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Synthesis and stereoelectronic properties of sugar-shaped polyhydroxylated hexahydropyrimidine-2-thiones

José L. Jiménez Blanco,[a] Carmen Ortiz Mellet,[a]* José Fuentes[a] and José M. García Fernández[b]*

[a] *Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 553, E-41071 Sevilla, Spain*
[b] *Instituto de Investigaciones Químicas, CSIC, Américo Vespucio s/n, Isla de la Cartuja, E-41092 Sevilla, Spain*

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Abstract

The reactivity and conformations in water solution of polyhydroxylated hexahydropyrimidine-2-thiones structurally related to biologically active nonulosonic acids and azaoctitols, obtained by intramolecular cyclization of sugar-derived γ-oxothioureas, have been investigated. The total preference for the axial orientation of the pseudoanomeric C—O bond and the high tendency to undergo acid-promoted intramolecular glycosylation are interpreted in terms of stabilizing hyperconjugative interactions in both the aminoketalic derivatives and the reactive azacarbenium cations. Moreover, repulsion between lone pairs and vicinal C—H bonds leads to a preference for structures bearing axial α-carbon substituents. The present results provide strong experimental evidence for the predominance of molecular orbital over electrostatic interactions in the stereoelectronic properties of these systems.

Keywords: Carbohydrate mimetics, aza compounds, thioureas, stereoelectronic effects

1. Introduction

Polyhydroxylated azaheterocycles embodying a resonance-stabilised π-system of the amidine [1-6] or cyclic guanidine type [7-11] have been suggested as mimicking the electronic character and conformation of the transition state of heterolytic glycoside hydrolysis. This means a flattened half-chair (or twist-boat) conformation, a trigonal anomeric centre with substantial sp^2 character and positive charge density, and the proper orientational pattern. Further theoretical and experimental studies indicate that true transition state analogs must also be essentially neutral or zwitterionic at physiological pH to keep specificity against the target enzyme [12-16]. Six-membered cyclic thioureas carrying properly placed hydroxy and hydroxymethyl substituents conform to these structural features [17], with the additional

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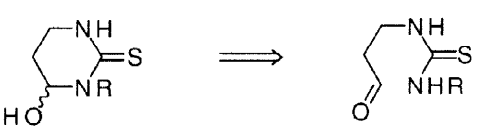
advantage that the thiourea group can be easily transformed into other functionalities, such as urea, isothiourea and guanidine, through standard transformations [18].

Replacement of the oxygen atom in pyranoses by an sp^2-hybridized nitrogen atom may, however, significantly alter the stereoelectronic relationships in the six-membered heterocycle, resulting in considerable differences in the conformational preferences and reactivity, an aspect that must be considered in glycomimetic design [19]. In the framework of a program aimed at the development of glycosyl hydrolase transition-state analog inhibitors with controlled stereoelectronic properties, we have been interested in the preparation of polyhydroxylated pyrimidine-2-thiones possessing an aminoketalic (pseudoanomeric) hydroxy substituent [20-22]. It has been recently shown [23,24] that the conformations of six-membered 1,3-diazacycles are governed by the generalized anomeric effect [25,26], although the relative contribution of hyperconjugative and electrostatic interactions remains controversial. This question is not trivial: while orbital interactions would be fully operative in polar solvents, dipole-dipole interactions should be minimized in water. The structural and electronic properties of the cyclic thiourea system, with planar nitrogen atoms and lone pair orbitals having π-symmetry, are ideally suited to optimize overlapping with contiguous orbitals. To gain information on the impact of this contribution to the generalized anomeric effect, an investigation of the conformational preferences of a series of configurationally different derivatives seemed intriguing.

Retrosynthetic analysis suggested that the aminoketalic stereocentre might be generated by the intramolecular cyclization of γ-oxothioureas (Scheme 1). Actually, reducing monosaccharides possess a masked aldehydo group that can be the electrophilic target for suitably located nucleophilic substituents (e.g. amino, thio) by a simple tautomeric rearrangement [27,28], thus allowing access to a variety of structural analogs with a hydroxylation profile defined by the starting sugar configuration. This concept has now been extended to 3-deoxy-3-thioureidoaldohexoses and applied to the synthesis of sugar-shaped 4,5-dihydroxy-6-(trihydroxypropyl)hexahydropyrimidine-2-thiones whose molecular frameworks bear close spatial relationships with those of 3-deoxy-2-nonulosonic acids (KDNs, sialic acids) [29,30] and 1,5-dideoxy-1,5-iminooctitols (azaoctitols) [31-33], two families of biologically important carbohydrate derivatives having a glycerol side-chain as a main structural feature. The influence of stereoelectronic factors in the conformation, pseudoanomeric configuration, tautomeric equilibrium and reactivity of the products has been evaluated and the results rationalized in terms of the generalized anomeric effect.

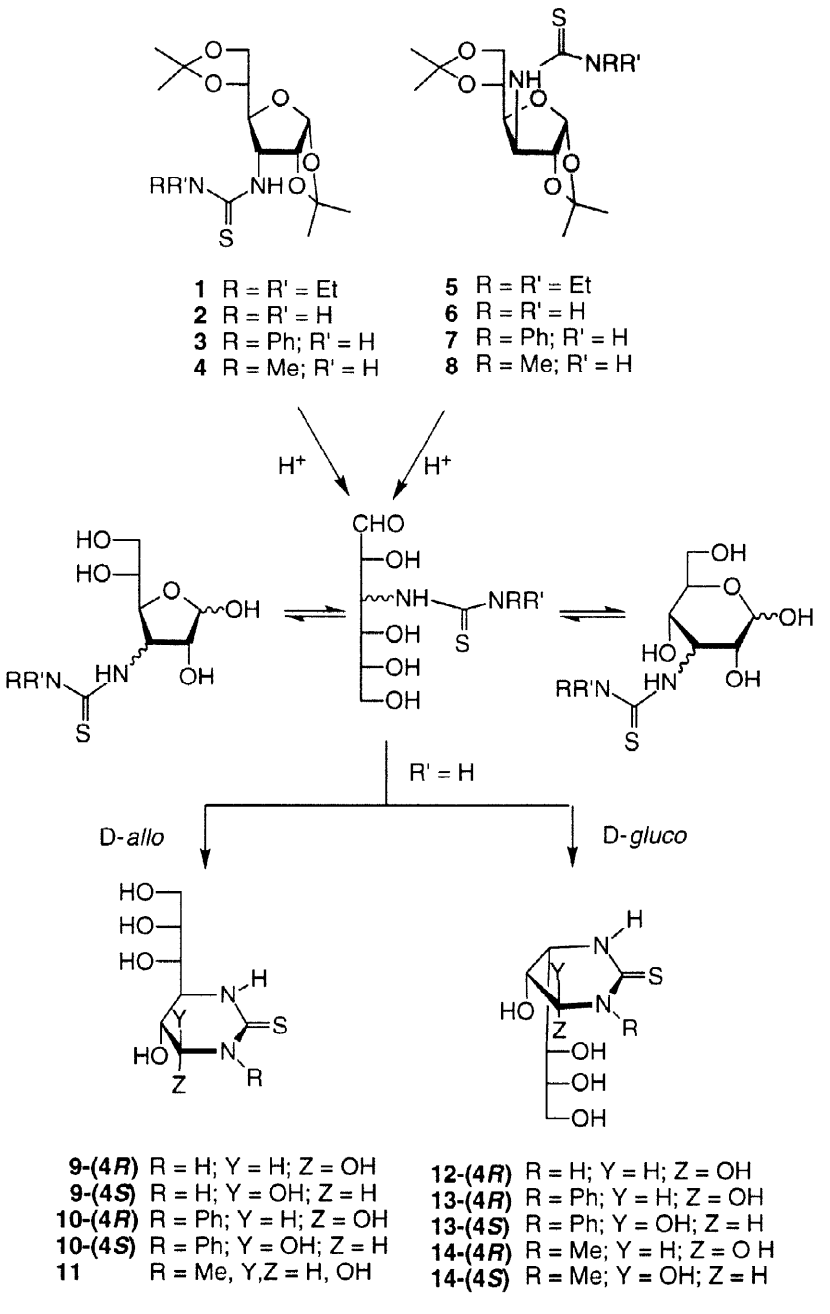


Scheme 1. Retrosynthetic scheme proposed for the preparation of 4-hydroxyhexahydropyrimidine-2-thiones.

2. Results and Discussion

2.1. Synthesis and Reactivity of polyhydroxylated hexahydropyrimidine-2-thiones

As depicted in Scheme 2, the key fully unprotected 3-deoxy-3-thioureido sugar precursors can be generated by hydrolysis of *O*-acetal protected derivatives under acidic conditions compatible with the stability of the thiourea group [34].



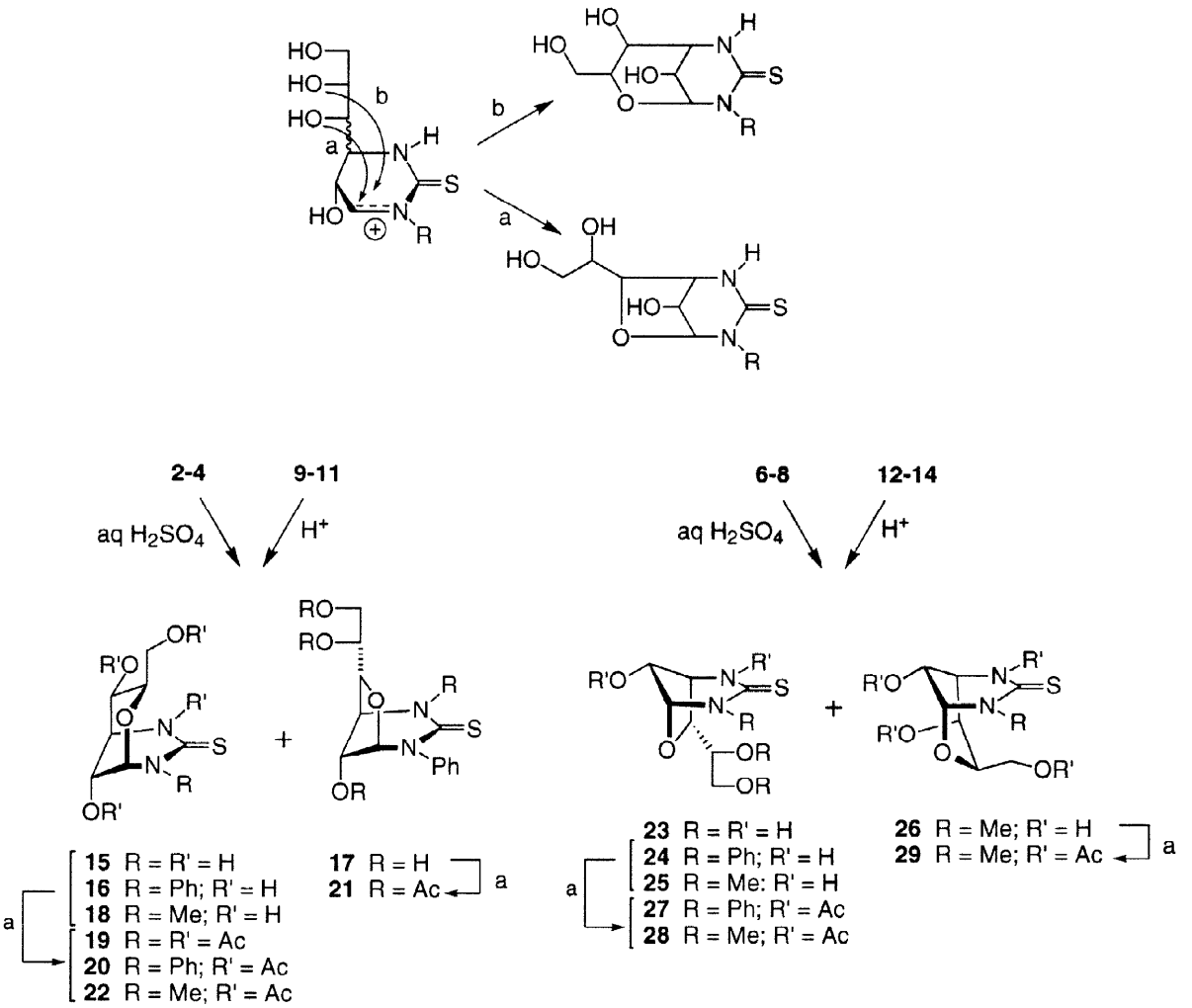
Scheme 2. Synthesis of sugar-shaped hexahydropyrimidine-2-thiones from D-glucose and D-allose precursors.

For practical reasons we have focused on compounds having the D-*allo* and D-*gluco* configurations. The starting diacetonides were efficiently obtained from the corresponding 3-amino-3-deoxy- or 3-deoxy-3-isothiocyanato derivatives [35], readily accessible in the two epimeric series from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (the chiral source), following previously reported protocols [36].

In principle, 3-deoxy-3-thioureido sugars may undergo intramolecular nucleophilic attack at the anomeric carbon atom (C-1) either in the hemiacetalic cyclic forms (Fischer-Helferich glycosylation-type reaction) or in the open-chain aldehyde form (tautomerization-type rearrangement). Although a rationalization of the ambident sulfur versus nitrogen reactivity in thioureas is controversial, from the ensemble of results available in the literature it appears that intramolecular glycosylation-type reactions involve preferentially sulfur, whereas additions to carbonyl groups proceed generally through nitrogen [18]. Nevertheless, a strong influence of the nature of the substituents has been obeserved in the latter case [37]. In order to estimate the proportion of S-attack in the outcome of the reaction, we first studied the reactivity of the *N',N'*-disubstituted thioureas **1** and **5** in mixtures of TFA-water at relative proportions ranging from 1:1 to 9:1. No formation of mono or bicyclic 2-amino-1,3-thiazine derivatives was detected even after prolonged heating at 40 °C. The fully unprotected furanose and pyranose forms were the only reaction products both in the crude reaction mixtures (thiouronium salts) and after neutralization (free bases), which reasonably rules out a significant participation of these alternative side-reactions in our synthetic scheme.

The behavior of substrates carrying an acidic hydrogen atom at N' (**2-4**, **6-8**) upon treatment with 9:1 TFA-water was, at the early stages, similar to that noted above for **1** and **5**, *i.e.* the acidic crude reaction mixtures consisted (^{13}C NMR) of an equilibrium mixture of hemiacetalic α,β-furanose and α,β-pyranose thiouronium derivatives. After neutralization, the equilibrium was spontaneously shifted toward the target hexahydropyrimidine-2-thione structure (Scheme 2). Eventually, concomitant formation of bicyclic derivatives resulting from further intramolecular glycosylation processes involving the glycerol side-chain was observed. The bicyclic intramolecular glycosides were the only reaction products when the deacetonation reaction was carried out with sulfuric acid (Scheme 3).

The much higher tendency of aminoketalic polyhydroxyhexahydropyrimidine-2-thiones to undergo intramolecular glycosylation reactions, as compared to the parent reducing pyranoses, is ascribable to the higher stability of the corresponding reaction intermediate. The π-symmetry of the lone-pair orbital in the ground state of the thiourea group and the facility of the nitrogen atom to accommodate a positive charge must strongly favor the formation of a transient azacarbenium pseudoglycosyl cation that is subsequently trapped by formation of O-1' or O-2' intramolecular glycosides (Scheme 3). The presence of an alkyl substituent at N' (*i.e.* **11**, **14**) stabilizes the charged intermediate by an inductive (+I) effect, leading to higher reaction rates. Thus, whereas compounds **9**, **10**, **12** and **13** were obtained in satisfactory yield (60-72%), the 3-methyl D-*allo* derivative **11** could not be isolated in pure form and the D-*gluco* counterpart **14** was obtained only in a rather moderate yield (35%).



Scheme 3. Intramolecular glycosylation reactions of polyhydroxyhexahydropyrimidines. [a] Ac_2O/pyridine/DMAP.

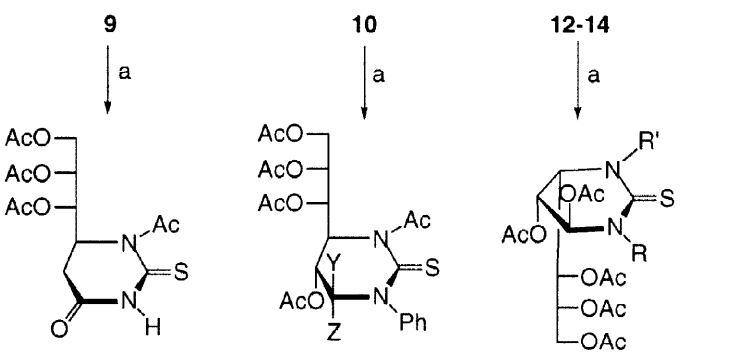
The planar cyclic thiourea moiety imposes a *syn* 1,3-diaxial disposition for the nitrogen atoms with respect to the oxaheterocycle in the bicyclic systems **15-18** and **23-26** (Scheme 3). In the D-*allo* configuration this situation can be conveniently achieved in a pyranose ring (O-2' intramolecular glycoside) in the $^4C_1$ chair conformation, with the hydroxy and hydroxymethyl groups in equatorial disposition. The analogous six-membered D-*gluco* intramolecular glycosides must adopt the reverse all-axial $^1C_4$ conformation, an unfavourable arrangement. Consequently, the alternative O-1' glycosylation pathway was preferred.

Except for **12**, in which a single diastereomer 4*R* was detected, the monocyclic sugar-shaped hexahydropyrimidine-2-thiones existed in deuterium oxide solution as equilibrium mixtures of the 4*R* and 4*S* diastereomers, as seen from their NMR spectra. Although the

epimerization process was relatively slow on the chromatographic time scale, fast equilibration occurred in solution. Only in the case of **14** could both isomers be characterized independently. It is noteworthy that the configurational patterns of the heterocyclic ring in the 4*R* diastereomers of D-*allo* and D-*gluco* derivatives are analogous to that present in several 1,5-anhydro-1,5-iminooctitols shown to be potent β-glucosidase and β-galactosidase inhibitors [33]. Moreover, compound **12** is the cyclic thiourea analog of the recently reported 3-deoxy-D-*glycero*-D-*gulo*-2-nonulosonic acid, the C-5 epimer of the naturally occurring KDN [38].

Structural proofs for the six-membered cyclic thiourea structure of compounds **9**, **10**, **12**, **15-18**, **23-26** were provided by both the ^{1}H and ^{13}C NMR spectra. The ^{13}C chemical shifts of C-4 and C-6 showed strong deshielding effects as compared with the homologous carbons (C-1 and C-3, respectively) in the parent hexoses, indicative of the C-4—NHCSNH—C-6 bridge. The signal at δ 175-185 confirmed the presence of the thiocarbonyl group. The involvement of O-1' or O-2' in the bicyclic skeleton of intramolecular glycosides was evident from the ^{1}H and ^{13}C chemical shifts as well as the $J_{H,H}$ values around the pyranose or furanose ring. The observation of long-range coupling constants between protons in W arrangement is consistent with the rigidity of the structures.

Additional evidence for the proposed mono- or bicyclic framework was obtained from the acetylated products **19-22**, **27-34**. As a general rule, treatment of the unprotected compounds with acetic anhydride and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in pyridine afforded the fully *O*,*N*-acetylated derivatives (Schemes 3 and 4).



Scheme 4. Acetylation reactions of compounds **9**, **10** and **12-14**. [a] Ac_2O/pyridine/DMAP.

Two notable exceptions are the 3-phenyl derivative **13**, for which only the tetra-*O*-acetate **33** could be isolated, and the 3-unsubstituted derivative **9**, which largely decomposed

upon acetylation, probably because of non specific dehydration in the reaction mixture. In the latter case a dihydrouracil derivative **30** was isolated in low yield. Interestingly, the monocyclic hexahydropyrimidine-2-thiones **12-14** derived from glucose afforded single diastereomers **32-34** having the (*S*)-configuration at the aminoketalic centre (C-4) upon acetylation, independently of the stereochemistry of the starting compound.

2.2 Configurational and Conformational Analysis

The poor overlap between the 2p and 3p orbitals of carbon and sulfur in the thiocarbonyl group leads to a relatively high double bond character of the adjacent N—C bonds and a planar framework for the thiourea group. In the case of six-membered heterocycles, this situation forces a flattened half-chair or envelope conformation (*E*) with the carbon atom opposite to the thiocarbonyl group (C-5) pointing up (^5E) or down (E_5) with respect to the main plane of the molecule. Therefore, each of the two possible diastereomers at C-4 of the aminoketalic cyclic thioureas derived from D-allose can adopt one of the two conformations depicted in Figure 1.

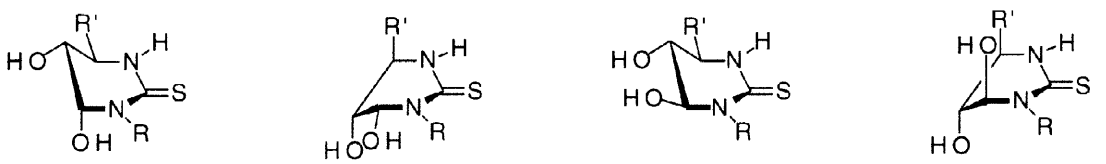


Figure 1. Flattened-chair or envelope conformers for hexahydropyrimidine-2-thiones derived from D-allose.

The configurational and conformational assignments in this series were immediate in view of the vicinal coupling constant values around the hexahydropyrimidine ring (Table 1). Thus, one of the two diastereomers of **9** and **10** showed a $J_{4,5}$ value indicative of a *gauche* disposition for the corresponding protons (3.2 and 3.3 Hz, respectively) and a $J_{5,6}$ value characteristic of a disposition close to *trans*-diaxial (7.8 and 8.7 Hz), which unambiguously pointed to the 4*R* diastereomer in the ^5E conformation. Consequently, the 4*S* configuration was assigned to the other isomer. The low $J_{4,5}$ and $J_{5,6}$ values (2.3-2.5 Hz) ruled out a significant participation of the ^5E conformer, supporting the alternative E_5 conformation with H-4, H-5 and H-5, H-6 in *trans*-diequatorial dispositions. This assignment is further corroborated by the observation of a $^4J_{4,6}$ (1.8 Hz) for (4*R*)-**10**, in agreement with a W arrangement for the corresponding protons.

The configurational assignment in the D-glucose series was less straightforward. The low $J_{4,5}$ values (3.2-3.6 Hz), indicative of *gauche* relative dispositions for the corresponding protons in both C-4 diastereomers (Table 1), and the absence of NOE between H-4 and H-6 ruled out a significant contribution of the (4*S*)-^5E and (4*R*)-E_5 conformers to the respective conformational equilibria (Figure 2). The alternative (4*R*)-^5E and (4*S*)-E_5 structures were ascribed to each set of signals on the basis of spectral correlations with the corresponding C-6 epimers (D-*allo* series). Thus, compounds **9** and **10** satisfied the following relationships: $\delta_{H\text{-}4}$ (4*R*) > $\delta_{H\text{-}4}$ (4*S*), $\delta_{H\text{-}5}$ (4*S*) > $\delta_{H\text{-}5}$ (4*R*). The differences are particularly significant for the H-5 resonance, which probably reflects the closer spatial proximity to OH-4 in the 4*S* diastereomer (*gauche* relationship) as compared with the 4*R* epimer (*trans*-diaxial relationship). The chemical shifts for H-4 and H-5 in **9** and **12** were very similar, and the same occurred for the 3-phenyl (**10** and **13**) and 3-methyl (**12** and **14**) pairs when the above relationships were used for configurational assignment. Moreover, a $^4J_{4,6}$ (1 Hz) was detected for the diastereomer of **14** having the (4*R*) configuration, which agrees with the expected W arrangement in the ^5E conformation.

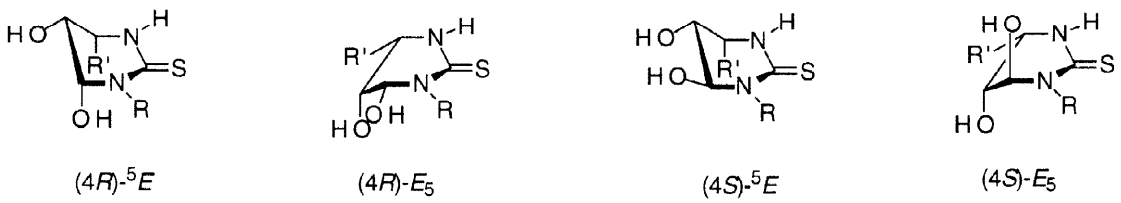


Figure 2. Flattened-chair or envelope conformers for hexahydropyrimidine-2-thiones derived from D-glucose.

The fact that conformations having the pseudoanomeric 4-OH in an axial disposition, *i.e.* fitting the anomeric effect at the N—C—O segment, were present exclusively in aqueous solutions for the four types of configurationally different polyhydroxylated hexahydropyrimidine-2-thiones considered in our study is noteworthy. Because N—C—O systems are highly reactive, experimental data on them are extremely scarce [39]. Although computational calculations show preferences for the nitrogen lone pair to be antiperiplanar to the C—O bond [40], the reported experimental data bearing on the cause of the preference [41,42] have been discussed to be consistent with electrostatic rather than hyperconjugative interactions as origin [24]. Nevertheless, this reasoning is limited to non-polar solvents, and can hardly apply to the sharp conformational preference observed in our systems. The above results strongly suggest that negative hyperconjugation between the π-type lone pair orbital of the thiourea nitrogen atom and the σ^* antibonding orbital of the C—O bond is the major

conformational requirement in this family of compounds. This stabilizing interaction overcomes even the sterically unfavorable *syn* 1,3-diaxial disposition between the bulky trihydroxypropyl substituent and the pseudoanomeric hydroxy group in structures such as the 4*S* anomers of **9** and **10** or the 4*R* anomers of **12-14**. Formation of intramolecular glycosides is likely favored, too, by the incipient anomeric effect stabilization in the corresponding transition states (Scheme 3).

Since the two epimers at the aminoketalic centre rapidly interconverted in solution, it could be expected that structures 4*R* in derivatives of D-allose and 4*S* in the D-gluco series, with the carbon substituent at C-6 in equatorial orientation, would be distinctly favored. Notwithstanding, the thermodynamic equilibria exhibited an almost equal proportion of both diastereomers in most cases, whereas compound **12** existed only in the 4*R* form. The so-called "*gauche* effect" [25,26,43], a manifestation of the generalized anomeric effect, has been previously put forward to explain the preference for the axial disposition of hydroxy substituents γ-located with respect to the carbonyl group in δ-lactams [44]. In our case, the stabilizing *gauche* disposition of the oxygen and nitrogen atoms around the C-4—C-5 and C-5—C-6 bonds would act in the same direction as 1,3-steric repulsions in hexahydropyrimidine-2-thione derivatives of D-glucose (**12-14**), favoring the 4*S* structure (Figure 2), which is inconsistent with the experimental results. An additional interaction, likely of orbital origin, must be responsible for the apparent axial preference of the carbon substituent at C-6.

Gleiter *et al.* [45] have recently postulated that lone pair—α-CH hyperconjugative destabilization is crucial for the preference of axial or equatorial conformers in six-membered azaheterocycles. In any case, axial lone pairs cause repulsive hyperconjugation with vicinal axial C—H bonds. In cyclic thioureas, the axial orientation of the nitrogen lone pair orbital is anchored by the intrinsic electronic properties of the thiourea functionality. Therefore, this effect should increase the axial preference for the pseudoanomeric hydroxy group at C-4 and favor the axial orientation of C-1', with H-4 and H-6 in equatorial disposition, in agreement with the experimental data. The latter effect is formally equivalent to a "deoxoanomeric effect", *i.e.* a preference of carbon substituents in six-membered heterocycles to adopt the axial arrangement.[1] The observed diastereomeric populations and conformations can thus be explained in terms of stabilizing (two-electron) $N_n—\sigma^*_{(CO)}$ and destabilizing (four electron) $N_n—\sigma_{(CH)}$ hyperconjugation, providing experimental evidence for the prominent role of both types of orbital interactions, together with competitive *syn* 1,3-diaxial interactions, in the generalized anomeric effect.

Acetylation of the hydroxy groups increased the steric repulsion term, disfavoring structures bearing substituents in 1,3-parallel arrangement as well as *gauche* dispositions (Figures 1 and 2). Consequently, *O*-acetylation of the diastereomeric mixture of **13** afforded

[1] The term "exo-deoxoanomeric effect" has been employed previously to designate the preference for the *gauche* O—C_1—C_{exo}—C torsional arrangement in C-glycosides, by analogy with the "exo-anomeric effect" displayed by glycosides [46]. By extension, we used the term "deoxoanomeric effect" to denote the preference for the axial disposition of the carbon-carbon bond in X—C—C_{exo} six-membered cyclic systems.

the (4*S*)-E_5 acetate **33** (a single *gauche* interaction against two *gauche* interactions and a *syn* 1,3-diaxial interaction in the (4*R*)-^5E diastereomer) as the sole reaction product. Similarly, only the 4*S* hexa-*O*,*N*-acetylated derivatives **32** and **34** were isolated from **12** and **14**, respectively. In the case of the D-allose derivative **10**, the peracetylation reaction led to an inseparable mixture of both the **31-(4*R*)** and **31-(4*S*)** hexa-acetates. It must be noticed that in this case the differences in steric hindrance between the 4*R* (two *gauche* interactions) and 4*S* (a *syn* 1,3-diaxial interaction) structures are not so pronounced.

The strong anomeric effect at the N—C—O moiety determined, likewise, the preferred conformation of the acetylated derivatives in $CDCl_3$ solution. The planar thiourea group forces the flattened half-chair arrangement for the selectively *O*-acetylated compound **33**, as discussed above for unprotected hexahydropyrimidines. In the case of the peracetates, the *N*-acetyl group tends to orientate the carbonyl group dipole in opposition to that of the thiocarbonyl group. This situation brings about a steric repulsion between the corresponding methyl group and the sulfur atom that causes a conformational change in the heterocyclic ring, as induced from the coupling constant values (Table 1). Probably the cross-conjugation of the acetylated thiourea nitrogen atom results in a lower double-bond character at the corresponding pseudoamide bond, allowing adoption of conformations close to a twist-boat (skew, *S*), with N-1 and C-6 out of the main plain of the molecule keeping the pseudoanomeric acetoxy group in axial disposition (Figure 3). The $J_{4,5}$ and $J_{5,6}$ values are consistent with the (4*S*)-$^1S_6$ (H-4 and H-5 *gauche*; H-5 and H-6 quasi-*anti*) and (4*R*)-$^6S_1$ (all-*gauche*) conformations for the two diastereomers of **33** and with the (4*S*)-$^1S_6$ (H-4 and H-5 *gauche*; H-5,H-6 quasi-*syn*) arrangement for compounds **32-34**.

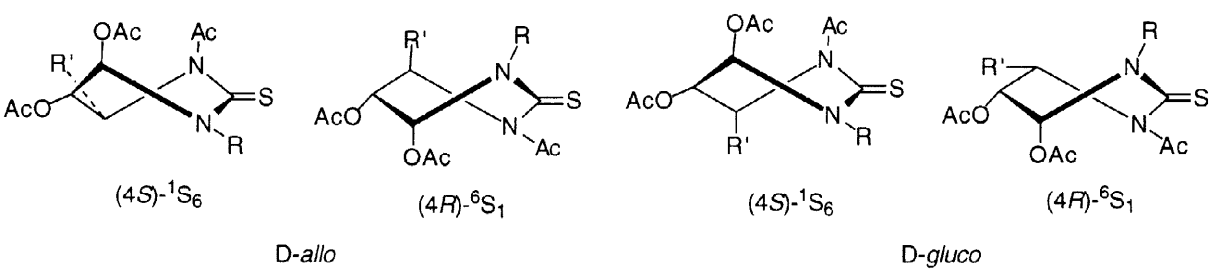


Figure 3. Twist-boat (skew, *S*) conformers for peracetylated hexahydropyrimidine-2-thiones derived from D-allose and D-glucose.

3. Conclusions

The spontaneous tautomeric rearrangement of fully unprotected 3-deoxy-3-thioureido sugars in neutral media is a convenient route to polyhydroxylated cyclic thioureas

incorporating an aminoketalic carbon atom. Our investigations of a series of distereomeric structures provide evidence which indicates that both the reactivity and the conformational preferences in these systems are under control of molecular orbital interactions. The n—σ* overlap between the filled nonbonding electron pair of the thiourea N-atom and the vacant σ* of the contiguous C—O bond is the main stereoelectronic requirement. Structures exclusively fitting the anomeric effect at the N—C—O segment were allowed. A similar delocalization interaction facilitates the formation of a transient azacarbenium cation under acid conditions, leading to bicyclic intramolecular glycosides that, likewise, fulfil the anomeric effect. In the absence of strong *syn* 1,3-diaxial interactions, repulsive hyperconjugation between the axial-oriented nitrogen lone pair orbitals and vicinal axial C—H bonds favores the axial disposition of α-carbon substituents, a formal "deoxoanomeric effect". Since the hydroxylation pattern can be tailored by judicious choice of the monosaccharide precursor, the understanding of these effects should assist the successful design of glycomimetic structures with controlled stereoelectronic properties in water solution.

4. Experimental Section

4.1. General Methods

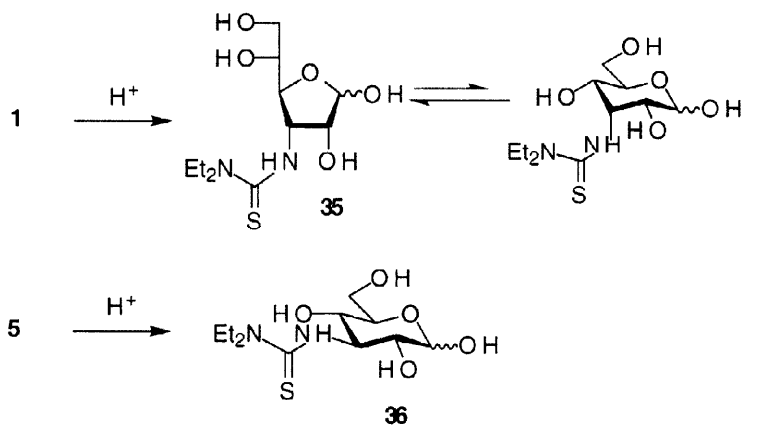
Melting points are uncorrected. Optical rotations were measured at room temperature in 1 cm or 1 dm tubes. IR spectra were recorded on an FT-IR instrument. ^{1}H (and ^{13}C NMR) spectra were recorded at 500 (125.7) and 300 (75.5) MHz. In the EI mass spectra, operating conditions were as follows: ionizing energy 35 eV, ionizing current 100 μA, accelerating voltage 4 kV, resolution 1000 (10% valley definition). In the FAB mode, the primary beam consisted of xenon atoms with a maximum energy of 8 keV. The samples were dissolved in thioglycerol (unprotected derivatives) or *m*-nitrobenzyl alcohol (peracetates), and the positive ions were separated and accelerated over a potential of 7 kV. NaI was added as cationizing agent. TLC was performed with E. Merck precoated TLC plates, silica gel 30F-245, with visualization by UV light and by charring with 10% sulfuric acid. Gel permeation chromatography (GPC) was performed on a column (29.5 x 3.0 cm) of Bio-Gel P-2 with 1:1 H_2O-MeOH. Microanalyses were performed by the Instituto Químico de Sarriá (Barcelona). Acetylation was effected with Ac_2O-pyridine (1:1 v/v, 10 mL for 1 g of sample) and DMAP (1 eq) overnight. The reaction mixture was then poured into ice-water and extracted with CH_2Cl_2 and the organic layer washed with 2 N H_2SO_4 and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated.

4.2. Materials

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-thioureido-α-D-glycofuranoses [36] (**2**, **6**) and the *N',N'*-diethyl derivatives [36] (**1**, **5**) were obtained from the corresponding 3-deoxy-

1,2:5,6-di-*O*-isopropylidene-3-isothiocyanato-α-D-allo(gluco)furanoses [35] by reaction with ammonium hydroxide or diethylamine, respectively. The *N'*-phenyl (**3**, **7**) and *N'*-methyl sugar thioureas (**4**, **8**) were prepared by coupling of the 3-amino-3-deoxy diacetonides with phenyl or methyl isothiocyanate, respectively [36]. Solvents were commercial grade and were used as supplied, with the following exceptions: methanol was distilled from methylmagnesium iodide; pyridine was distilled from KOH; acetic anhydride was distilled from freshly melted sodium acetate.

*4.3. Reactions of 3-deoxy-3-(3',3'-diethylthioureido)-1,2:5,6-di-O-isopropylidene-α-D-allo(gluco)furanose (**1** and **5**) with 90% TFA-H_2O*



Scheme 5. Deacetalation reactions of compounds **1** and **5**.

A solution of **1** (or **5**) (0.22 g, 0.59 mmol) in 90% TFA-H_2O (5 mL) was stirred under reduced pressure (15 mm Hg) until distillation of acetone ceased (10-15 min). The solvent was evaporated under vacuum (0.1 mm Hg) and traces of acid were eliminated by coevaporation with water and further neutralization with anion-exchange resin to give the fully unprotected thioureidosugars **35** (or **36**) (Scheme 5).

*3-Deoxy-3-(3',3'-diethylthioureido)-D-allose (**35**):* amorphous solid; 0.173 g, 100%; $[\alpha]_D$ -65.1 (*c* 0.8, MeOH); R_f (45:5:3 EtOAc-EtOH-H_2O) 0.42; α-pyrano:β-furano:α-furano:β-pyrano ratio 9:5:2.5:0.5 (C-1 integration); FABMS *m/z* 317 ($[M + Na]^+$), 295 ($[M + H]^+$); UV (MeOH) 209, 245 nm (ε_{mM} 10.6, 10.5); IR (film) 3439, 1645, 1549, 1206, 1044 cm^{-1}; ^{13}C NMR (75.5 MHz, D_2O): α-pyrano δ 181.0 (C=S), 94.3 (C-1), 70.0 (C-5), 69.1 (C-2), 68.0 (C-4), 62.6 (C-6), 60.2 (C-3); β-furano, δ 179.2 (C=S), 103.4 (C-1), 82.4 (C-4),

76.5 (C-2), 75.2 (C-5), 64.4 (C-6), 60.0 (C-3); α-furano, δ 179.0 (C=S), 98.3 (C-1), 85.0 (C-4), 74.3 (C-2), 72.1 (C-5), 64.3 (C-6), 58.4 (C-3), 47.9 (2 CH_2CH_3), 13.9 (2 CH_2CH_3). Anal. Calcd for $C_{11}H_{22}N_2O_5S$: C, 44.88; H, 7.53; N, 9.52; S, 10.89. Found: C, 44.98; H, 7.46; N, 9.42; S, 10.91.

*3-Deoxy-3-(3',3'-diethylthioureido)-D-glucopyranose (**36**):* amorphous solid; 0.303 g, 100%; $[\alpha]_D$ +59.7 (*c* 1.0, MeOH); R_f (45:5:3 EtOAc-EtOH-H_2O) 0.4; β-pyrano-α-pyrano ratio 3:1 (H-1 integration); FABMS *m/z* 317 ([M + Na]$^+$), 295 ([M + H]$^+$); UV (MeOH) 209, 246 nm (ε_{mM} 10.6, 9.6); IR (film) 3422, 1647, 1551, 1038 cm^{-1}; ^{13}C NMR (75.5 MHz, D_2O): α-pyrano δ, 181.0 (C=S), 94.0 (C-1), 74.2 (C-2), 73.0 (C-5), 70.9 (C-4), 62.0 (C-6), 61.5 (C-3); β-pyrano δ, 180.9 (C=S), 98.9 (C-1), 79.4 (C-5), 75.5 (C-2), 71.1 (C-4), 64.7 (C-6), 62.8 (C-3), 47.8 (2 CH_2CH_3), 14.0 (2 CH_2CH_3). Anal. Calcd for $C_{11}H_{22}N_2O_5S$: C, 44.88; H, 7.53; N, 9.52; S, 10.89. Found: C, 45.15; H, 7.70; N, 9.86; S, 10.70.

4.4. General procedure for the preparation of 4,5-dihydroxy-6-(1',2',3'-trihydroxypropan-1'-yl)-hexahydropyrimidine-2-thiones

A solution of the corresponding 3-deoxy-3-thioureido sugar diacetonides (**2-4**, **6-8**) (0.61 mmol) in 90% TFA-H_2O (5 mL) was stirred under reduced pressure (15 mm Hg) until distillation of acetone ceased (15-30 min). The solvent was evaporated under vacuum (0.1 mm Hg) at room temperature and traces of acid were eliminated by coevaporation with H_2O and final neutralization with Amberlite IR-45 (OH^-) ion exchange resin. The resulting residue was purified by GPC, concentrated and freeze-dried. The fully unprotected cyclic thiourea compounds **9**, **10**, **12-14** were obtained in this way. In the case of the *N'*-methyl-D-allose derivative **4**, separation of the corresponding hexahydropyrimidine (**11**) from intramolecular glycosides present in the reaction mixture was not possible.

*(4R and 4S,5R,6R)-4,5-Dihydroxy-6-(D-*erythro*-triitol-1'-yl)-hexahydropyrimidine-2-thione (**9**):* amorphous solid; 0.105 g, 72%; R_f 0.18 (45:5:3 EtOAc-EtOH-H_2O); (4*R*):(4*S*) ratio 3:2 (H-5 integration); $[\alpha]_D$ +26.2 (*c* 0.8, H_2O); UV (H_2O) 242 nm (ε_{mM} 17.6); FABMS *m/z* 261 ([M + Na]$^+$); IR (KBr) 3374, 1648, 1559, 1204, 1134, 1036 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) Table1; ^{13}C NMR (75.5 MHz, D_2O): (4*R*), δ 177.2 (C=S), 75.9 (C-4), 74.7 (C-1'), 73.2 (C-2'), 65.3 (C-3'), 64.7 (C-5), 60.1 (C-6); (4*S*), δ 176.3 (C=S), 77.8 (C-4), 73.8 (C-1'), 73.1 (C-2'), 65.3 (C-3'), 65.0 (C-5), 57.4 (C-6). Anal. Calcd for $C_7H_{14}N_2O_5S$: C, 35.29; H, 5.92; N, 11.76; S, 13.45. Found: C, 35.07; H, 5.98; N, 11.70; S, 13.28.

*(4R and 4S,5R,6R)-4,5-Dihydroxy-3-phenyl-6-(D-*erythro*-triitol-1'-yl)-hexahydropyrimidine-2-thione (**10**):* amorphous solid; 115 mg, 60%; R_f 0.34 (45:5:3 EtOAc-EtOH-H_2O); (4*R*):(4*S*) ratio 3:2 (H-4 integration); $[\alpha]_D$ +1.1 (*c* 0.9, MeOH); UV (MeOH) 206, 250 nm (ε_{mM} 23.3, 13.1); FABMS *m/z* 337 ([M + Na]$^+$), 315 ([M + H]$^+$); IR (film) 3393, 3212,

3020, 1638, 1493, 1262, 1206, 1088, 1033 cm^{-1}; ^1H NMR (300 MHz, D_2O) Table 1 and δ 7.32 (m, 5 H, Ph); ^{13}C NMR (125.7 MHz, D_2O): (4*R*), δ 176.6 (C=S), 142.6, 128.9, 127.9 (Ph), 80.5 (C-4), 70.9 (C-1'), 70.2 (C-2'), 62.7 (C-3'), 62.5 (C-6), 54.3 (C-5); (4*S*), δ 175.6 (C=S), 142.9, 128.9, 127.9 (Ph), 82.5 (C-1), 72.5 (C-1'), 70.0 (C-2'), 63.5 (C-3'), 62.1 (C-5), 57.3 (C-6). Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91; S, 10.20. Found: C, 49.40; H, 5.45; N, 8.96; S, 10.28.

*(4R,5R,6S)-4,5-Dihydroxy-6-(D-*erythro*-triitol-1'-yl)-hexahydropyrimidine-2-thione* ***(12)****:* 101 mg, 70%; R_f 0.44 (4:5:1 BuOH-AcOH-H_2O); $[\alpha]_D$ -93 (*c* 1.0, H_2O); UV (H_2O) 242 nm (ε_{mM} 17.6); FABMS *m/z* 261 [(M + Na)$^+$]; IR (KBr) 3393, 3250, 1547, 1036 cm^{-1}; ^1H NMR (300 MHz, D_2O) Table 1; ^{13}C NMR (75.5 MHz, D_2O): δ 175.4 (C=S), 77.3 (C-4), 74.5 (C-2'), 72.6 (C-1'), 66.1 (C-5), 64.6 (C-3'), 54.7 (C-6). Anal. Calcd for $C_7H_{14}N_2O_5S$: C, 35.29; H, 5.92; N, 11.76; S, 13.45. Found: C, 35.28; H, 5.85; N, 11.91; S, 13.45.

*(4R and 4S,5R,6S)-4,5-Dihydroxy-3-phenyl-6-(D-*erythro*-triitol-1'-yl)-hexahydropyrimidine-2-thione* ***(13)****:* syrup; 136 mg, 71%; R_f 0.40 (4*R*) and 0.33 (4*S*) (45:5:3 EtOAc-EtOH-H_2O); (4*R*):(4*S*) ratio 1:1 (H-5 integration); $[\alpha]_D$ -10.9 (*c* 0.55, MeOH); UV (MeOH) 206, 248 nm (ε_{mM} 28.4, 15.1); FABMS *m/z* 337 [(M + Na)$^+$]; IR (film) 3322, 1659, 1514, 1074 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 1; ^{13}C NMR (75.5 MHz, D_2O): (4*R*), δ 178.8 (C=S), 145.7, 131.7, 130.7 (Ph), 85.3 (C-4), 74.2 (C-2'), 72.2 (C-1'), 66.8 (C-5), 64.6 (C-3'), 54.7 (C-6); (4*S*), δ.178.4 (C=S), 145.7, 131.7, 130.7 (Ph), 93.2 (C-4), 74.2 (C-2'), 72.1 (C-1'), 64.1 (C-5), 63.9 (C-3'), 55.0 (C-6). Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91; S, 10.20. Found: C, 49.74; H, 5.84; N, 8.86; S, 10.12.

*(4R and 4S,5R,6S)-4,5-Dihydroxy-3-methyl-6-(D-*erythro*-triitol-1'-yl)-hexahydropyrimidine-2-thione* ***(14)****:* 54 mg, 35%; (4*R*):(4*S*) ratio 1:1 (H-4 integration). Preparative thin-layer chromatography (45:5:3 EtOAc-EtOH-H_2O) afforded both epimers in pure diasteromeric form. **14-(4*R*):** R_f 0.14 (45:5:3 EtOAc-EtOH-H_2O); $[\alpha]_D$ -29.0 (*c* 1.24, Me_2SO); UV (Me_2SO) 258 nm (ε_{mM} 4.4); FABMS *m/z* 275 [(M + Na)$^+$]; IR (KBr) 3397, 1684, 1507, 1121 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 1; ^{13}C NMR (125.7 MHz, D_2O) δ 175.3 (C=S), 81.2 (C-4), 71.4 (C-2'), 69.5 (C-1'), 64.3 (C-5), 61.4 (C-3'), 51.5 (C-6), 39.3 (NMe). Anal. Calcd for $C_8H_{16}N_2O_5S$: C, 38.08; H, 6.39; N, 11.10; S, 12.71. Found: C, 37.97; H, 6.54; N, 11.07; S, 12.62. **14-(4*S*):** R_f 0.2 (45:5:3 EtOAc-EtOH-H_2O); $[\alpha]_D$ -55.6 (*c* 0.7, H_2O); UV (H_2O) 208, 242 nm (ε_{mM} 14.1, 15.3); FABMS *m/z* 275 [(M + Na)$^+$]; IR (KBr) 3353, 3250, 1648, 1522, 1279, 1049 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 1; ^{13}C NMR (125.7 MHz, D_2O) δ 175.3 (C=S), 81.4 (C-4), 71.5 (C-2'), 69.5 (C-1'), 64.4 (C-5), 61.5 (C-3'), 51.5 (C-6), 39.3 (NMe). Anal. Calcd for $C_8H_{16}N_2O_5S$: C, 38.08; H, 6.39; N, 11.10; S, 12.71. Found: C, 38.07; H, 6.48; N, 11.00; S, 12.54.

Table 1.
^{1}H NMR spectral parameters of hexahydropyrimidine-2 thiones **9**, **10**, and **12-14**.

Comp.	H-4	H-5	H-6	H-1'	H-2'	H-3'a	H-3'b
	Chemical shifts (δ, ppm)						
(4*R*)-9[a,b]	4.78d	4.10dd	3.74m	<----------3.87-3.67m--------->			3.60dd
(4*S*)-9[a,b]	4.75d	4.22t	3.72m	<----------3.87-3.67m--------->			3.60dd
(4*R*)-10[a,b]	5.07d	4.36dd	<----------3.99-3.74m---------->				3.63m
(4*S*)-10[a,b,c]	4.93dd	4.46t	<----------3.99-3.74m---------->				3.63m
(4*R*)-12[a,d]	4.79d	4.08t	3.70dd	3.96t	3.86ddd	3.79dd	3.69dd
(4*R*)-13[a,d]	4.95d	4.21dd	3.78dd	3.95dd	3.84ddd	3.77dd	3.65dd
(4*S*)-13[a,d]	4.72d	4.38t	3.78m	3.97m	3.86ddd	3.77m	3.66dd
(4*R*)-14[a,d]	4.78d	4.09t	3.61dd	3.86dd	3.79ddd	3.73dd	3.63dd
(4*S*)-14[a,d,e]	4.53d	4.25t	3.55dd	3.85dd	3.78ddd	3.72dd	3.62dd

	Coupling constants (*J*, Hz)						
	$J_{4,5}$	$J_{5,6}$	$J_{6,1'}$	$J_{1',2'}$	$J_{2',3'a}$	$J_{2',3'b}$	$J_{3'a,3'b}$
(4*R*)-9	3.2	7.8	---	---	---	---	---
(4*S*)-9	2.5	2.5	---	---	---	---	---
(4*R*)-10	3.3	8.7	---	---	---	---	---
(4*S*)-10	2.3	2.3	---	---	---	---	---
(4*R*)-12	3.2	3.2	6.2	6.2	3.7	6.6	11.7
(4*R*)-13	3.4	2.9	5.5	7.2	3.7	6.8	11.8
(4*S*)-13	3.6	3.6	---	5.7	4.3	5.7	11.8
(4*R*)-14	3.2	3.2	6.9	5.6	3.2	6.8	11.8
(4*S*)-14	3.2	3.2	7.6	5.3	4.0	6.7	11.8

[a] In D_2O.
[b] At 300 MHz.
[c] $J_{4,6}$ = 1.8 Hz.
[d] At 500 MHz.
[e] $J_{4,6}$ = 1.0 Hz.

4.5. General procedure for the preparation of bicyclic intramolecular glycosides of hexahydropyrimidine-2-thiones

Treatment of **2-4**, **6-8** (0.61 mmol) in dioxane (1.5 mL) with 0.05 M H_2SO_4 (1.9 mL) under reflux for 5 h followed by evaporation of the solvents afforded a crude reaction mixture containing intramolecular glycosides in virtually quantitative yield, as seen from ^{13}C NMR spectra. Purification was effected either by column chromatography (45:5:3 EtOAc-EtOH-H_2O) on the fully unprotected compounds (→**15**, **18**, **23-26**) or by acetylation and further separation of the peracetates by column chromatography using 1:1 EtOAc-petroleum ether (→**20**, **21**).

*3-Amino-3-deoxy-α-D-allopyranosylamine 1,3-(cyclic thiourea) (**15**):* 107 mg, 80%; m.p.> 150 °C dec. (from EtOH); R_f 0.3 (45:5:3 EtOAc-EtOH-H_2O); $[\alpha]_D$ +28.6 (*c* 0.8, H_2O);

UV (H_2O) 204, 244 nm (ε_{mM} 6.4, 9.1); FABMS *m/z* 243 ([M + Na]$^+$), 221 ([M + H]$^+$); IR (KBr) 3393, 3256, 1648, 1541, 1040 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) Table 2; ^{13}C NMR (125.7 MHz, D_2O) δ 176.4 (C=S), 75.6 (C-1), 70.2 (C-4), 66.5 (C-5), 59.3 (C-2), 58.4 (C-6), 55.4 (C-3). Anal. Calcd for $C_7H_{12}N_2O_4S$: C, 38.17; H, 5.49; N, 12.72; S, 14.56. Found: C, 37.94; H, 5.41; N, 12.50; S, 14.62.

*3-Amino-3-deoxy-*N*-methyl-α-D-allopyranosylamine 1,3-(cyclic thiourea) (**18**):* 121 mg, 85%; m.p. 210-213 °C (from EtOH); R_f 0.07 (45:5:3 EtOAc-EtOH-H_2O); $[\alpha]_D$ +3.1 (*c* 0.9, MeOH); UV (MeOH) 204, 249 nm (ε_{mM} 12.2, 14.9); FABMS *m/z* 257 ([M + Na]$^+$), 235 ([M + H]$^+$); IR (KBr) 3351, 3297, 1648, 1522, 1298, 1209, 1018 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) Table 2 and δ 3.32 (s, 3 H, NMe); ^{13}C NMR (75.5 MHz, D_2O) δ 178.2 (C=S), 83.2 (C-1), 71.2 (C-5), 67.1 (C-4), 60.5 (C-2), 60.0 (C-6), 55.9 (C-3), 40.5 (Me). Anal. Calcd for $C_8H_{14}N_2O_4S$: C, 41.01; H, 6.02; N, 11.96; S, 13.69. Found: C, 40.94; H, 6.00; N, 12.04; S, 13.50.

*3-Acetamido-*N*-acetyl-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-allopyranosylamine 1,3-(cyclic thiourea) (**19**).* Acetylation of **15** (50 mg, 0.226 mmol) in the presence of a catalytic amount of DMAP followed by TLC (1:1 EtOAc-petroleum ether) yielded **19**: syrup; 44 mg, 85%; R_f 0.4; $[\alpha]_D$ +53 (*c* 0.6, $CHCl_3$); UV ($CHCl_3$) 229, 284 nm (ε_{mM} 17.9, 7.8); EIMS *m/z* 430 (M^+), 388 (M^+ - CH_2CO), 346 (30, M^+ - 2 CH_2CO); IR (film) 1750, 1700, 1505, 1219, 1184, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) Table 2 and δ 2.77, 2.74 (2 s, NAc), 2.09, 2.08, 2.03 (3 s, 3 OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.0 (C=S), 175.8, 174.2 (2 CO amide), 170.4, 169.2, 168.9 (3 CO ester), 77.7 (C-1), 67.2 (C-4), 66.8 (C-5), 61.9 (C-2), 61.2 (C-6), 54.7 (C-3), 28.3, 28.1 (2 NCO*CH*$_3$), 20.6, 20.5, 20.3 (3 CO*CH*$_3$). Anal. Calcd for $C_{17}H_{22}N_2O_9S$: C, 47.44; H, 5.15; N, 6.51. Found: C, 47.77; H, 5.07; N, 6.51.

*3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-*N*-phenyl-α-D-allopyranosylamine 1,3-(cyclic thiourea) (**20**):* syrup; 16 mg, 12%; R_f 0.25 (1:1 EtOAc-petroleum ether); $[\alpha]_D$ -11.8 (*c* 0.9, $CHCl_3$); UV ($CHCl_3$) 230, 259 nm (ε_{mM} 11.6, 8.7); EIMS *m/z* 464 (M^+), 405 (M^+ - AcO); IR (film) 1748, 1697, 1525, 1505, 1217, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) Table 2 and δ 7.37 (m, 5 H, Ph), 2.21 (s, NAc), 2.15, 2.14, 2.11 (3 s, 3 OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.0 (C=S), 170.9 (CO amide), 169.9, 169.5 169.0 (3 CO ester), 143.5 (C-1, Ph), 129.4 (C-3,5, Ph), 128.5 (C-4, Ph), 128.1 (C-2,6, Ph), 79.7 (C-1), 71.1 (C-5), 69.1 (C-4), 63.1 (C-2), 61.8 (C-6), 55.1 (C-3), 29.6 (NCO*CH*$_3$), 20.8, 20.7, 20.5 (3 CO*CH*$_3$). Anal. Calcd for $C_{21}H_{24}N_2O_8S$: C, 54.30; H, 5.21; N, 6.03; S, 6.90. Found: C, 54.38; H, 5.04; N, 5.98; S, 6.95.

*3-Acetamido-2,5,6-tri-*O*-acetyl-3-deoxy-*N*-phenyl-α-D-allofuranosylamine 1,3-(cyclic thiourea) (**21**):* syrup; 92 mg, 62%; R_f 0.56 (1:1 EtOAc-petroleum ether); $[\alpha]_D$ +19.9 (*c* 1, $CHCl_3$); UV ($CHCl_3$) 242, 289 nm (ε_{mM} 14.2, 9.7); EIMS *m/z* 464 (M^+), 421 (M^+ - Ac); IR (film) 3010, 1748, 1697, 1414, 1219, 1184, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) Table 2

and δ 7.38 (m, 5 H, Ph), 2.90 (s, NAc), 2.26, 2.23, 2.18 (3 s, 3 OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.8 (C=S), 174.8 (CO amide), 170.4, 170.0 169.7 (3 CO ester), 144.1 (C-1, Ph), 129.6 (C-3,5, Ph), 128.3 (C-4, Ph), 127.9 (C-2,6, Ph), 86.8 (C-1), 83.4 (C-4), 69.9 (C-5), 65.1 (C-2), 61.8 (C-6), 55.5 (C-3), 28.9 (NCO*CH*$_3$), 20.7, 20.6, 20.5 (3 CO*CH*$_3$). Anal. Calcd for $C_{21}H_{24}N_2O_8S$: C, 54.30; H, 5.21; N, 6.03; S, 6.90. Found: C, 54.47; H, 5.37; N, 6.02; S, 7.12.

*3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-*N*-methyl-α-D-allopyranosylamine 1,3-(cyclic thiourea) (**22**).* Conventional acetylation of **18** (95.1 mg, 0.40 mmol) with Ac_2O-pyridine and later column chromatography (1:1 EtOAc-petroleum ether) yielded **22**: syrup; 117 mg, 80%; R_f 0.55; $[\alpha]_D$ +12.4 (*c* 1, $CHCl_3$); UV ($CHCl_3$) 241, 284 nm (ε_{mM} 11.6, 11.6); EIMS *m/z* 402 (M^+), 360 (M^+ - CH_2CO); IR (film) 1753, 1709, 1483, 1225, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) Table 2 and δ 3.46 (s, 3 H, NMe), 2.76 (s, NAc), 2.10, 2.09, 2.05 (3 s, 3 OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.6 (C=S), 176.4 (CO amide), 170.2, 169.2, 169.1 (3 CO ester), 81.7 (C-1), 66.9 (C-5), 66.7 (C-4), 62.1 (C-2), 61.1 (C-6), 53.9 (C-3), 41.7 (Me), 29.1 (NCO*CH*$_3$), 20.4 (3 C) (3 CO*CH*$_3$). Anal. Calcd for $C_{16}H_{22}N_2O_8S$: C, 47.75; H, 5.51; N, 6.96; S, 7.97. Found: C, 47.60; H, 5.51; N, 7.04; S, 7.79.

*3-Amino-3-deoxy-β-D-glucofuranosylamine 1,3-(cyclic thiourea) (**23**):* 120 mg, 90%; R_f 0.36 (4:5:1 BuOH-AcOH-H_2O); $[\alpha]_D$ -10.2 (*c* 0.8, H_2O); UV (H_2O) 247 nm (ε_{mM} 8.6); ^{1}H NMR (300 MHz, D_2O) Table 2; ^{13}C NMR (75.5 MHz, D_2O) δ 181.2 (C=S), 87.7 (C-1), 85.7 (C-4), 72.5 (C-2), 72.4 (C-5), 65.6 (C-6), 58.4 (C-3). Anal. Calcd for $C_7H_{12}N_2O_4S$: C, 38.17; H, 5.49; N, 12.72; S, 14.56. Found: C, 37.95; H, 5.22; N, 12.63; S, 14.49.

*3-Amino-3-deoxy-*N*-phenyl-β-D-glucofuranosylamine 1,3-(cyclic thiourea) (**24**):* syrup; 150 mg, 83%; R_f 0.5 (45:5:3 EtOAc-EtOH-H_2O); $[\alpha]_D$ -27.4 (*c* 0.7, MeOH); UV (MeOH) 206, 256 nm (ε_{mM} 26.5, 19.2); FABMS *m/z* 319 [(M + Na)$^+$]; IR (film) 3405, 3050, 1638, 1497, 1254, 1169 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) Table 2; ^{13}C NMR (125.7 MHz, CD_3OD) δ 178.3 (C=S), 142.6 (C-1, Ph), 129.1 (C-3,5, Ph), 128.1 (C-4, Ph), 127.3 (C-2,6, Ph), 93.8 (C-1), 87.1 (C-4), 72.4 (C-2), 72.0 (C-5), 65.3 (C-6), 58.5 (C-3). Anal. Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69 H, 5.44; N, 9.45; S, 10.82. Found: C, 52.20; H, 5.51; N, 9.24; S, 11.00.

*3-Amino-3-deoxy-*N*-methyl-β-D-glucofuranosylamine 1,3-(cyclic thiourea) (**25**):* 57 mg, 40%; R_f 0.34 (45:5:3 EtOAc-EtOH-H_2O); $[\alpha]_D$ -5.9 (*c* 0.7, H_2O); UV (H_2O) 245 nm (ε_{mM} 8.4); FABMS *m/z* 257 [(M + Na)$^+$], 235 [(M + H)$^+$]; IR (KBr) 3420, 3287, 1507, 1127 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) Table 2; ^{13}C NMR (125.7 MHz, CD_3OD) δ 181.3 (C=S), 92.7 (C-1), 86.8 (C-4), 72.3 (C-2), 72.0 (C-5), 65.3 (C-6), 58.5 (C-3), 40.3 (NMe). Anal. Calcd for $C_8H_{14}N_2O_4S$: C, 41.01; H, 6.02; N, 11.96; S, 13.69. Found: C, 41.09; H, 6.10; N, 11.95; S, 13.64.

3-Amino-3-deoxy-N-*methyl*-*β*-*D*-*glucopyranosylamine 1,3-(cyclic thiourea)* (**26**): 60 mg, 42%; R_f 0.45 (45:5:3 EtOAc-EtOH-H_2O); $[\alpha]_D$ +61.3 (*c* 0.7, H_2O); UV (H_2O) 207, 243 nm (ε_{mM} 6.1, 8.7); FABMS *m/z* 235 [(M + H)$^+$]; IR (KBr) 3387, 1516, 1044 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) Table 2; ^{13}C NMR (125.7 MHz, CD_3OD) δ 180.0 (C=S), 83.8 (C-1), 78.3 (C-4), 70.8 (C-5), 64.7 (C-2), 64.0 (C-6), 51.7 (C-3), 40.9 (NMe). Anal. Calcd for $C_8H_{14}N_2O_4S$: C, 41.01; H, 6.02; N, 11.96; S, 13.69. Found: C, 41.27; H, 5.69; N, 11.95; S, 13.48.

3-Acetamido-2,5,6-tri-O-*acetyl-3-deoxy*-N-*phenyl*-*β*-*D*-*glucofuranosylamine 1,3-(cyclic thiourea)* (**27**). Acetylation of **24** (0.12 g, 0.4 mmol) in the presence of DMAP and purification by column chromatography (1:1 EtOAc-hexanes) gave **27**: syrup; 160 mg, 85%; R_f 0.67; $[\alpha]_D$ +30.6 (*c* 0.9, $CHCl_3$); UV ($CHCl_3$) 248, 282 nm (ε_{mM} 11.2, 7.8); EIMS *m/z* 464 (M$^+$); IR (film) 3405, 3010, 1748, 1697, 1495, 1221, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) Table 2; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.2 (C=S), 174.3 (CO amide), 170.5, 169.5 (2 C) (3 CO ester), 144.3 (C-1, Ph), 129.6 (C-3,5, Ph), 128.3 (C-4, Ph), 127.6 (C-2,6, Ph), 90.1 (C-1), 81.0 (C-4), 72.7 (C-2), 68.4 (C-5), 63.0 (C-6), 56.7 (C-3), 29.4 (NCO*CH*$_3$), 20.7, 20.6, 20.5 (3 OCO*CH*$_3$). Anal. Calcd for $C_{21}H_{24}N_2O_8S$: C, 54.30; H, 5.21; N, 6.03; S, 6.90. Found: C, 54.09; H, 5.23; N, 5.87; S, 6.59.

3-Acetamido-2,4,6-tri-O-*acetyl-3-deoxy*-N-*methyl*-*β*-*D*-*glucofuranosylamine 1,3-(cyclic thiourea)* (**28**). Acetylation of **25** (27 mg, 0.115 mmol) and purification by chromatography of the acetylated mixture (1:1 EtOAc-hexanes) yielded **28**: 37.7 mg, 89%; R_f 0.26; $[\alpha]_D$ +111 (*c* 1.0, $CHCl_3$); UV ($CHCl_3$) 230, 280 nm (ε_{mM} 14.3, 11.0); EIMS *m/z* 402 (M$^+$); IR (film) 1748, 1694, 1225, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) Table 2; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.6 (C=S), 173.8 (CO amide), 170.4, 169.5, 169.3 (3 CO ester), 42.5 (NMe), 29.1 (NCO*CH*$_3$), 20.6 (3 C, 3 OCO*CH*$_3$). Anal. Calcd for $C_{16}H_{22}N_2O_8S$: C, 47.75; H, 5.51; N, 6.96; S, 7.97. Found: C, 47.97; H, 5.41; N, 6.95; S, 8.11.

3-Acetamido-2,4,6-tri-O-*acetyl-3-deoxy*-N-*methyl*-*β*-*D*-*glucopyranosylamine 1,3-(cyclic thiourea)* (**29**). Compound **29** was prepared by conventional acetylation of **28** (20 mg, 0.084 mmol) in the presence of DMAP and purification by preparative thin layer chromatography (1:1 EtOAc-hexanes): syrup; 27 mg, 80%; R_f 0.44; $[\alpha]_D$ +20.3 (*c* 0.9, $CHCl_3$); UV ($CHCl_3$) 235, 280 nm (ε_{mM} 16.9, 15.8); EIMS *m/z* 402 (M$^+$); IR (film) 1748, 1703, 1225, 1047 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) Table 2; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.8 (C=S), 173.2 (CO amide), 170.5, 169.3, 168.8 (3 CO ester), 80.7 (C-1), 68.9 (C-4), 68.7 (C-5), 65.2 (C-2), 62.8 (C-6), 51.8 (C-3), 41.5 (NMe), 28.5 (NCO*CH*$_3$), 20.1 (3 C, 3 OCO*CH*$_3$). Anal. Calcd for $C_{16}H_{22}N_2O_8S$: C, 47.75; H, 5.51; N, 6.96; S, 7.97. Found: C, 47.58; H, 5.30; N, 7.11; S, 8.10.

Tabla 2.

^{1}H NMR spectral parameters of 1,3-cyclic thioureas **15** and **18-29**.

	Chemical shifts (δ, ppm)						
Comp	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
15[a,d]	4.81d	3.94dd	3.80m	3.73dd	3.25ddd	3.79dd	3.68dd
18[a,d]	4.87dd	3.97dd	3.74m	3.72dd	3.10ddd	3.78dd	3.67dd
19[b,d]	5.98dd	5.22dd	5.36m	5.01dd	3.78dt	<-----4.21d----->	
20[b,d]	6.31dd	5.15dd	3.75m	5.81dd	5.37ddd	4.53dd	4.15dd
21[b,d]	5.37d	5.19dd	5.56d	4.58d	5.23ddd	4.94dd	4.22dd
22[b,d]	5.05dd	5.12t	5.09ddd	4.89dd	3.55ddd	4.25dd	4.19dd
23[b,d]	4.75m	4.63dd	3.75m	4.26dd	3.75m	3.81dd	3.63dd
24[c,e]	4.90sa	4.76d	3.81m	4.37dd	<-----3.96m----->		3.72dd
25[c,e]	4.80d	4.95d	3.63ddd	4.23dd	3.70ddd	3.81dd	3.60dd
26[c,e]	4.86d	3.74m	3.96ddd	3.57dt	3.99td	3.46dd	3.44dd
27[b,d]	5.26d	5.54d	5.66dt	4.71dd	5.25ddd	4.72dd	4.25dd
28[b,d]	5.12d	5.31d	5.54dt	4.62dd	4.98ddd	4.58dd	4.10dd
29[b,e]	5.17dd	4.93td	4.99dt	5.02dd	4.12ddd	4.15dd	4.00dd

	Coupling constants (J, Hz)							
	$J_{1,2}$	$J_{2,3}$	$J_{1,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
15[a,d]	2.4	3.3	---	3.2	10.0	2.4	5.0	12.4
18[a,d]	3.2	2.4	1.8	3.0	10.0	2.3	5.0	12.4
19[b,d]	3.3	2.8	2.5	3.2	10.5	3.2	3.2	---
20[b,d]	2.8	1.7	1.7	10.5	2.6	4.3	6.5	12.3
21[b,d]	3.6	4.6	---	0	6.1	3.6	5.0	12.3
22[b,d]	3.1	3.1	0.8	3.4	10.4	2.6	3.2	12.4
23[b,d]	---	1.8	---	3.1	9.2	3.1	5.0	11.7
24[c,e]	0	1.7	---	2.7	9.5	---	6.5	12.4
25[c,e]	0	1.8	1.1	2.7	9.8	2.5	5.8	11.5
26[c,e]	---	2.4	1.8	4.2	2.3	7.0	7.0	11.6
27[b,d]	0	1.5	1.5	3.8	10.1	2.6	4.7	12.3
28[b,d]	0	1.2	1.2	3.9	10.4	2.4	4.3	12.4
29[b,e]	3.2	3.2	1.8	1.8	7.4	3.9	4.2	11.6

[a] In D_2O.

[b] In $CDCl_3$.

[c] In CD_3OD.

[d] At 300 Mhz.

[e] At 500 MHz.

(6R)-1-Acetyl-5,6-dihydro-2-thio-6-(1',2',3'-tri-O-*acetyl-D*-erythro-*triitol-1'-yl)uracil* ***(30)***. Treatment of **9** (95 mg, 0.40 mmol) with Ac_2O-pyridine (1:1, 2 mL, 24 h) led to a complex mixture of products from which **30** were isolated by TLC (1:1 EtOAc-petroleum ether): syrup; 11 mg, 7%; $[\alpha]_D$ -14.5 (*c* 1.1, $CHCl_3$); UV (CH_2Cl_2) 242, 288 nm (ε_{mM} 6.8, 7.9); EIMS *m/z* 388 (M^+), 346 (M^+ - CH_2CO); IR (film) 3260, 1751, 1711, 1478, 1223, 1189, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Table 3 and δ 8.90 (s, 1 H, NH), 2.75 (s, 3 H, NAc), 2.15, 2.07, 2.04 (3 s, 3 Oac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 179.3 (C=S), 173.9 (CO amide), 170.3, 169.9, 168.8 (3 CO ester), 164.2 (C-4), 71.6 (C-2'), 69.6 (C-1'), 61.4 (C-3'), 52.6 (C-6), 30.9 (C-5), 27.9 (NCO*CH*$_3$), 20.7, 20.5, (3 CO*CH*$_3$). Anal. Calcd for $C_{15}H_{20}N_2O_8S$: C, 46.38; H, 5.19; N, 7.21; S, 8.26. Found: C, 46.51; H, 5.13; N, 7.11; S, 8.38.

(4R and 4S,5R,6R)-1-Acetyl-4,5-diacetoxy-3-phenyl-6-(1',2',3'-tri-O-*acetyl-D*-erythro-*triitol-1'-yl)-hexahydropyrimidine-2-thione* ***(31)***. An inseparable mixture of (4*R*) and (4*S*)-**31** (1:1, 41 mg, 57%) was obtained by acetylation of **10** (41 mg, 0.13 mmol): syrup; 149 mg, 80% ; R_f 0.52 (1:1 EtOAc-hexanes); UV ($CHCl_3$) 233, 286 nm (ε_{mM} 14.3, 10.0); EIMS *m/z* 566 (M^+), 507 (M^+ - AcO); IR (film) 3010, 1755, 1694, 1495, 1424, 1223, 1061, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Table 3 and δ 7.36 (m, Ph), 2.68, 2.58 (2s, 2 NAc), 2.14, 2.13, 2.12, 2.11, 2.10, 2.09, 2.08, 2.06, 2.04 , 2.00 (10s, 10 OAc); ^{13}C NMR (75.5 MHz, $CDCl_3$): (4*R*), δ 183.6 (C=S), 173.2 (CO amide), 170.5, 169.7, 169.0, 168.8 (CO ester), 142.6, 129.8, 129.0, 126.8 (Ph), 81.4 (C-4), 71.5 (C-2'), 69.5 (C-1'), 64.4 (C-5), 61.5 (C-3'), 51.5 (C-6), 24.8 (NCO*CH*$_3$), 21.0-19.8 (CO*CH*$_3$); (4*S*), δ 183.2 (C=S), 173.2 (CO amide), 170.3, 170.1, 169.6, 168.6 (CO ester), 139.4, 129.4, 128.9, 128.8 (Ph), 81.2 (C-4), 71.4 (C-2'), 69.5 (C-1'), 64.3 (C-5), 61.4 (C-3'), 51.5 (C-6), 25.9 (NCO*CH*$_3$), 21.0-19.8 (CO*CH*$_3$). Anal. Calcd for $C_{25}H_{30}N_2O_{11}S$: C, 53.00; H, 5.34; N, 4.94; S, 5.66. Found: C, 52.97; H, 5.46; N, 4.78; S, 5.50.

(4R,5R,6S)-1,3-Di-N-*acetyl-4,5-diacetoxy-4,5-dihydroxy-6-(1',2',3'-tri*-O-*acetyl-D*-erythro-*triitol-1'-yl)-hexahydropyrimidine-2-thione* ***(32)***: R_f 0.55 (1:1 EtOAc-hexanes); $[\alpha]_D$ +52.2 (*c* 0.9, CH_2Cl_2); UV (CH_2Cl_2) 255, 292 nm (ε_{mM} 4.2, 4.3); IR (film) 1748, 1700, 1514, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Table 3; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.7 (C=S), 172.7, 171.9 (2 CO amide), 170.8, 169.8, 169.3, 168.9, 167.8 (5 CO ester), 77.1 (C-4), 72.3 (C-2'), 69.6 (C-5), 68.3 (C-1'), 61.1 (C-3'), 50.7 (C-6), 29.7, 28.0 (2 NCO*CH*$_3$), 20.9, 20.5 (2 C), 20.1 (2 C) (5 OCO*CH*$_3$). Anal. Calcd for $C_{21}H_{28}N_2O_{12}S$: C, 47.36; H, 5.30; N, 5.26; S, 6.02. Found: C, 47.27; H, 5.12; N, 5.00; S, 5.84.

(4R,5R,6S)-4,5-Diacetoxy-3-phenyl-6-(1',2',3'-tri-O-*acetyl-D*-erythro-*triitol-1'-yl)-hexahydropyrimidine-2-thione* ***(33)***. Acetylation of **13** (105.9 mg, 0.34 mmol) and purification by column chromatography (1:3 EtOAc-hexanes) gave **33**: syrup; 155 mg, 90%; R_f 0.49 (1:1 EtOAc-hexanes); $[\alpha]_D$ -24.8 (*c* 0.8, $CHCl_3$); UV ($CHCl_3$) 229, 263 nm (ε_{mM} 13.7, 15.2); EIMS *m/z* 504 (M^+); IR (film) 3349, 1748, 1510, 1217, 1049 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) Table 3; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.6 (C=S), 170.5, 169.8, 169.7, 169.6, 168.0 (5 CO ester), 143.3 (C-1, Ph), 129.4 (C-3,5, Ph), 128.5 (C-4, Ph), 128.1 (C-2,6, Ph), 79.6 (C-4), 70.6 (C-2'), 69.9 (C-1'), 62.3 (C-5), 61.1 (C-3'), 50.0 (C-6), 20.7 (2 C), 20.6 (3 C) (5 OCO*CH*$_3$). Anal. Calcd for $C_{23}H_{28}N_2O_{10}S$: C, 52.66; H, 5.38; N, 5.34; S, 6.11. Found: C, 52.40; H, 5.33; N, 5.17; S, 5.99.

*(4S,5R,6S)-1-Acetyl-4,5-diacetoxy-3-methyl-6-(1',2',3'-tri-*O*-acetyl-D-*erythro*-triitol-1'-yl)-hexahydropyrimidine-2-thione (**34**).* Conventional acetylation of **14** (10.1 mg, 0.04 mmol) and purification by preparative TLC (1:1 EtOAc-hexanes) gave **34**: 15 mg, 74%; R_f 0.4; $[\alpha]_D$ +125.7 (*c* 0.7, $CHCl_3$); UV ($CHCl_3$) 257, 278 nm (ε_{mM} 19.5, 18.4); EIMS *m/z* 504 (M^+); IR (film) 1748, 1690, 1221, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Table 3; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 183.3 (C=S), 171.2 (CO amide), 170.5, 169.7, 169.5, 169.1, 168.9 (5 CO ester), 81.1 (C-4), 71.9 (C-2'), 69.9 (C-1'), 67.8 (C-5), 60.3 (C-3'), 50.3 (C-6), 41.8 (NMe), 29.6 (NCO*CH*$_3$), 20.9, 20.6 (2 C), 20.5, 20.4 (5 OCO*CH*$_3$). Anal. Calcd for $C_{20}H_{28}N_2O_{11}S$: C, 47.61; H, 5.59; N, 5.55; S, 6.35. Found: C, 47.60; H, 5.51; N, 5.74; S, 6.51.

Table 3.
^1H NMR Spectral Parameters of compounds **30-34**.

	Chemical shifts (δ, ppm)						
Comp.	H-4	H-5	H-6	H-1'	H-2'	H-3'a	H-3'b
30[a,c,e]	---	3.03d	5.08ddd	5.40dd	5.25ddd	4.25dd	4.18dd
		2.78dd					
(4*R*)-31[a,c]	6.37d	5.70dd	4.99dd	5.65dd	5.18m	4.43dd	4.26m
(4*S*)-31[a,c]	6.15d	5.22t	5.14dd	5.82dd	5.18m	4.26m	4.26m
(4*S*)-32[a,c]	6.91d	5.49dd	5.58dd	5.43dd	5.14ddd	4.33dd	4.07dd
(4*S*)-33[a,c]	6.17d	5.35dd	4.20dd	5.48dd	4.97ddd	4.40dd	4.10dd
(4*S*)-34[a,c]	5.83d	5.48dd	5.56dd	5.37dd	5.17ddd	4.38dd	4.11dd

	Coupling constants (*J*, Hz)						
	$J_{4,5}$	$J_{5,6}$	$J_{6,1'}$	$J_{1',2'}$	$J_{2',3'a}$	$J_{2',3'b}$	$J_{3'a,3'b}$
30	---	1.4	3.2	6.5	3.5	5.6	12.3
		7.2					
(4*R*)-31	3.8	6.2	2.6	7.6	3.1	---	12.2
(4*S*)-31	4.5	4.5	7.6	4.9	---	---	---
(4*S*)-32	1.7	9.1	5.2	6.8	3.4	5.4	12.5
(4*S*)-33	3.3	2.7	8.5	2.5	3.9	6.7	12.3
(4*S*)-34	2.7	8.5	4.3	6.7	3.2	5.2	12.6

[a] In $CDCl_3$.

[c] At 300 Mhz.

[d] At 500 Mhz.

[e] The upper line data correspond to H-5a and the lower ones to H-5b, $J_{5a,5b}$ = 17.7.

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