of the observed increase of diastereoselectivity moving from Bn- to Boc-imidazolidinone could be a TS1 stabilization over TS2 because of the increase of hindrance for the Boc group with respect to the Bn group.



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34. No NOE effect was measured from H-6a (4.62 ppm) and H-3 (4.31 ppm). The measure of NOE between H-6b and H-3 was impossible because of their close chemical shifts.