Tautomeric rearrangement of 3-deoxy-3-thioureidoaldoses: a novel synthetic route to carbohydrate mimics having a cyclic thiourea structure

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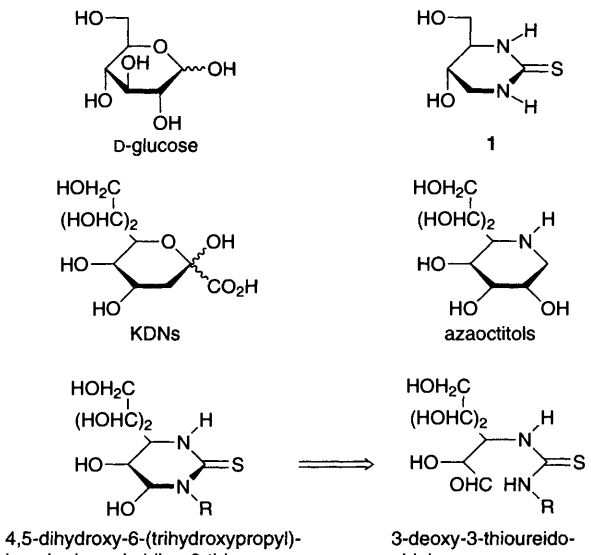
Cyclic thiourea glycomimetics structurally related to 3-deoxy-2-nonulosonic acids (KDNs) and 1,5-dideoxy-1,5-iminooctitols (azaoctitols) have been prepared by tautomeric rearrangement of 3-deoxy-3-thioureidoaldohexoses; the conformational properties of these compounds are governed by stereoelectronic requirements, mainly the anomeric effect.

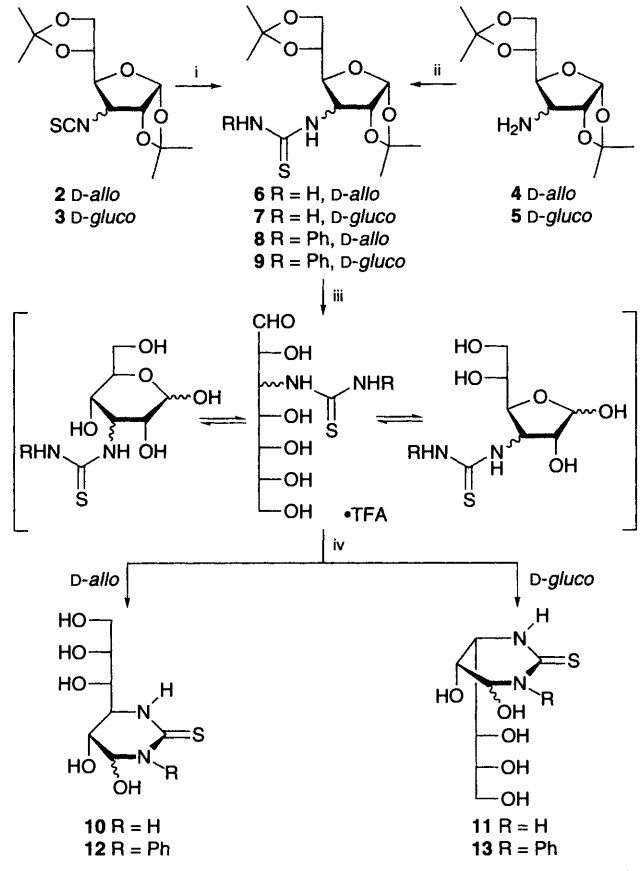
The prominence of glycobiology in the carbohydrate field has stimulated the development of specific glycomimetics, *i.e.* analogues of sugars that mimic the structure and properties of carbohydrates, as potential epitopes for the understanding of recognition events involving protein–carbohydrate interactions.[1] Considerable effort has been directed towards the design of structures that resemble the glycosyl cation involved in enzymatic glycoside cleavage,[2] generally referred to as 'transition state analogues', that can serve as glycosyl hydrolase inhibitors useful for the treatment of diseases such as diabetes, cancer, viral infections or inflammation. All these compounds have in common a carbocyclic or heterocyclic structure preferentially flattened and, ideally, a positive charge density in the area of the anomeric carbon. Six-membered cyclic thioureas carrying properly placed hydroxy and hydroxyalkyl groups conform to these structural features, with the additional advantage that the thiourea group can be easily transformed into other functionalities, such as urea, isothiourea or guanidine, by standard reactions.[3]

A D-glucose analogue having a hexahydropyrimidine-2-thione structure **1** has been previously prepared by thiocarbonylation of a 1,3-diamine precursor.[4] Although a high specificity for sweet almond β-glucosidase was observed **1** was a very weak enzyme inhibitor, probably because of the absence of the hydroxy substituents at the homologous positions of C-2 and C-3 in pyranosides (*i.e.* N-3 and C-4), a limitation that is implicit in the above synthetic approach.

Reducing monosaccharides possess a masked carbonyl group that can actually act as the electrophilic target for suitably located nucleophilic substituents (*e.g.* amino, mercapto) by a simple tautomeric rearrangement. In connection with our continuing interest in sugar thioureas,[5] we have now extended this concept to 3-deoxy-3-thioureidoaldoses[6] and applied it in the synthesis of 4,5-dihydroxy-6-(trihydroxypropyl) hexahydropyrimidine-2-thione heterocycles whose molecular frameworks bear close spatial relationships with those of 3-deoxy-2-nonulosonic acids[7] (KDNs) and 1,5-dideoxy-1,5-iminooctitols[8] (azaoctitols)—two families of biologically important carbohydrate derivatives having a glycerol side chain as main a structural feature.

Condensation of the readily accessible 3-deoxy-3-isothiocyanato diacetonides[9] **2** and **3** with ammonia afforded the corresponding D-*allo* (**6**) and D-*gluco* (**7**) thioureas in excellent





Scheme 1 *Reagents and conditions*: i, NH_3, diethyl ether, room temp., 30 min, 97–98%; ii, PhNCS, pyridine, room temp., 15 h, 90–91%; iii, TFA–H_2O (9 : 1), room temp., 15–30 min; iv, coevaporation with water, then IR-45 (OH^-) ion exchange resin, GPC (1 : 1 H_2O–MeOH), 60-72%

yield. Hydrolysis of the acetal protecting groups under acidic conditions compatible with the stability of the thiourea functionality led to the fully unprotected compounds as a complex mixture of furanoid and pyranoid thiouronium derivatives, as seen from ^{13}C NMR spectra of the crude products. After neutralisation, the equilibrium was spontaneously shifted to the target hexahydropyrimidine tautomers **10** and **11** (Scheme 1).† No isomeric structures resulting from participation of sulfur in the cyclisation step were detected. Compounds **10** and **11** were stable for days in neutral or slightly basic aqueous solution. In the presence of mineral acid the formation of bicyclic derivatives, resulting from intramolecular glycosylation reactions, was observed.

It is noteworthy that azaoctitols with identical configurational patterns have been found to possess a high glycosyl hydrolase inhibitory activity.[8a] Moreover, compound **11** is the cyclic thiourea analogue of the recently reported[7a] 3-deoxy-D-*glycero*-D-*gulo*-2-nonulopyranosidic acid, the C-5 epimer of the naturally occurring KDN.

The synthetic potential of the thiourea group allows controlled structural modifications without undue synthetic effort, *e.g.* by judicious choice of the monosaccharide template and the *N*-substituents, that may facilitate further structure activity studies. The preparation of the 3-*N*-phenyl derivatives **12** and **13**, as depicted in Scheme 1, illustrates this possibility. The starting *N'*-phenylthioureido sugars **8** and **9** were conveniently obtained from the condensation reaction of the respective aminosugars[9] **4** and **5** with phenyl isothiocyanate and further processed as commented above for their unsubstituted counterparts.†

Excepting **11**, isolated in pure diastereomeric form, these cyclic thioreas existed as equilibrium mixtures of the (4*R*) and (4*S*) isomers in water solution. The configurational assignment at the hemiacetalic centre was supported by the vicinal proton–proton coupling constants, the existence of long-range coupling between protons in W-arrangement, and by NOE experiments.

The conformational properties of **10–13** were found to be governed by stereoelectronic requirements (Fig. 1). Exclusively

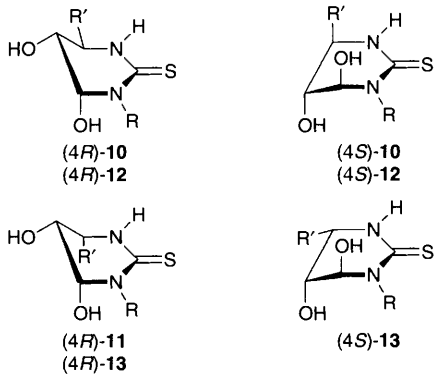


Fig. 1 Ring conformation of compounds **10–13**

flattened chair conformations with OH-4 in an axial position, fitting the anomeric effect, were detected by ^1H NMR in D_2O. Since polar interactions in water look improbable, a delocalization interaction between the π-type lone-pair orbital of the sp^2-hybridized N atom in the thiourea ground state and the σ* antibonding orbital of the vicinal C–O bond must be responsible.

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Footnotes

† All new compounds gave satisfactory microanalytical, NMR (^1H and ^{13}C) and mass spectral data in accord with the proposed structures. *Selected data* for **10**: (4*R*) : (4*S*) ratio 3 : 2 (H-5 integration); $[\alpha]_D$ +26.2 (*c* 0.8, H_2O); ^1H NMR (300 MHz, D_2O): δ 4.10 [1 H, dd, $J_{4,5}$ 3.2, $J_{5,6}$ 7.8, H-5 (4*R*)], 4.22 [1 H, t, *J* 2.5, H-5 (4*S*)], 4.75 [1 H, d, H-4 (4*S*)], 4.78 [1 H, d, H-4 (4*R*)]. For **11**: $[\alpha]_D$ −93.0 (*c* 1, H_2O); ^1H NMR (300 MHz, D_2O): δ 4.08 (1 H, t, *J* 3.2, H-5), 4.79 (1 H, t, H-4). For **12**: (4*R*) : (4*S*) ratio 3 : 2 (H-4 integration); $[\alpha]_D$ +1.1 (*c* 0.9, MeOH); ^1H NMR (300 MHz, D_2O): δ 4.36 [1 H, dd, $J_{4,5}$ 3.3, $J_{5,6}$ 8.7, H-5 (4*R*)], 4.46 [1 H, t, *J* 2.3, H-5 (4*S*)], 4.93 [1 H, dd, $^3J_{4,6}$ 1.8, H-4 (4*S*)], 5.07 [1 H, d, H-4 (4*R*)]. For **13**: (4*R*) : (4*S*) ratio 4 : 3 (H-4 integration); $[\alpha]_D$ −10.9 (*c* 0.6, MeOH); ^1H NMR (500 MHz, D_2O): δ 4.21 [1 H, t, *J* 3.4, H-5 (4*R*)], 4.38 [1 H, t, *J* 3.6, H-5 (4*S*)], 4.72 [1 H, d, H-4 (4*S*)], 4.95 [1 H, d, H-4 (4*R*)].

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