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Non-biaryl atropisomers derived from carbohydrates. Part 3: Rotational isomerism of sterically hindered heteroaryl imidazolidine-2-ones and 2-thiones☆

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Abstract—The present work describes in detail the preparation and structural characterization of a series of heteroaryls in which an *o*,*o*′-disubstituted phenyl ring is connected through a single C–N bond to a heterocyclic fragment of a chiral imidazolidine-2-one or 2-thione. As a consequence of hindered rotation, some of these substances exist as stable rotamers at room temperature and can easily be separated and characterized. Molecular mechanic calculations have also been carried out to evaluate the barriers to rotation.

1. Introduction

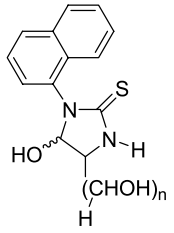
It is now unnecessary to emphasize the importance of biaryl atropisomers with a well-defined sense of helicity, as these substances have found numerous applications in asymmetric catalysis and materials chemistry.[3]

In stark contrast, non-biaryl atropisomers still represent an underestimated family of chiral conveyors. This concept, however, is hardly new. Atropisomerism in heterocycles bearing naphtyl and *o*-substituted phenyl groups have been previously reported.[4] Anyhow, atroposelective reactions with this kind of substances are a rather unexplored domain and offer promising perspectives.[5]

More recent challenges involving atropisomerism and conformational control include the design of chiral motors or switches, which can eventually be incorporated into parts of data storage units or electronic circuits,[6] as well as the mimicing of allosteric functions characteristic of biological systems.[7]

Controlling molecular motion in axially chiral systems, however, requires the easy preparation, isolation, and characterization of single molecules, together with an in-depth understanding of their physical properties.

A few years ago we introduced a new family of heteroaryl atropisomers that combine both central and axial chirality.[2,8,9] Thus, 1-naphtylimidazolidine-2-thiones appended to an acyclic sugar fragment with different configurations (**1**), exhibit atropisomerism due to hindered rotation around the C–N bond between the aryl group and the heterocyclic ring. Compounds **1** can easily be converted into more rigid structures such as **2** by acid-catalyzed cyclization. However, the barriers to rotation for compounds **1** and **2** were too low to allow us their separation at room temperature.



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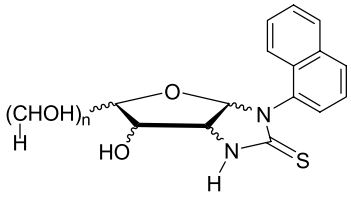

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We have also synthesized a large variety of compounds featuring structures **3**–**5** (X=S or O) which bear and *ortho*-substituted benzene ring. In all cases and, like **1** and **2**, their barriers to rotation are low and cannot be separated.[2] The

☆ See Refs. 1,2.

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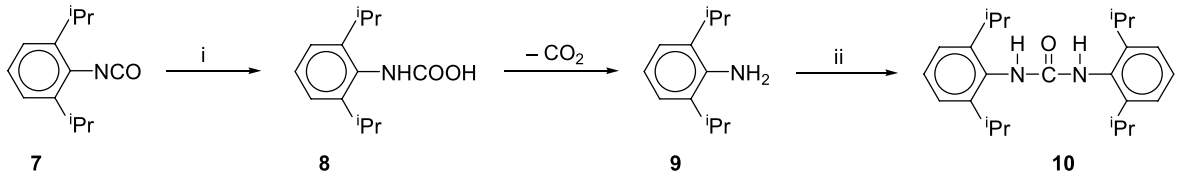
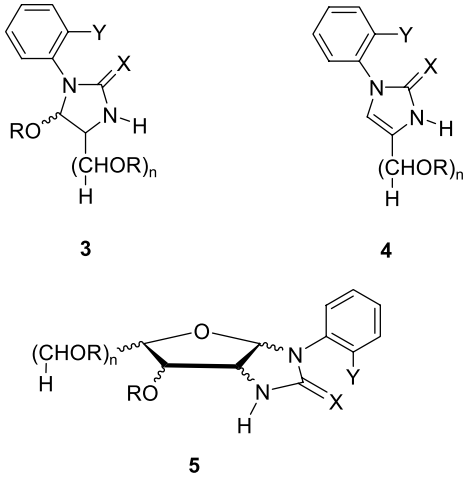


Scheme 1. (i) H_2O; (ii) **7**.

presence of a C=S bond is specially noticeable as this structural feature largely increases the barrier to rotation, whereas lower barriers were observed for their oxoanalogs. The MM2 calculations support these experimental results.

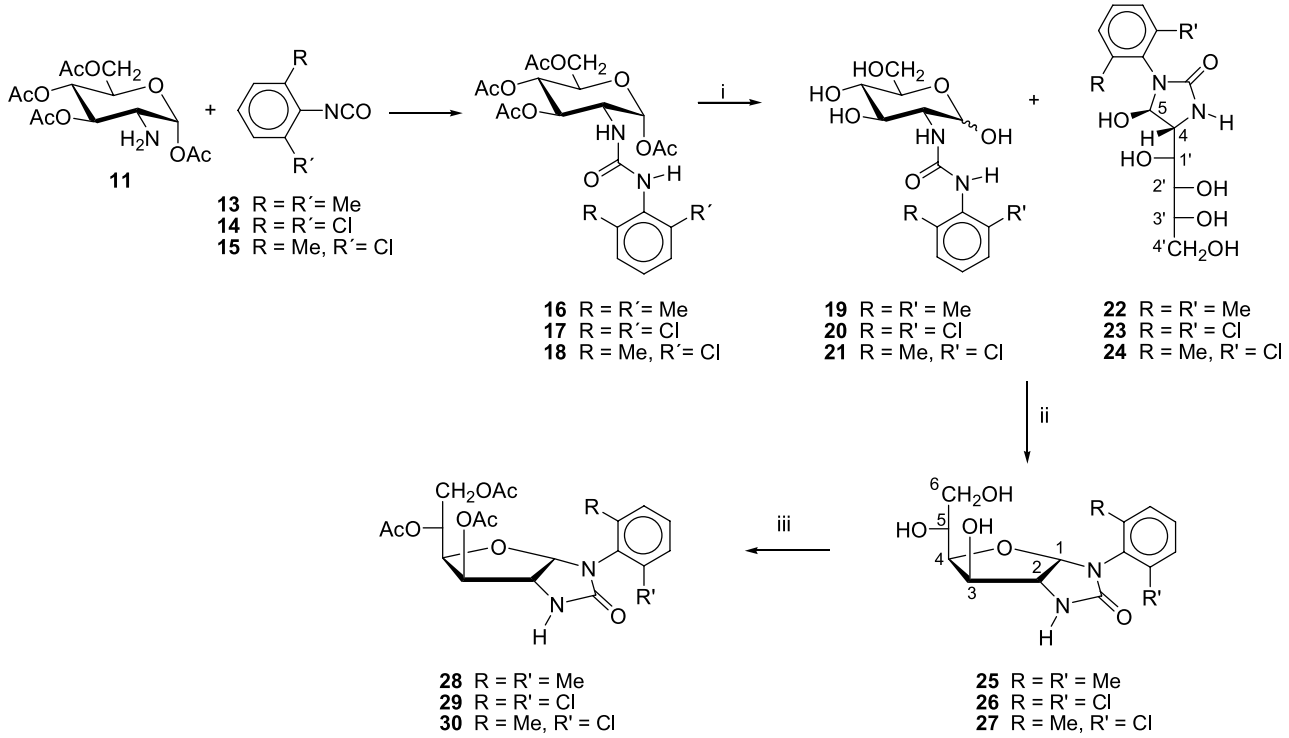


In two consecutive papers we now extend these previous results to imidazolidine-2-one and 2-thione derivatives linked to *o*,*o*′-disubstituted phenyl rings. Such rotational isomers[10] are stable entities at room temperature, and therefore the diastereomeric rotamers could be isolated by chromatography and/or crystallization, and unequivocally identified by NMR and X-ray diffraction analyses.

2. Results

2.1. Synthesis of *o*,*o*′-disubstituted 1-aryl-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-ones

Our first attempts to prepare *o*,*o*′-disubstituted 1-aryl-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-ones involved the well-established reaction between 2-amino-2-deoxy-D-glucopyranose (**6**) and aryl isocyanates in aqueous media, followed by acid-catalyzed cyclization of the ureido derivative.[2b,11] Nevertheless, aryl isocyanates bearing large groups at their *ortho* positions failed to react with aminosugars in an aqueous medium owing to steric hindrance. Under such circumstances, hydrolysis of the isocyanate occurs leading to the unwanted *N*,*N*′-diarylurea. Thus, for example, the reaction of **6** with 2,6-diisopropylphenyl isocyanate (**7**) afforded exclusively 1,3-bis(2,6-diisopropylphenyl)urea (**10**), through the intermediate carbamic acid **8**, and not the expected ureidosugar derivative (Scheme 1).



Scheme 2. (i) NH_3/MeOH; (ii) AcOH 30%, △; (iii) Ac_2O/C_5H_5N, −20 °C.

Conversely, it is possible to accomplish successfully the synthesis of *o*,*o*′-disubstituted derivatives starting from 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose[12] (**11**), thereby facilitating the condensation with aryl isocyanates in an aprotic solvent and avoiding hydrolysis side reactions. Following this procedure and using 2,6-dimethylphenyl, 2,6-dichlorophenyl and 2-chloro-6-methylphenyl isocyanates (**13**–**15**), the corresponding arylureido derivatives **16**–**18** were obtained (Scheme 2). Although symmetrically substituted isocyanates **13** and **14** cannot induce atropisomerism, such derivatives are useful in determining experimental rotational barriers and have been employed to optimize the synthetic procedure.

Compounds **16**–**18** were prepared in good to excellent yields; however variable amounts of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose (**12**) were often obtained as by-product. This substance was unequivocally identified by comparison of its physical properties and spectroscopic data with an authentic sample[13] (see Section 3).

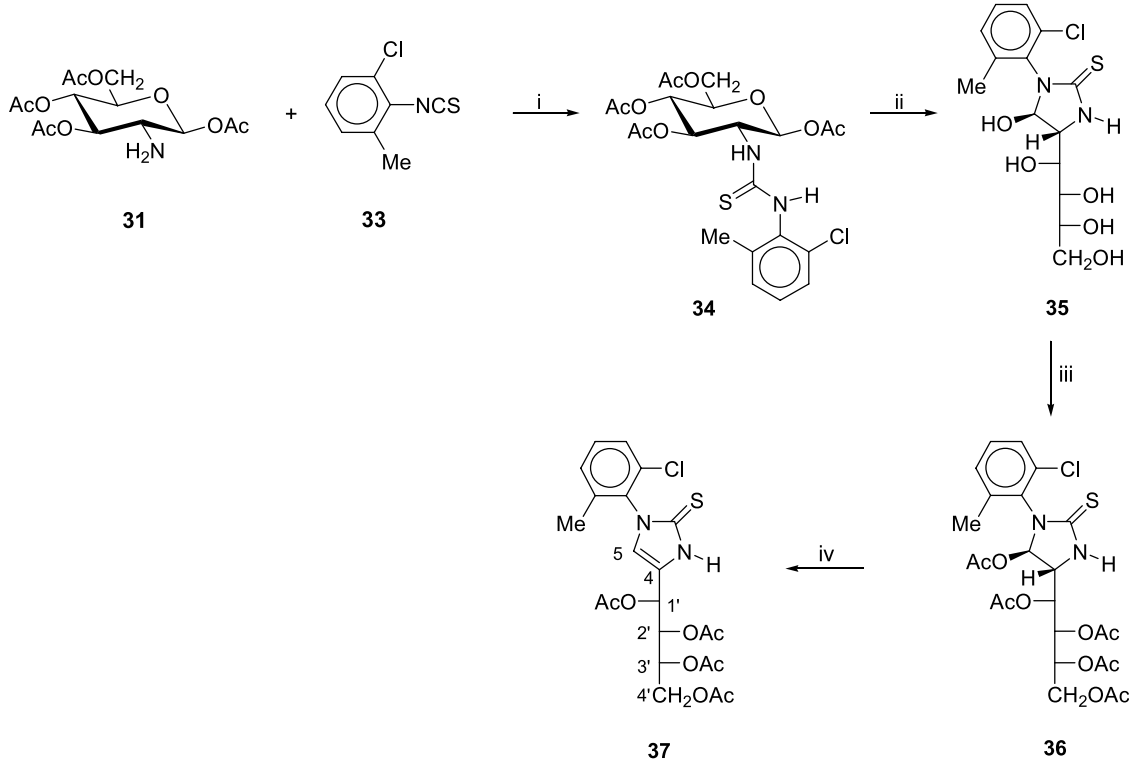
The structures attributed to **16**–**18** are supported by their physical, spectroscopic, and polarimetric data, analogous to those of other per-*O*-acetylated sugar ureas previously described.[2b,11] IR spectra show both the stretching (3400–3300 cm^{-1}) and deformation (~1500 cm^{-1}) bands of the NH group as well as the carbonyl stretching band (~1690 cm^{-1}), different from the ester carbonyl absorption (~1750 cm^{-1}). The α-anomeric configuration agrees with the small value of $J_{1,2}$ (<4 Hz) and the high values of optical rotation.

Further treatment of compounds **16**–**18** with ammonia in methanol at room temperature provided, after complete deacetylation, mixtures of the unprotected ureido derivatives **19**–**21** and the corresponding 5-hydroxyimidazolidine-2-ones **22**–**24**. The later substances are generated in different ratios by easy cyclization of ureas **19**–**21**.[11] Such mixtures could not be separated, although were identified by their spectroscopic data and used in subsequent steps without purification.

The subsequent treatment of these mixtures with hot aqueous acetic acid leads to a high-yielding preparation of the corresponding 1-aryl-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-ones **25**–**27**. The structures of these compounds are consistent with their elemental analyses, polarimetric and spectroscopic data, analogous to similar bicycles.[2b,11] The small value of $J_{2,3}$ (~0 Hz) rules out a pyranose structure and confirms that **25**–**27** are glycofuranoses in which H-2 and H-3 display a *trans* arrangement. On the contrary, $J_{1,2}$ values (>6.2 Hz) show the existence of *cis*-fused rings. The ^{13}C NMR spectra show that C-4 (and not C-5) is the most deshielded signal, a fact also accounting for the furanoid character of the sugar moiety.

As expected, ^{1}H and ^{13}C NMR spectra for **27** show duplicated and close signals corresponding to a mixture of two atropisomers in ~2:1 (*P*:*M*) ratio,[14] which could not be separated by crystallization. Isolation of these rotamers was attempted by preparing their per-*O*-acetyl derivatives. In this way, treatment of **25**–**27** with acetic anhydride and pyridine at −20 °C provided the corresponding **28**–**30** in high yields.

^{1}H NMR spectra show the absence of *N*-acetylation and IR data for **28** show absorption bands at 3500–3000 cm^{-1} due



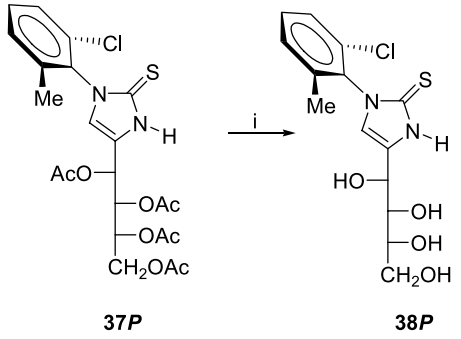
Scheme 3. (i) CH_2Cl_2, △; (ii) NH_3/MeOH; (iii) Ac_2O/C_5H_5N, −20 °C; (iv) $KHCO_3/C_6H_6$, △.

to the presence of water in the crystal lattice.[15] Again, NMR spectra show **30** as a mixture of *M* and *P* atropisomers, each separated by preparative chromatography (benzene–acetone 3:1) and crystallized from ethanol. The absolute configuration of **30***P* was determined by X-ray diffraction analysis.[1,16]

2.2. Synthesis of *o*,*o*′-disubstituted 1-aryl-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-thiones

Initially we followed a synthetic pathway analogous to that described for aryl ureido derivatives, but using the protected amino sugar **31** as starting material,[17] in order to avoid the formation of compound **12**. Condensation at room temperature with 2-chloro-6-methylphenyl isothiocyanate (**33**) allowed the preparation of thioureido derivative **34** (Scheme 3). When the reaction was carried out under reflux, significant amounts of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (**32**) were formed. This substance was identified by comparison of its physical and spectroscopic properties with an authentic sample.[18]

Pure imidazolidine-2-thione **35** was obtained in high yield by treatment of compound **34** with a saturated solution of ammonia in methanol at room temperature. The ^{1}H NMR spectrum of a crude sample of **35** showed a mixture of two *M*:*P* rotamers in a 70:30 ratio.[16] Both of them presented *R* absolute configuration at C-5 as it could be inferred from the small values of $J_{4,5}$ (~0 Hz) upon the addition of D_2O.[2b,8,11] Compound **35** could be characterized by treatment with acetic anhydride and pyridine at low temperature to afford the per-*O*-acetyl derivative **36** in almost quantitative yield and, as mixture of two atropisomers again. The major rotamer **36***P* could be isolated by fractional crystallization.[16] The small value of $J_{4,5}$ (1.4 Hz) reveals that configuration at C-5 should be *R*.

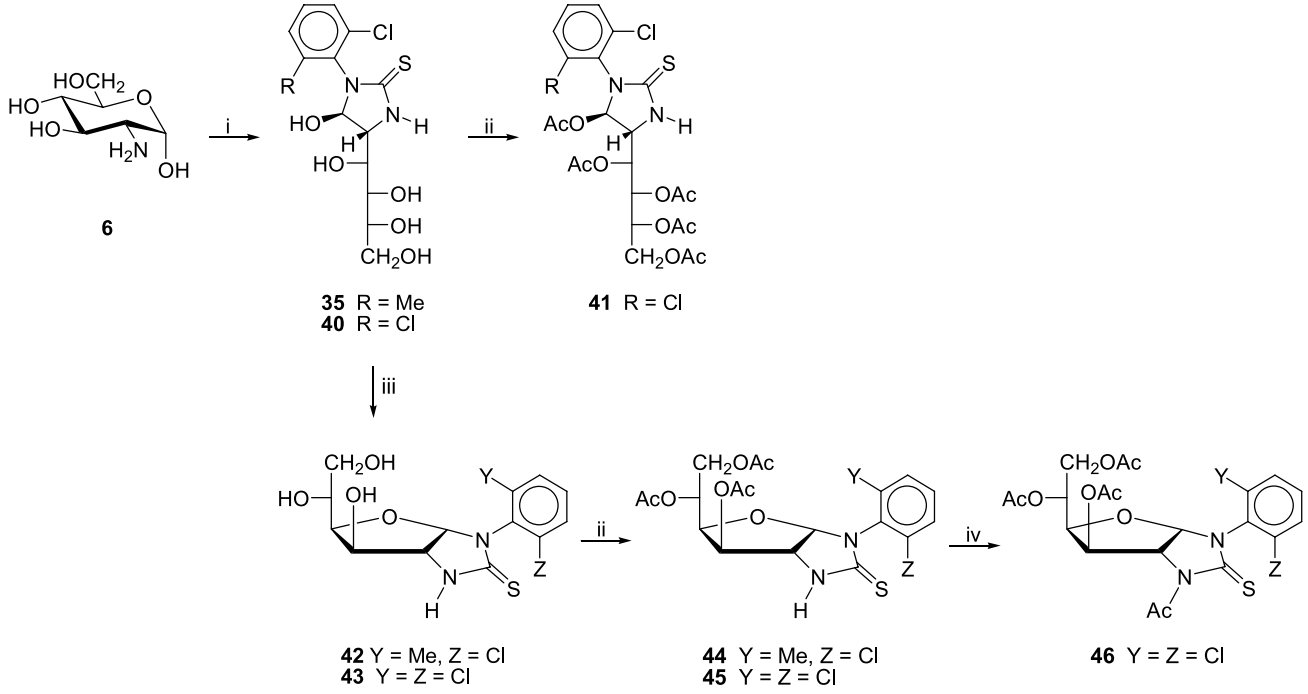


37*P* **38***P*

Scheme 4. (i) NH_3/MeOH.

Following the procedure previously described in one of our former works[2a] and starting from the atropisomeric mixture of **36***M* and **36***P*, compound **37** was obtained by acetic acid elimination as a mixture of two rotamers (85:15). The major rotamer **37***P*[16] was isolated by fractional crystallization in 42% yield. Treatment of this atropisomer with a saturated solution of ammonia in methanol gave the corresponding deprotected *P* rotamer **38**[16] (Scheme 4). Again, the structures assigned to **36–38** are supported by their spectral data and elemental analyses.

Since compound **35** represents a salient precursor en route to the bicyclic imidazolidine-2-thiones we are aiming to obtain, a more direct synthetic route was attempted. *o*,*o*′-Disubstituted aryl isocyanates with large groups failed to react with aminosugars in an aqueous medium due to the hydrolysis of isocyanate. However, reactions with aryl isothiocyanates can advantageously be conducted in the presence of water because the competing hydrolysis proceeds slowly. The direct condensation between *o*,*o*′-disubstituted aryl isothiocyanates and **6** in ethanol–water proved to be completely satisfactory. Thus,



6

35 R = Me
40 R = Cl

41 R = Cl

42 Y = Me, Z = Cl
43 Y = Z = Cl

44 Y = Me, Z = Cl
45 Y = Z = Cl

46 Y = Z = Cl

Scheme 5. (i) 2-Cl-6-RC_6H_3NCS; (ii) Ac_2O, C_5H_5N, −20 °C; (iii) AcOH 30%, △, (iv) Ac_2O, C_5H_5N, 40 °C.

compounds **35** and **40** were obtained in high yields when reaction between **6** and 2-chloro-6-methylphenyl isothiocyanate (**33**) or 2,6-dichlorophenyl isothiocyanate (**39**) took place (Scheme 5). Although the symmetrically disubstituted derivative **40** does not allow atropisomerism, this condensation was carried out to test the feasibility of the process. The structure attributed to **40** was further characterized as its per-*O*-acetyl counterpart **41**.

Treatment of **35** or **40** with hot aqueous acetic acid resulted in high yields of the corresponding 1-aryl-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-thiones **42** or **43**, respectively. The structure assigned to these compounds is consistent with their spectroscopic data and elemental analyse. Compound **42** was found to be an unequal mixture of two atropisomers as revealed by NMR analyses. The major atropisomer **42***P* was isolated after several crystallizations from 96% aqueous ethanol.[16] Compounds **42** and **43** could be characterized as their acetylated derivatives **44** and **45**, which were prepared by reaction with acetic anhydride and pyridine at −20 °C.

Isolation of *M* and *P* rotamers of **44** by flash chromatography (ethyl acetate- *n*-hexane 1:2), followed by treatment with saturated solution of ammonia in methanol at room temperature, afforded the corresponding pure atropisomers **42***M* and **42***P*. ^{1}H and ^{13}C NMR spectra for these two rotamers showed a single signal set, thereby evidencing that the axial chirality in atropisomers of compound **44** remained unaffected by deacetylation. The absolute configurations of **42***M* and **42***P* could be unambiguously determined by single-crystal X-ray diffractometry as depicted in their ORTEP diagrams with the crystallographic numbering (Figs. 1 and 2).[19]

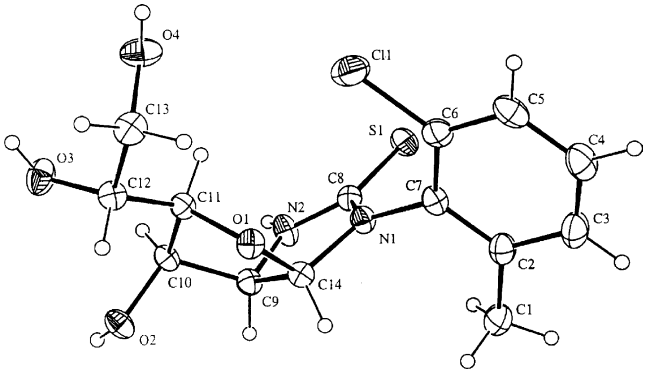


Figure 1. X-ray diffraction analysis of compound **42***P*.

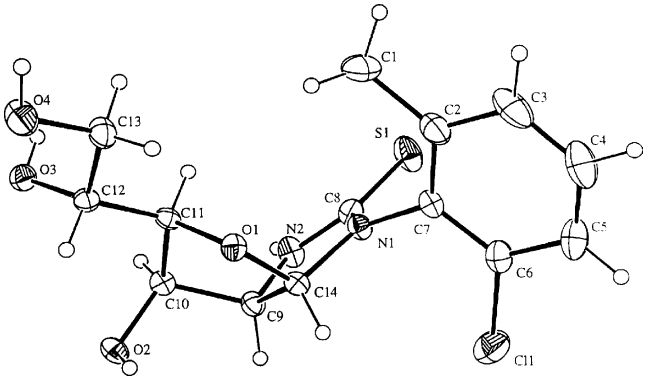


Figure 2. X-ray diffraction analysis of compound **42***M*.

Since all attempts to crystallize **45** were unsuccessful, this product was transformed into the *N*-acyl derivative **46** running the acetylation at 40 °C.[20] The IR spectra of **46** exhibits the amide band at 1675 cm^{-1} and its ^{1}H and ^{13}C NMR spectra show the characteristic chemical shifts at 2.92 and 27.1 ppm, respectively, due to the *N*-Ac methyl group. A comparison of the optical rotations of compounds **45** and **46** indicates that *N*-acetylation causes a significant decrease of ∼28°.[20]

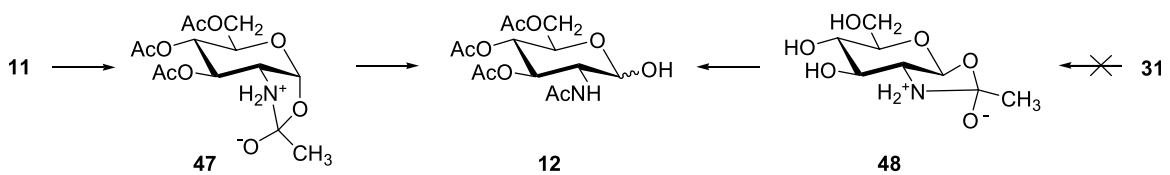
3. Discussion

As mentioned, condensation of 2-amino-2-deoxy-D-glucopyranose (**6**) with *o*,*o*′-disubstituted aryl isocyanates is more difficult than when monosubstituted aryl isocyanates are employed. On the other hand, with less reactive isothiocyanates, the direct condensation between **6** and *o*,*o*′-disubstituted aryl isothiocyanates was successfully carried out in aqueous media.

When 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose[12] (**11**) is used in an aprotic solvent, hydrolysis of isocyanate is avoided and the expected ureidosugars are formed. However, 2-acetamido-3,4,6-tri-*O*-acetyl-D-glucopyranose (**12**) is often obtained from **11**, probably due to an intramolecular migration of the acetyl group located at the anomeric position to the free amine group at C-2, through the intermediate **47** (Scheme 6). The rationale appears to be plausible as reactions employing the β-anomer **31** were not contaminated with **12**. The *trans* relationship between the anomeric acetate and the amino group at C-2 avoids the rearrangement because intermediate **48** is more strained and therefore less stable than **47**.[21]

These results along with the extensive formation of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (**32**) in reactions at reflux, show that steric effects play a key role and undesirable reactions such as the rearrangement of **11** to **12** or the formation of **32** from **31** are favored.

It is interesting to point out that the thioureido derivative **34**



Scheme 6.

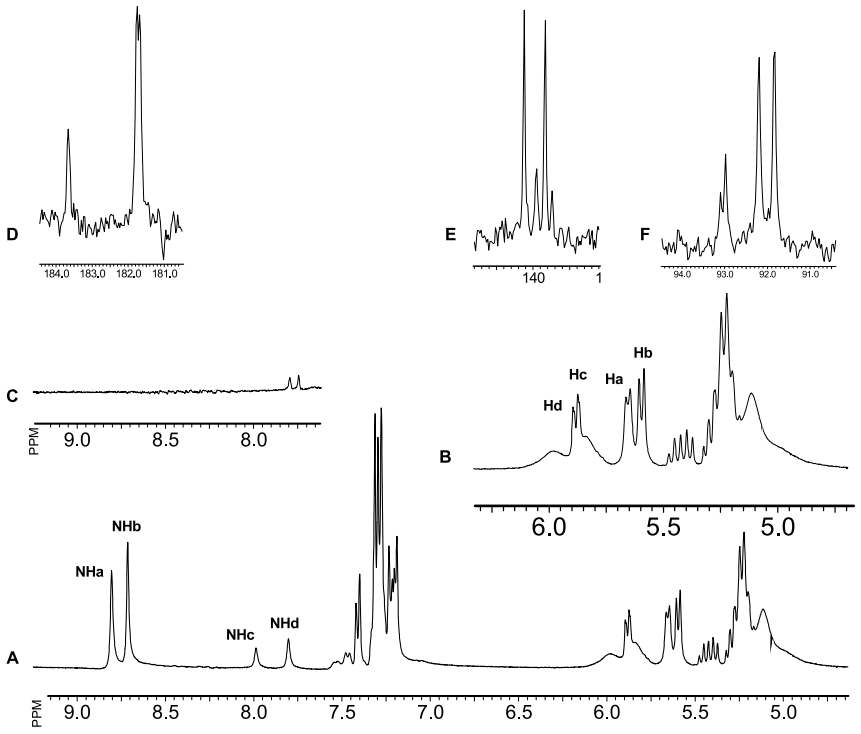


Figure 3. (A) ^{1}H NMR spectrum of **34** at −30 °C. (B) Amplified area of anomeric protons in the ^{1}H NMR spectrum. (C) D_2O exchange experiment. (D), (E) and (F) Amplified area of urea carbonyl groups, some aromatic carbons and anomeric carbons peaks, respectively, in the ^{13}C NMR spectrum of **34** at −23 °C.

Table 1. Selected spectroscopic data and population for rotamers of **34**[a]

Rotamer	NH	H-1	$J_{1,2}$	C-1	C=O	Population (%)[b]
a	8.65	5.65	7.6	91.88	139.93	38.9
b	8.56	5.59	8.4	91.53	139.36	42.2
c	7.94	5.87	8.8	92.79	139.16	7.6
d	7.78	5.88	8.8	92.66	139.60	11.4

[a] In $CDCl_3$.
[b] From digital integration of ^{1}H NMR signals at 250 K.

has an important barrier to rotation. The ^{1}H NMR spectrum at room temperature showed broad signal sets. When this spectrum was recorded at 60 °C all signals coalesced, while at −30 °C they were split into four, corresponding to a complex conformational equilibrium (Fig. 3). Some spectroscopic data as well as the relative populations observed at −30 °C for the four rotamers are showed in Table 1.

Considering that H-2 and the NH bonded to C-2 always show an antiperiplanar disposition, as it has been previously described for other sugar-based ureas and thioureas,[22] the possible conversion among the different conformers are reduced to eight (Fig. 4).

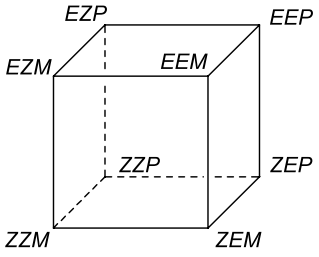
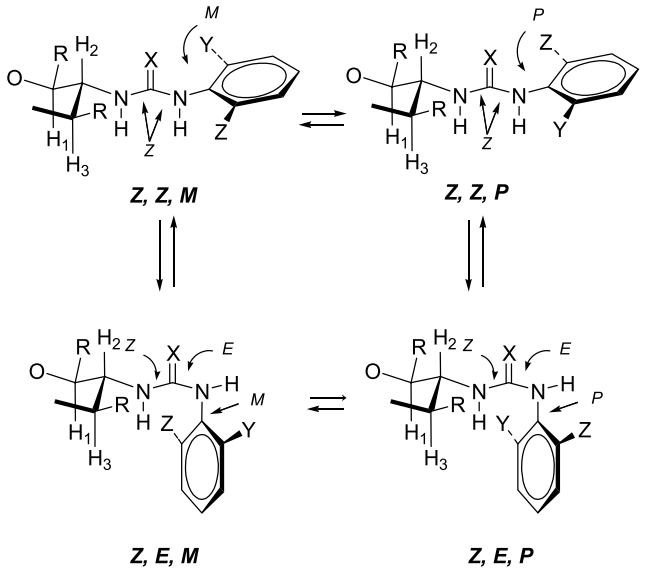


Figure 4. Diagram showing the interconversion of ureido and thioureido conformers.

Of such conformers, the more stable ones are depicted in Scheme 7 and show a less steric hindrance. Rotamers **a** and **b** should correspond to *ZZM* and *ZZP* geometries, as these would show similar chemical shifts for NH, H-1 and C-1. On the same way, geometries *ZEM* and *ZEP* would correspond to rotamers **c** and **d**. In addition, NH_c and NH_d peaks collapse at 9 °C (T_c=282 K) and NH_a and NH_b at 19 °C (T_c=292 K). The barriers to rotation calculated from these data and the difference in frequency units (Hz) between the NH signals for **c** and **d** ($\Delta\nu$=61.20 Hz) and for **a** and **b** ($\Delta\nu$=35.20 Hz) in the spectrum recorded at low temperature are 13.7 and 14.6 kcal mol^{-1}, respectively.[23] Both barriers are of the same order and should correspond to conversion between *M* and *P* atropisomers. A more accurate study on these equilibria lie beyond the scope of the present study and will be subject of future research.

Both ureido and thioureido compounds (**49**, X=O or S) were deacetyled by treatment with a saturated solution of ammonia in methanol to give the unprotected derivatives **50** (X=O or S) and hence the corresponding imidazolidine-2-ones and 2-thiones **51** (X=O or S). These substances were



Scheme 7. Stable rotamers of (thio)ureido derivatives (priority order according to Cahn–Ingold–Prelog rules: Y>Z).

later transformed into bicyclic structures **52**, under mild acid catalysis (Scheme 8). These results support the mechanism previously proposed for these transformations.[9,11]

Structures **51** and **52** with different substituents at both *ortho* positions could be resolved as stable atropisomers and fully characterized. The same fact happens with the imidazoline-2-thione derivatives **37** and **38**, suggesting that the substituent at C-5 does not affect markedly the magnitude of the barrier to rotation. This value is due exclusively to the interactions between an *ortho* substituent and either O or S atoms at C-2.[2] When both *ortho* substituents have different sizes, one should expect a large atropisomeric ratio, as it happens with Cl and methyl group, a fact in agreement with the magnitude of their steric parameters: $E_s=-0.97$ for chlorine and $E_s=-1.24$ for the methyl group.[24]

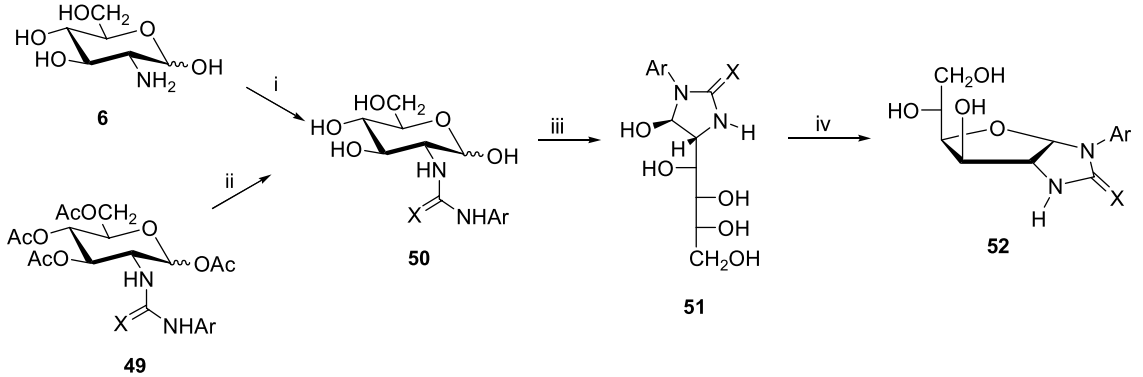
In previous papers we have described an experimental and theoretical study on several heteroaryl imidazolidine-2-one(thione) and imidazoline-2-thione derivatives with hindered rotation around a single bond.[2] Some structural variations were evaluated such as length of bond types, C=O versus C=S; nature of substituents at C-5; *cis* or *trans* stereochemistry between the heterocyclic ring and the carbohydrate moiety, and nature of substituents at the *ortho* position of the aromatic ring.

Free rotation around a single bond converts the *M* (a*R*) isomer into its *P* (a*S*) counterpart and vice versa.[14] Such an interconversion takes place by rotation around the N–C(aryl) single bond and the corresponding transition states are the peaks of highest potential energy through a 360° rotation. The potential energy was determined by means of molecular mechanics (MM2) calculations.[25,26] Starting from the *P* isomer, which is a conformation of low potential energy, rotation of the dihedral angle θ [$C_{(sp3)}$–$N_{(sp2)}$–$C_{(sp2)}$–$C_{(sp2)}$] at 30° intervals gives rise to a conformational energy diagram for the interconversion of atropisomers. A further refinement was also accomplished to determine the conformations when the energy is at a maximum, simply by rotation of the angle of torsion every 5° within the interval between −30 and +30° around the maxima previously reached. It was found that the conformations of lower potential energy corresponded to dihedral angles of ∼90° (E_P) and ∼270° (E_M). The points of higher potential energy are observed at ∼0° ($E^{\neq}_{min}$) and ∼180° ($E^{\neq}_{max}$) due to coplanarity of both the aromatic ring and the heterocyclic moiety. All of the studied cases showed barriers to rotation too low to make it possible to isolate rotational isomers at room temperature.[2]

However, molecular mechanics calculations predicted that *o*,*o*′-disubstitution will cause high enough barriers to rotation to allow isolation of atropisomers. According to our theoretical results for compounds **25**–**27** and their thioanalogous **42**, **43** and **53**, it will be possible to have barriers to rotation higher than 23 kcal mol^{-1} and hence rotamer separation at room temperature,[27] when the aromatic ring bears two substituents at the *ortho* positions. In this situation there will always be an important steric interaction between either substituent and the C=X group in both transition structures, **54** or **55** (Table 2).

However, the presence of two substituents at the *ortho* positions moved the peaks of higher potential energy from $\theta=0$ and 180° to $\theta=30$ and 210°, respectively. As an example, the potential energy diagram (MM2) for **53** is shown in Figure 5.

In order to confirm the above-mentioned predictions we have studied the thermal stability of the isolated



Scheme 8. (i) ArNCX; (ii) NH_3/MeOH; (iii) pH ≥7; (iv) AcOH 30%, △.

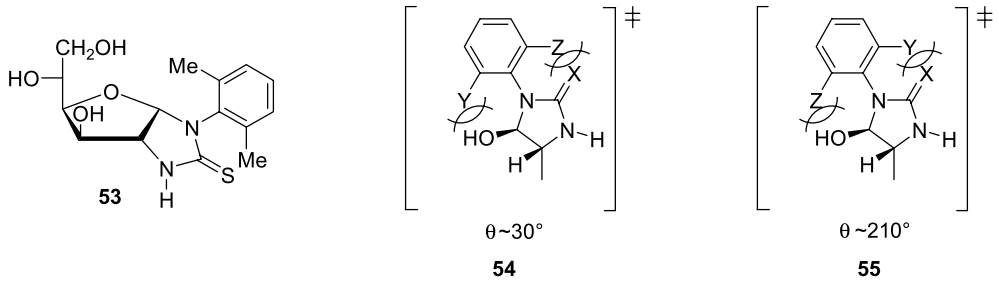


Table 2. Barriers to rotation (kcal mol^{-1})[a,b] for **25**–**27**, **42**, **43** and **53**

Compound	E_M	E_P	$\Delta H^{\ddagger}_{min}$	$\Delta H^{\ddagger}_{max}$	$\Delta\Delta H^{\ddagger}$	ΔH°
25	23.60		36.48		0.00	0.00
26	25.36		34.85		0.00	0.00
27	24.39	24.52	30.31	34.69	4.38	0.13
42	24.87	24.74	37.91	43.09	5.18	0.10
43	25.73		42.36		0.00	0.00
53	23.94		50.35		0.00	0.00

[a] Determined by MM2.
[b] E_M or E_P denotes the potential energy of *M* or *P* conformers; $E^{\ddagger}_{min}$ ($E^{\ddagger}_{max}$) is the potential energy for the transition structure of the lowest (highest) energy; $\Delta H^{\ddagger}_{min}$ ($\Delta H^{\ddagger}_{max}$)$=E^{\ddagger}_{min}$ ($E^{\ddagger}_{max}$)$-E_P$; $\Delta\Delta H^{\ddagger}=\Delta H^{\ddagger}_{max}$-$\Delta H^{\ddagger}_{min}$; $\Delta H^{\circ}=|E_M-E_P|$; 1 kcal$=$4.18 kJ.

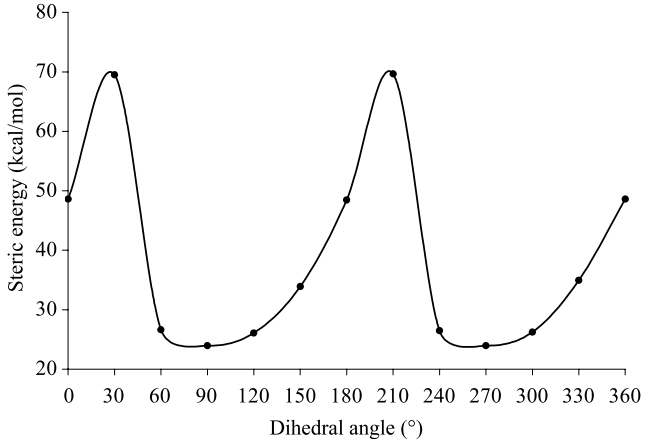


Figure 5. Plot of potential energy versus the angle of torsion for **53** (MM2 calculations).

atropisomers, using NMR techniques. All atropisomers are stable at room temperature as they did not show any change for a period of three weeks in DMSO-d_6. Furthermore, imidazolidine-2-thione derivatives **36***P*, **42***P*, **42***M*, **44***P* and **44***M* were heated for 4 h in DMSO-d_6 at 160 °C, and in some cases decomposition was observed but not the interconversion between atropisomers.

Experiments of dynamic NMR were conducted for some atropisomeric mixtures of **27**, **30**, **35**, **42** and **44**. Neither of such mixtures coalesced under heating up to 150 °C. This temperature ($T_c>423$ K) and the chemical shifts for analogous signals in each pair of atropisomers at room temperature, allowed us to establish a threshold value of 20–22 kcal mol^{-1} for their barriers to rotation,[23,28] in total agreement with our theoretical data obtained by MM2.

In conclusion, we have reported that MM2 calculations predict the possibility of obtaining room-temperature stable non-biaryl rotamers derived from carbohydrates. These predictions were found to be correct by a successful synthesis and isolation of these sort of compounds.

4. Experimental

4.1. General methods

All solvents were purchased from commercial sources and used as received unless otherwise stated. Melting points were determined on Gallenkamp and Electrothermal apparatus and are uncorrected. Analytical and preparative TLC were performed on precoated Merck 60 GF_{254} silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm and iodine vapors. Flash chromatography[29] was performed on Merck 60 silica gel (230–400 mesh). Optical rotations were measured at the sodium line (589 nm) at 20$\pm$2 °C on a Perkin–Elmer 241 polarimeter. IR spectra were recorded in the range 4000–600 cm^{-1} on Perkin–Elmer 399 or a FT-IR MIDAC spectrophotometers. Solid samples were recorded on KBr (Merck) pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 AC/PC instrument at 400 and 100 MHz, respectively, or with a Bruker AC 200-E instrument at 200 and 50.3 MHz, respectively, in different solvent systems. Assignments were confirmed by homo- and hetero-nuclear double-resonance, DEPT (distortionless enhancement by polarization transfer), and variable temperature experiments. TMS was used as the internal standard ($\delta=$ 0.00 ppm) and all *J* values are given in Hz. Microanalyses were determined on a Leco 932 analyser at the Universidad de Extremadura (Spain), and by the Servei de Microanàlisi del CSIC at Barcelona (Spain), and the Instituto de Investigaciones Químicas del CSIC at Sevilla (Spain). High resolution mass spectra (chemical ionization) were recorded on a VG Autospec spectrometer by the Servicio de Espectrometría de Masas de la Universidad de Córdoba (Spain).

4.1.1. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-[3-(2,6-dimethylphenyl)ureido]-α-D-glucopyranose (16). To a solution of

1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose[12] (**11**) (0.35 g, 1.0 mmol) in dichloromethane (5 mL) was added 2,6-dimethylphenyl isocyanate, **13** (1.0 mmol). The reaction was controlled by TLC (benzene–methanol 3:1). After three days the mixture was evaporated to dryness and the residue was crystallized from ethanol 96% giving **16** (83%), mp 196–198 °C, $[\alpha]_D$ +108.5 (*c* 0.5, $CHCl_3$); ν_{max} 3600–3200 (H_2O, NH)[15], 1540 (NH), 1740 (C=O), 1220 (C–O–C), 1630 (NC=O), 1030, 1000 (C–O), 755 cm^{-1} (aromatics); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.10 (m, 3H, Ar), 6.98 (bs, 1H, Ar–NH), 6.15 (d, $J_{1,2}=2.8$ Hz, 1H, H-1), 5.15–5.04 (m, 3H, NH, H-3, H-4), 4.34 (m, 1H, H-2), 4.20 (dd, $J_{5,6}=4.1$ Hz, $J_{6,6'}=12.5$ Hz, 1H, H-6), 4.01 (dd, $J_{5,6'}=2.0$ Hz, $J_{6,6'}=12.4$ Hz, 1H, H-6′), 3.90 (m, 1H, H-5), 2.19 (s, 6H, CH_3), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (CH_3–*C*O), 170.5 (CH_3–*C*O), 169.0 (CH_3–*C*O), 168.4 (CH_3–*C*O), 156.0 (NH–*C*O–NH), 137.0 (2C), 133.2 (2C), 128.5 (2C) (aromatics), 90.7 (C-1), 70.4 (C-3), 69.5 (C-5), 67.5 (C-4), 61.4 (C-6), 51.3 (C-2), 20.5 (2C, *C*H_3–CO), 20.4 (2C, *C*H_3–CO), 17.8 (2C, CH_3). Anal. Calcd for $C_{23}H_{30}N_2O_{10}\cdot 1/2\ H_2O$: C, 54.87; H, 6.20; N, 5,56. Found: C, 54.98; H, 6.15; N, 5.62.

4.1.2. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-[3-(2,6-dichlorophenyl)ureido]-α-D-glucopyranose (17). From 2,6-dichlorophenyl isocyanate (**14**) and following the above procedure, **17** was obtained (87%), mp 172–175 °C, $[\alpha]_D$ +77 (*c* 0.5, $CHCl_3$); ν_{max} 3320, 1540 (NH), 1730 (C=O), 1210 (C–O–C), 1635 (NC=O), 1030, 1000 (C–O), 760 cm^{-1} (aromatics); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.06 (m, 4H, Ar, Ar–NH), 6.24 (d, $J_{1,2}=3.7$ Hz, 1H, H-1), 5.40 (bs, 1H, NH), 5.22 (m, 2H, H-3, H-4), 4.41 (ddd, $J_{1,2}=3.7$, $J_{2,NH}=10.2$ Hz, $J_{2,3}=9.1$ Hz, 1H, H-2), 4.24 (dd, $J_{5,6}=4.4$ Hz, $J_{6,6'}=12.4$ Hz, 1H, H-6), 4.05 (m, 1H, H-6′), 3.99 (m, 1H, H-5), 2.18 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (CH_3–*C*O), 170.7 (CH_3–*C*O), 169.1 (CH_3–*C*O), 168.7 (CH_3–*C*O), 154.7 (NH–*C*O–NH), 134.3, 131.9, 128.4 (4C) (aromatics), 90.9 (C-1), 70.5 (C-3), 69.6 (C-5), 67.6 (C-4), 61.8 (C-6), 51.7 (C-2), 20.7 (*C*H_3–CO), 20.6 (2C, *C*H_3–CO), 20.4 (*C*H_3–CO). Anal. Calcd for $C_{21}H_{24}Cl_2N_2O_{10}$: C, 47.12; H, 4.52; N, 5.23. Found: C, 47.00; H, 4.55; N, 5.15.

4.1.3. 1,3,4,6-Tetra-*O*-acetyl-2-[3-(2-chloro-6-methylphenyl)ureido]-2-deoxy-α-D-glucopyranose (18). From 2-chloro-6-methylphenyl isocyanate (**15**) and following the described procedure, **18** was obtained (99%), mp 162–165 °C, $[\alpha]_D$ +100 (*c* 0.5, $CHCl_3$); ν_{max} 3340, 3270, 1550 (NH), 1740 (C=O), 1230 (C–O–C), 1645 (NC=O), 1050, 1015 (C–O), 770 cm^{-1} (aromatics); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.10 (m, 3H, Ar), 7.01 (s, 1H, ArNH), 6.21 (d, $J_{1,2}=3.6$ Hz, 1H, H-1), 5.22–5.14 (m, 3H, NH, H-3, H-4), 4.39 (m, 1H, H-2), 4.22 (dd, $J_{5,6}=4.3$ Hz, $J_{6,6'}=12.5$ Hz, 1H, H-6), 4.04 (dd, $J_{5,6'}=2.1$ Hz, $J_{6,6'}=12.4$ Hz, 1H, H-6′), 3.96 (m, 1H, H-5), 2.23 (s, 3H, CH_3), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (CH_3–*C*O), 170.6 (CH_3–*C*O), 169.0 (CH_3–*C*O), 168.5 (CH_3–*C*O), 155.4 (NH–*C*O–NH), 139.0, 133.0, 132.3, 129.3, 128.3, 127.3 (aromatics), 90.8 (C-1), 70.4 (C-3), 69.5 (C-5), 67.5 (C-4), 61.6 (C-6), 51.7 (C-2), 20.5 (2C, *C*H_3–CO), 20.4 (2C, *C*H_3–CO), 18.3 (CH_3). Anal. Calcd for $C_{22}H_{27}ClN_2O_{10}$: C, 51.32; H, 5.29; N, 5.44. Found: C, 51.35; H, 5.36; N, 5.59.

4.1.4. 1-(2,6-Dimethylphenyl)-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-one (25). To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-[3-(2,6-dimethylphenyl)-ureido]-α-D-glucopyranose, **16**, (0.5 g, 1.0 mmol) in methanol (16 mL), was added a saturated solution of ammonia in methanol (16 mL). The reaction was controlled by TLC (chloroform–methanol 3:1). After ten hours at room temperature the mixture was evaporated to dryness and the residue treated with acetic acid (15 mL), and heated at ~100 °C (external bath) for 30 min. The solution was evaporated to dryness and the resulting solid was crystallized from 96% aqueous ethanol affording **25** (0.17 g, 55%), mp 245–247 °C, $[\alpha]_D$ +96.5 (*c* 0.5, DMF); ν_{max} 3480, 3380, 3250 (OH, NH), 1470 (NH), 1660 (C=O), 1080, 1030 (C–O), 1580, 790, 780 cm^{-1} (aromatics); ^1H NMR (400 MHz, DMSO-d_6) δ 7.21 (d, $J_{2,NH}=1.2$ Hz, 1H, NH), 7.15–7.07 (m, 3H, Ar), 5.65 (d, $J_{1,2}=6.2$ Hz, 1H, H-1), 5.21 (d, $J_{3,OH}=4.8$ Hz, 1H, C3–OH), 4.72 (d, $J_{5,OH}=6.0$ Hz, 1H, C5–OH), 4.45 (t, $J_{6,OH}=J_{6',OH}=5.6$ Hz, 1H, C6–OH), 4.10–4.07 (m, 2H, H-2, H-3), 3.86 (dd, $J_{3,4}=2.2$ Hz, $J_{4,5}=8.6$ Hz, 1H, H-4), 3.72 (m, 1H, H-5), 3.55 (m, 1H, H-6), 3.34 (m, 1H, H-6′), 2.18 (s, 3H, CH_3), 2.12 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.3 (C=O), 139.0, 136.7, 135.5, 128.2, 128.1, 127.8 (aromatics), 91.1 (C-1), 79.7 (C-4), 74.5 (C-3), 68.8 (C-5), 64.1 (C-6), 61.8 (C-2), 18.4 (CH_3), 17.7 (CH_3). Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.09; H, 6.64; N, 9.19.

4.1.5. 1-(2,6-Dichlorophenyl)-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]-imidazolidine-2-one (26). From **17** and following the procedure described for **25**, compound **26** was obtained (95%), mp 255–257 °C, $[\alpha]_D$ +89.0 (*c* 0.5, DMF); ν_{max} 3300 (OH, NH), 1470 (NH), 1695 (C=O), 1080, 1020, 1010 (C–O), 775 cm^{-1} (aromatics); ^1H NMR (400 MHz, DMSO-d_6) δ 7.59–7.40 (m, 4H, Ar, NH), 5.79 (d, $J_{1,2}=6.4$ Hz, 1H, H-1), 5.23 (d, $J_{3,OH}=5.1$ Hz, 1H, C3–OH), 4.74 (d, $J_{5,OH}=5.9$ Hz, 1H, C5–OH), 4.41 (t, $J_{6,OH}=J_{6',OH}=5.6$ Hz, 1H, C6–OH), 4.11 (d, $J_{1,2}=6.5$ Hz, 1H, H-2), 4.07 (m, 1H, H-3), 3.93 (dd, $J_{3,4}=2.0$ Hz, $J_{4,5}=8.7$ Hz, 1H, H-4), 3.78 (m, 1H, H-5), 3.53 (m, 1H, H-6), 3.33 (m, 1H, H-6′); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0 (C=O), 137.1, 134.9, 132.7, 130.6, 129.2, 128.9 (aromatics), 89.9 (C-1), 80.2 (C-4), 74.6 (C-3), 68.9 (C-5), 64.5 (C-6), 62.2 (C-2). Anal. Calcd for $C_{13}H_{14}Cl_2N_2O_5$: C, 44.72; H, 4.04; N, 8.02. Found: C, 44.59; H, 4.10; N, 7.87.

4.1.6. 1-(2-Chloro-6-methylphenyl)-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]-imidazolidine-2-one (27). From **18** and following the procedure described for **25**, compound **27** was obtained (83%) as mixture of rotamers with a 35:65 (*M*:*P*) ratio, mp 252–254 °C, $[\alpha]_D$ +87.5 (*c* 0.5, DMF); ν_{max} 3480, 3380, 3250 (OH, NH), 1475 (NH), 1660 (C=O), 1080, 1030, (C–O), 1585, 790, 780 cm^{-1} (aromatics); ^1H NMR (400 MHz, DMSO-d_6) δ 7.40–7.16 (m, 8H, Ar, NH, *M* and *P*), 5.73 (d, $J_{1,2}=6.4$ Hz, 1H, H-1, *M*), 5.71 (d, $J_{1,2}=6.3$ Hz, 1H, H-1, *P*), 5.24 (d, $J_{3,OH}=5.2$ Hz, 1H, C3–OH, *M*), 5.19 (d, $J_{3,OH}=4.8$ Hz, 1H, C3–OH, *P*), 4.73 (d, $J_{5,OH}=6.2$ Hz, 1H, C5–OH, *M*), 4.70 (d, $J_{5,OH}=5.8$ Hz, 1H, C5–OH, *P*), 4.46 (t, $J_{6,OH}=J_{6',OH}=5.6$ Hz, 1H, C6–OH,

M), 4.38 (t, $J_{6,OH}=J_{6',OH}=5.7$ Hz, 1H, C6–OH, *P*), 4.08 (m, 4H, H-2, H-3, *M* and *P*), 3.94 (dd, $J_{3,4}=2.2$ Hz, $J_{4,5}=8.7$ Hz, 1H, H-4, *P*), 3.87 (dd, $J_{3,4}=2.2$ Hz, $J_{4,5}=8.7$ Hz, 1H, H-4, *M*), 3.72 (m, 2H, H-5, *M* and *P*), 3.55 (m, 2H, H-6, *M* and *P*), 3.33 (m, 2H, H-6′, *M* and *P*), 2.24 (s, 3H, CH_3, *M*), 2.20 (s, 3H, CH_3, *P*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9 C=O, (*M*), 157.6 C=O, (*P*), 141.9, 139.8, 135.6, 133.7, 133.2, 129.6, 129.5, 129.3, 127.6, 127.5 (aromatics), 90.7 C-1 (*M*), 90.2 C-1 (*P*), 80.2 C-4 (*P*), 79.8 C-4 (*M*), 74.7 C-3 (*P*), 74.4 C-3 (*M*), 69.0 C-5 (*P*), 68.6 C-5 (*M*), 64.7 C-6 (*P*), 64.1 C-6 (*M*), 62.1 C-2 (*M*), 62.0 C-2 (*P*), 18.5 CH_3 (*M*), 18.0 CH_3 (*P*). Anal. Calcd for $C_{14}H_{17}ClN_2O_5$: C, 51.15; H, 5.21; N, 8.52. Found: C, 51.00; H, 5.24; N, 8.45.

4.1.7. 1-(2,6-Dimethylphenyl)-(3,5,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-one (28). To a solution of 1-(2,6-dimethylphenyl)-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-one, **25** (0.8 g, 2.6 mmol) in pyridine (10.0 mL), cooled at −20 °C, was added acetic anhydride (8.0 mL) and the reaction mixture was kept at that temperature for 12 h. Then it was poured into ice-water and the resulting solid was filtered and washed with cold water and identified as **28** (0.8 g, 71%). Recrystallized from 96% aqueous ethanol it had mp 230–232 °C, $[\alpha]_D$ +116.0 (*c* 0.5, $CHCl_3$); ν_{max} 3600–3100 (H_2O, NH),[15] 1435 (NH), 1750 (C=O), 1710 (NC=O), 1230 (C–O–C), 1030, (C–O), 1580, 1470, 770 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20–7.10 (m, 3H, Ar), 6.13 (d, $J_{2,NH}=1.8$ Hz, 1H, NH), 5.80 (d, $J_{1,2}=6.4$ Hz, 1H, H-1), 5.36 (d, $J_{3,4}=2.8$ Hz, 1H, H-3), 5.20 (m, 1H, H-5), 4.59 (m, 2H, H-4, H-6), 4.29 (dd, $J_{1,2}=6.4$, $J_{2,NH}=2.3$ Hz, 1H, H-2), 4.04 (dd, $J_{5,6'}=4.3$ Hz, $J_{6,6'}=12.4$ Hz, 1H, H-6′), 2.32 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (CH_3–*C*O), 169.8 (CH_3–*C*O), 169.7 (CH_3–*C*O), 158.9 (C=O), 138.8, 136.2, 133.8, 128.9, 128.7 (2C) (aromatics), 92.1 (C-1), 75.8 (C-3), 75.7 (C-4), 67.6 (C-5), 62.9 (C-6), 60.5 (C-2), 20.8 (2C, *C*H_3–CO), 20.7 (*C*H_3–CO), 18.4 (CH_3), 18.0 (CH_3). Anal. Calcd for $C_{21}H_{26}N_2O_8\cdot\frac{1}{2}H_2O$: C, 56.88; H, 6.14; N, 6.32. Found: C, 56.56; H, 5.98; N, 5.92.

4.1.8. 1-(2,6-Dichlorophenyl)-(3,5,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-one (29). From **26** and following the procedure described for **28**, compound **29** was obtained (96%), mp 214–216 °C, $[\alpha]_D$ +102.0 (*c* 0.5, $CHCl_3$), ν_{max} 3380 (NH), 1740 (C=O), 1690 (NC=O), 1220 (C–O–C), 1055, 1030, (C–O), 1560, 1470, 785, 770 cm^{-1}(aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.26 (m, 3H, Ar), 6.17 (d, $J_{2,NH}=1.7$ Hz, 1H, NH), 6.06 (d, $J_{1,2}=6.5$ Hz, 1H, H-1), 5.34 (d, $J_{3,4}=2.8$ Hz, 1H, H-3), 5.24 (m, 1H, H-5), 4.70 (dd, $J_{3,4}=2.8$ Hz, $J_{4,5}=9.4$ Hz, 1H, H-4), 4.55 (dd, $J_{5,6}=2.4$ Hz, $J_{6,6'}=12.3$ Hz, 1H, H-6), 4.31 (dd, $J_{2,NH}=2.2$ Hz, $J_{1,2}=6.5$ Hz, 1H, H-2), 4.03 (dd, $J_{5,6'}=5.4$ Hz, $J_{6,6'}=12.3$ Hz, 1H, H-6′), 2.07 (s, 6H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (CH_3–*C*O), 169.8 (CH_3–*C*O), 169.7 (CH_3–*C*O), 157.4 (C=O), 137.2, 135.1, 131.4, 130.2, 129.1, 128.7 (aromatics), 90.5 (C-1), 76.2 (C-3), 75.7 (C-4), 67.5 (C-5), 63.1 (C-6), 60.7 (C-2), 20.8 (3C, *C*H_3–CO). Anal. Calcd for $C_{19}H_{20}Cl_2N_2O_8$: C, 48.02; H, 4.24; N, 5.89. Found: C, 47.82; H, 4.21; N, 5.90.

4.1.9. 1-(2-Chloro-6-methylphenyl)-(3,5,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-one (30). From **27** and following the procedure described for **28**, the titled compound **30** was obtained as a mixture of rotamers in a ∼1:3 (*M*: *P*) ratio (88%). Both rotamers were isolated by preparative TLC (benzene–acetone 3:1). After extracting silica-gel with ethyl acetate and evaporating to dryness, they were crystallized from 96% aqueous ethanol.

Compound **30***P*. Cubic transparent crystals, mp 193–196 °C, $[\alpha]_D$ +93.5 (*c* 0.5, $CHCl_3$), $R_f=0.3$ (benzene–acetone 3:1); ν_{max} 3390 (NH), 1740 (C=O), 1690 (NC=O), 1220 (C–O–C), 1070, 1045, 1030 (C–O), 1590, 1560, 1470, 780, 750, 710 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 3H, Ar), 5.85 (d, $J_{1,2}=6.4$ Hz, 1H, H-1), 5.80 (d, $J_{2,NH}=1.6$ Hz, 1H, NH), 5.33 (d, $J_{3,4}=2.8$ Hz, 1H, H-3), 5.24 (m, 1H, H-5), 4.74 (dd, $J_{3,4}=2.8$ Hz, $J_{4,5}=9.4$ Hz, 1H, H-4), 4.56 (dd, $J_{5,6}=2.4$ Hz, $J_{6,6'}=12.3$ Hz, 1H, H-6), 4.29 (dd, $J_{2,NH}=2.2$ Hz, $J_{1,2}=6.4$ Hz, 1H, H-2), 4.04 (dd, $J_{5,6'}=5.6$ Hz, $J_{6,6'}=12.3$ Hz, 1H, H-6′), 2.27 (s, 3H, CH_3), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (CH_3–*C*O), 169.9 (CH_3–*C*O), 169.7 (CH_3–*C*O), 157.7 (C=O), 138.8, 135.8, 132.1, 129.6, 129.5, 128.2 (aromatics), 90.9 (C-1), 76.3 (C-3), 76.0 (C-4), 67.7 (C-5), 63.2 (C-6), 60.5 (C-2), 20.8 (2C, *C*H_3–CO), 20.7 (*C*H_3–CO), 18.2 (CH_3). Anal. Calcd for $C_{20}H_{23}ClN_2O_8$: C, 52.81; H, 5.10; N, 6.16. Found: C, 52.80; H, 5.06; N, 6.19.

Compound **30***M*. Needle shaped crystals, mp 170 °C, $[\alpha]_D$ +109 (*c* 0.5, $CHCl_3$), $R_f=0.4$ (benzene- acetone 3:1), ν_{max} 3300 (NH), 1730 (C=O), 1690 (NC=O), 1230 (C–O–C), 1040 (C–O), 1590, 1570, 1480, 750 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 3H, Ar), 6.35 (s, 1H, NH), 5.99 (d, $J_{1,2}=6.4$ Hz, 1H, H-1), 5.35 (d, $J_{3,4}=2.7$ Hz, 1H, H-3), 5.21 (m, 1H, H-5), 4.58 (m, 2H, H-4, H-6), 4.33 (dd, $J_{2,NH}=2.1$ Hz, $J_{1,2}=6.4$ Hz, 1H, H-2), 4.04 (dd, $J_{5,6'}=4.4$ Hz, $J_{6,6'}=12.4$ Hz, 1H, H-6′), 2.36 (s, 3H, CH_3), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (CH_3–*C*O), 169.8 (CH_3–*C*O), 169.7 (CH_3–*C*O), 158.7 (C=O), 141.3, 133.6, 132.8, 129.6 (2C), 127.8 (aromatics), 91.9 (C-1), 75.9 (C-3), 75.6 (C-4), 67.6 (C-5), 63.0 (C-6), 60.7 (C-2), 20.7 (3C, *C*H_3–CO), 18.6 (CH_3). HRMS: *m/z* found 455.1225. $M+H^+$ required for $C_{20}H_{23}ClN_2O_8$: 455.1221.

4.1.10. 1,3,4,6-Tetra-*O*-acetyl-2-[3-(2-chloro-6-methylphenyl)thioureido]-2-deoxy-β-D-glucopyranose (34). To a solution of $NaHCO_3$ (2.74 g, 32.6 mmol) in water (130 mL) was added under stirring 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride **31**,[17] (10.4 g, 27.1 mmol) and dichloromethane (130 mL), keeping the stirring for 30 min. The organic layer was separated and the aqueous extracted with dichloromethane (50 mL). The combined organic fractions were washed with water and dried over anhydrous magnesium sulfate and concentrated to approx. 50 mL. 2-Chloro-6-methylphenyl isothiocyanate, **33**, (5.0 g, 27.2 mmol) was then added and the reaction mixture was left at room temperature for 48 h. Compound **34** separated spontaneously as a white solid, which was filtered and washed with cold diethyl ether (75%), mp 174–176 °C, $[\alpha]_D$ −15.0 (*c* 1.0, $CHCl_3$); ν_{max} 3300, 2940, 1530 (NH), 1730 (C=O), 1230 (C–O–C), 1070, 1030 (C–O), 770 cm^{-1} (aromatics); ^{1}H NMR

(400 MHz, $CDCl_3$, $T=333$ K) δ 7.50 (d, $J_{2,NH}=6.4$ Hz, 1H, NH), 7.34–7.19 (m, 3H, Ar), 5.64 (m, 2H, H-1, NH), 5.10 (m, 3H, H-2, H-3, H-4), 4.21 (dd, $J_{5,6}=4.7$, $J_{6,6'}=12.4$ Hz, 1H, H-6), 4.12 (dd, $J_{5,6'}=2.5$, $J_{6,6'}=12.4$ Hz, 1H, H-6′), 3.77 (m, 1H, H-5), 2.24 (s, 3H, CH_3), 2.11 (s, 3H, OAc), 2.05 (s, 6H, OAc), 1.98 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$, $T=295$ K) δ 182.3 (C=S), 171.1 (CH_3–*C*O), 170.7 (2C, CH_3–*C*O), 169.4 (CH_3–*C*O), 139.5, 133.9, 129.7 (2C), 128.1 (2C) (aromatics), 92.5 (C-1), 72.6 (C-3, C-5), 68.1 (C-4), 61.6 (C-6), 57.8 (C-2), 20.9 (*C*H_3–CO), 20.8 (*C*H_3–CO), 20.7 (*C*H_3–CO), 20.5 (*C*H_3–CO) 18.0 (CH_3). Anal. Calcd for $C_{22}H_{27}ClN_2O_9S$: C, 49.77; H, 5.13; N, 5.28; S, 6.04. Found: C, 49.66; H, 5.16; N, 5.28; S, 5.80.

4.1.11. (4*R*,5*R*)-1-(2-Chloro-6-methylphenyl)-5-hydroxy-4-(D-*arabino*-tetritol-1-yl)imidazolidine-2-thione (35). *Procedure A*. To a solution of 2-amino-2-deoxy-α-D-glucopyranose hydrochloride, **6**, (10.8 g, 50.0 mmol) in water (60.0 mL) was added $NaHCO_3$ (4.6 g, 55.0 mmol) and 2-chloro-6-methylphenyl isothiocyanate (50.0 mmol) under stirring. The mixture was diluted with ethanol (90.0 mL) to obtain a homogeneous solution that was then heated at 45 °C (external bath) for 30 min. When the mixture was left to room temperature, **35** spontaneously crystallized as a white solid, mixture of two rotamers (72%) in a ~3:1(*P*:*M*) ratio, mp 173–175 °C (ethanol 96%), $[\alpha]_D$ −23.5 (*c* 1.0, DMF), ν_{max} 3500–3000 (OH, NH), 1450 (NH), 1470 and 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H, NH, *P*), 8.17 (s, 1H, NH, *M*), 7.37–7.25 (m, 6H, Ar, *P* and *M*), 6.80 (d, $J_{5,OH}=7.4$ Hz, 1H, C5–OH, *P*), 6.62 (d, $J_{5,OH}=7.9$ Hz, 1H, C5–OH, *M*), 5.26 (d, $J_{5,OH}=7.2$ Hz, 2H, H-5, *P* and *M*), 4.85 (d, $J_{1',OH}=6.9$ Hz, 1H, C1′–OH, *M*), 4.74 (d, $J_{1',OH}=6.5$ Hz, 1H, C1′–OH, *P*), 4.59 (d, $J_{2',OH}=5.6$ Hz, 1H, C2′–OH, *P*), 4.47 (d, $J_{3',OH}=8.3$ Hz, 1H, C3′–OH, *P*), 4.40 (t, $J_{4',OH}=J_{4'',OH}=5.7$ Hz, 1H, C4′–OH, *P*), 3.80–3.31 (m, 12H, H-4, H-1′, H-2′, H-3′, H-4′, H-4″, *P* and *M*), 2.36 (s, 3H, CH_3, *P*), 2.18 (s, 3H, CH_3, *M*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.6 (C=S, *M*), 180.2 (C=S, *P*), 142.7, 139.8, 136.1, 134.8, 134.6, 133.2, 129.4 (3C), 129.3, 127.6, 127.3 (aromatics, *P* and *M*), 87.7 (C-5, *M*), 87.0 (C-5, *P*), 71.4 (C-1′, *M*), 71.2 (C-1′, *P*), 70.2 (C-2′, *P* and *M*), 70.0 (C-3′, *P*), 69.7 (C-3′, *M*), 66.1 (C-4, *M*), 65.7 (C-4, *P*), 63.6 (C-4′, *P*), 63.4 (C-4′, *M*), 19.3 (CH_3, *P*), 18.1 (CH_3, *M*). Anal. Calcd for $C_{14}H_{19}ClN_2O_5S$: C, 46.35; H, 5.28; N, 7.78; S, 8.84. Found: C, 46.08; H, 5.34; N, 7.55; S, 8.63.

Procedure B. To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-[3-(2-chloro-6-methylphenyl)thioureido]-β-D-glucopyranose (**34**) (5.4 g, 10.2 mmol) in methanol (160 mL), was added under vigorous stirring a saturated solution of ammonia in methanol (160 mL). The process was followed by TLC (chloroform–methanol, 3:1) and after 6 h at room temperature the reaction mixture was evaporated to dryness. The crude was crystallized from 96% aqueous ethanol. The title compound was filtered and washed with cold 96% aqueous ethanol and diethyl ether (3.5 g, 94%).

4.1.12. (4*R*,5*R*)-4-(1,2,3,4-Tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-5-acetoxy-1-(2-chloro-6-methylphenyl)-imidazolidine-2-thione (36*P*). To a solution of **35** (2.4 mmol) in pyridine (10.0 mL), cooled at −20 °C for 15 min, was added acetic anhydride (6.0 mL) and the reaction mixture was kept at this temperature for 24 h. The mixture was then poured into ice-water and the resulting solid was filtered and washed with cold water affording **36** (94%) as a rotamer mixture in a ~6:1 (*P*:*M*) ratio. Fractional crystallization from 96% aqueous ethanol allowed the major rotamer **36*P*** to be isolated, mp 181–183 °C, $[\alpha]_D$ +28.0 (*c* 0.5, $CHCl_3$), ν_{max} 3320 (NH), 1760, 1730 (C=O), 1240, 1220, 1200 (C–O–C), 1500, 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H, NH), 7.35–7.19 (m, 3H, Ar), 6.58 (d, $J_{4,5}=1.4$ Hz, 1H, H-5), 5.65 (dd, $J_{4,1'}=8.8$, $J_{1',2'}=1.6$ Hz, 1H, H-1′), 5.32 (dd, $J_{1',2'}=1.5$ Hz, $J_{2',3'}=9.0$ Hz, 1H, H-2′), 5.00 (m, 1H, H-3′), 4.21 (m, 2H, H-4′, H-4″), 3.93 (dd, $J_{4,5}=1.4$ Hz, $J_{4,1'}=8.7$ Hz, 1H, H-4), 2.37 (s, 3H, CH_3), 2.16 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.03 (s, 6H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7 (C=S), 170.6 (CH_3–*C*O), 169.8 (CH_3–*C*O), 169.7 (2C, CH_3–*C*O), 169.3 (CH_3–*C*O), 141.3, 133.5, 132.8, 130.1, 129.5, 127.7, (aromatics), 85.6 (C-5), 68.7 (C-2′), 68.3 (C-1′), 67.6 (C-3′), 61.2 (C-4′), 61.1 (C-4), 20.8 (*C*H_3–CO), 20.7 (*C*H_3–CO), 20.6 (3C, *C*H_3–CO), 18.7 (CH_3). Anal. Calcd for $C_{24}H_{29}ClN_2O_{10}S$: C, 50.31; H, 5.10; N, 4.89; S, 5.59. Found: C, 50.58; H, 5.05; N, 4.96; S, 5.14.

4.1.13. Transformation of (4*R*,5*R*)-4-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-5-acetoxy-1-(2-chloro-6-methylphenyl)imidazolidine-2-thione (36) into 4-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-1-(2-chloro-6-methylphenyl)imidazoline-2-thione (37). A solution of **36** (0.08 g) in DMSO-d_6 (0.5 mL) was heated at 80 °C and the transformation was monitored by ^{1}H NMR. Compound **37** was characterized by NMR spectroscopy. ^{1}H NMR (400 MHz, DMSO-d_6, 295 K) δ 9.92 (s, 1H, NH), 7.46–7.32 (m, 6H, Ar, *P* and *M*), 7.09 (s, 1H, H-5, *P*), 7.07 (s, 1H, H-5, *M*), 5.90 (d, $J_{1',2'}=2.7$ Hz, 1H, H-1′, *M*), 5.89 (d, $J_{1',2'}=3.5$ Hz, 1H, H-1′, *P*), 5.47 (dd, $J_{1',2'}=3.4$ Hz, $J_{2',3'}=8.1$ Hz, 1H, H-2′, *P*), 5.46 (dd, $J_{1',2'}=3.3$ Hz, $J_{2',3'}=8.0$ Hz, 1H, H-2′, *M*), 5.16 (m, 2H, H-3′, *P* and *M*), 4.21 (dd, $J_{3',4'}=2.7$ Hz, $J_{4',4''}=12.5$ Hz, 2H, H-4′, *P* and *M*), 4.15 (dd, $J_{3',4'}=5.0$ Hz, $J_{4',4''}=12.4$ Hz, 1H, H-4″, *M*), 4.14 (dd, $J_{3',4''}=5.1$ Hz, $J_{4',4''}=12.4$ Hz, 1H, H-4″, *P*), 2.07 (s, 3H, CH_3), 2.02 (s, 6H, OAc), 2.01 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.97 (s, 3H, OAc), 1.95 (s, 6H, OAc).

4.1.14. 4-(1,2,3,4-Tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-1-(2-chloro-6-methylphenyl)imidazoline-2-thione (37*P*). To a solution of **36** (0.6 g, 1.05 mmol) in benzene (23 mL) was added $KHCO_3$ (0.2 g) and heated at reflux under stirring for 20 h. The reaction was followed by TLC (benzene–acetone, 3:1). The salt was filtered and the organic phase washed twice with water, dried over magnesium sulphate and evaporated to dryness. The crude was crystallized from 96% aqueous ethanol, affording a mixture of both rotamers (0.32 g, 60%). Recrystallization from 96% aqueous ethanol afforded the major rotamer *P* (0.08 g, 42%), mp 176–178 °C, $[\alpha]_D$ −89.4 (*c* 0.5, $CHCl_3$), ν_{max} 3200 (NH), 1750 (C=O), 1270, 1210 (C–O–C), 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H, NH), 7.38–7.25 (m, 3H, Ar), 6.64 (s, 1H, H-5), 6.07 (d, $J_{1',2'}=3.1$ Hz, 1H, H-1′), 5.48 (dd, $J_{1',2'}=3.1$ Hz, $J_{2',3'}=8.6$ Hz, 1H, H-2′), 5.20 (m, 1H, H-3′), 4.23 (dd, $J_{3',4'}=2.7$ Hz, $J_{4',4''}=12.6$ Hz, 1H, H-4′), 4.13 (dd, $J_{3',4''}=4.3$ Hz, $J_{4',4''}=12.5$ Hz, 1H,

H-4″), 2.18 (s, 3H, CH_3), 2.17 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (CH_3–*C*O), 169.9 (CH_3–*C*O), 169.7 (CH_3–*C*O), 169.5 (CH_3–*C*O), 163.3 (C=S), 139.2, 133.6, 132.7, 130.5, 129.4, 127.7 (aromatics), 124.5 (C-4), 116.1 (C-5), 70.6 (C-2′), 68.2 (C-3′), 64.4 (C-1′), 61.5 (C-4′), 20.8 (*C*H_3–CO), 20.7 (*C*H_3–CO), 20.6 (2C, *C*H_3–CO), 18.3 (CH_3). Anal. Calcd for $C_{22}H_{25}ClN_2O_8S$: C; 51.51, H; 4.91, N; 5.46, S; 6.25. Found: C; 51.14, H; 5.00, N; 5.60, S; 6.18.

4.1.15. 1-(2-Chloro-6-methylphenyl)-4-(D-*arabino*-tetritol-1-yl)imidazoline-2-thione (38*P*). Compound **37***P* (0.11 g, 0.21 mmol) was dissolved in methanol (3 mL), a saturated solution of ammonia in methanol (5.5 mL) was added and the mixture kept at room temperature overnight. The reaction was controlled by TLC (chloroform–methanol, 3:1). The mixture was then evaporated to dryness and crystallized from 96% aqueous ethanol, affording pure compound **38***P* (0.05 g, 62%), mp 207–209 °C, $[\alpha]_D$ −73.4 (*c* 0.5, DMF), ν_{max} 3530, 3500 (NH, OH), 1610 (C=C), 1120–1000 (C–O), 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (bs, 1H, NH), 7.47–7.34 (m, 3H, Ar), 6.82 (s, 1H, H-5), 5.09 (d, $J_{1',OH}$=6.9 Hz, 1H, C1′–OH), 4.71(d, $J_{1',OH}$=5.9 Hz, 1H, H-1′), 4.66 (s, 1H, C2′–OH), 4.60 (s, 1H, C3′–OH), 4.39 (t, $J_{4',OH}$=$J_{4'',OH}$= 5.3 Hz, 1H, C4′–OH), 3.62–3.35 (m, 4H, H-2′, H-3′, H-4′, H-4″), 2.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7 (C=S), 139.2, 134.8, 132.2, 132.1, 130.3, 129.5 (aromatics), 127.6 (C-4), 115.2 (C-5), 73.5 (C-2′), 71.4 (C-3′), 64.4 (C-1′), 63.4 (C-4′), 18.3 (CH_3). Anal. Calcd for $C_{14}H_{17}ClN_2O_4S$: C; 48.77, H; 4.97, N; 8.12, S; 9.30. Found: C; 48.31, H; 5.00, N; 8.12, S; 9.18.

4.1.16. (4*R*,5*R*)-1-(2,6-Dichlorophenyl)-5-hydroxy-4-(D-*arabino*-tetritol-1-yl)imidazolidine-2-thione (40). From 2,6-dichlorophenyl isothiocyanate (**39**) and following the procedure described for **35**, compound **40** was obtained (71%) by spontaneous crystallization when the mixture was cooled to room temperature: mp 201–202 °C (96% aqueous ethanol), $[\alpha]_D$ −20.5 (*c* 1.0, DMF), ν_{max} 3460–3000 (OH, NH), 1470 (NH), 1550 and 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H, NH), 7.56–7.39 (m, 3H, Ar), 6.75 (d, $J_{5,OH}$=7.3 Hz, 1H, C5–OH), 5.30 (dd, $J_{4,5}$=3.5 Hz, $J_{5,OH}$=7.3 Hz, 1H, H-5), 4.76 (d, $J_{1',OH}$= 6.7 Hz, 1H, C1′–OH), 4.59 (d, $J_{2',OH}$=5.1 Hz, 1H, C2′–OH), 4.50 (d, $J_{3',OH}$=8.0 Hz, 1H, C3′–OH), 4.40 (t, $J_{4',OH}$=$J_{4'',OH}$=4.9 Hz, 1H, C4′–OH), 3.83–3.39 (m, 6H, H-4, H-1′, H-2′, H-3′, H-4′, H-4″); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.3 (C=S), 137.9, 135.0, 133.8, 130.6, 129.1, 128.7 (aromatics), 87.0 (C-5), 71.2 (C-1′), 70.4 (C-2′), 69.9 (C-3′), 65.9 (C-4), 63.6 (C-4′). Anal. Calcd for $C_{13}H_{16}Cl_2N_2O_5S$: C, 40.74; H, 4.21; N, 7.31; S, 8.37. Found: C, 40.49; H, 4.02; N, 7.35; S, 8.61.

4.1.17. (4*R*,5*R*)-4-(1,2,3,4-Tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-5-acetoxy-1-(2,6-dichlorophenyl)imidazolidine-2-thione (41). From **40** and following the procedure described for **36**, compound **41** was obtained (97%), mp 191–193 °C, $[\alpha]_D$ +63.5 (*c* 0.5, $CHCl_3$), ν_{max} 3300 (NH), 1750, 1720 (C=O), 1260, 1200 (C–O–C), 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, NH), 7.46–7.27 (m, 3H, Ar), 6.50 (s, 1H, H-5), 5.60 (dd, $J_{4,1'}$=9.5 Hz, $J_{1',2'}$=1.6 Hz, 1H, H-1′), 5.34 (dd, $J_{1',2'}$= 1.6 Hz, $J_{2',3'}$=9.2 Hz, 1H, H-2′), 5.00 (m, 1H, H-3′), 4.20 (m, 2H, H-4′, H-4″), 3.93 (d, $J_{4,1'}$=9.4 Hz, 1H, H-4), 2.17 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4 (C=S), 170.6 (CH_3–*C*O), 169.8 (2C, CH_3–*C*O), 169.5 (2C, CH_3–*C*O), 137.1, 135.4, 132.8, 130.7, 129.0, 128.7 (aromatics), 84.4 (C-5), 68.5 (C-1′), 68.1 (C-2′), 67.1 (C-3′), 61.1 (C-4′), 61.0 (C-4), 20.8 (*C*H_3–CO), 20.7 (*C*H_3–CO), 20.6 (*C*H_3–CO), 20.5 (*C*H_3–CO), 20.4 (*C*H_3–CO). Anal. Calcd for $C_{23}H_{26}Cl_2N_2O_{10}S$: C, 46.55; H, 4.42; N, 4.72; S, 5.40. Found: C, 46.40; H, 4.60; N, 4.79; S, 5.53.

4.1.18. 1-(2-Chloro-6-methylphenyl)-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-thione (42). A solution of **35** (1.5 g, 4.13 mmol) in aqueous acetic acid (53.0 mL) was heated at ~100 °C (external bath) for 30 min. The mixture was then evaporated to dryness and the residue crystallized from 96% aqueous ethanol, affording a crystalline product that was filtered and washed with cold ethanol, being a mixture of both rotamers of **42** (1.1 g, 75%).

Compound **42***P*. From a mixture of atropisomers of **42** (1.8 g, 5.12 mmol) the major rotamer was separated by fractional crystallization from 96% aqueous ethanol (0.342 g, 19%). An analytic sample showed R_f=0.6, mp 238–240 °C, $[\alpha]_D$ +92 (*c* 0.5, DMF), ν_{max} 3480, 3320, 3200 (OH, NH), 1475 (NH), 1040 (C–O), 790 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H, NH), 7.36–7.27 (m, 3H, Ar), 5.88 (d, $J_{1,2}$=6.6 Hz, 1H, H-1), 5.34 (d, $J_{3,OH}$=4.7 Hz, 1H, C3–OH), 4.74 (d, $J_{5,OH}$=6.1 Hz, 1H, C5–OH), 4.42 (t, $J_{6,OH}$=$J_{6'\text{-}OH}$=5.6 Hz, 1H, C6–OH), 4.27 (d, $J_{1,2}$=6.7 Hz, 1H, H-2), 4.13 (m, 1H, H-3), 3.85 (dd, $J_{3,4}$=2.3 Hz, $J_{4,5}$=8.7 Hz, 1H, H-4), 3.75 (m, 1H, H-5), 3,62 (m, 1H, H-6), 3.31 (m, 1H, H-6′), 2.17 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.5 (C=S), 139.6, 135.4, 134.8, 129.6, 129.5, 127.6 (aromatics), 94.1 (C-1), 80.5 (C-4), 74.1 (C-3), 68.8 (C-5), 66.3 (C-2), 64.5 (C-6), 17.9 (CH_3). Anal. Calcd for $C_{14}H_{17}ClN_2O_4S$: C, 48.77; H, 4.97; N, 8.12; S, 9.30. Found: C, 49.07; H, 5.14; N, 8.23; S, 8.99.

Rotamer **42***P* was also obtained by the following procedure: to a solution of **44***P* (0.47 g, 0.99 mmol) in methanol (16 mL), was added a saturated solution of ammonia in methanol (16 mL) and the mixture kept at room temperature overnight. The reaction was followed by TLC (chloroform–methanol, 3:1). After that time it was evaporated to dryness and the residue crystallized from 96% aqueous ethanol, affording **42***P* (0.28 g, 81%).

Compound **42***M*. To a solution of **44***M* (0.15 g, 0.31 mmol) in methanol (5 mL) was added a saturated solution of ammonia in methanol (5 mL) and the mixture was kept at room temperature overnight. The reaction was controlled by TLC (chloroform–methanol, 3:1). After that time it was evaporated to dryness and the residue crystallized from 96% aqueous ethanol, affording **42***M* (0.07g, 64%), R_f=0.7, mp 209–211 °C, $[\alpha]_D$ +193.0 (*c* 0.7, DMF), ν_{max} 3500–3000 (OH, NH), 1500 (NH), 1030 (C–O), 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H, NH), 7.42–7.27 (m, 3H, Ar), 5.85 (d, $J_{1,2}$=6.6 Hz, 1H, H-1), 5.40 (d,

$J_{3,OH}$=5.3 Hz, 1H, C3–OH), 4.78 (d, $J_{5,OH}$=6.0 Hz, 1H, C5–OH), 4.50 (t, $J_{6,OH}$=$J_{6',OH}$=5.5 Hz, 1H, C6–OH), 4.28 (d, $J_{1,2}$=6.6 Hz, 1H, H-2), 4.15 (dd, $J_{3,4}$=2.1 Hz, $J_{3,OH}$= 5.2 Hz, 1H, H-3), 3.78 (dd, $J_{3,4}$=2.1 Hz, $J_{4,5}$=8.7 Hz, 1H, H-4), 3.75–3.53 (m, 3H, H-5, H-6, H-6′), 2.29 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.6 (C=S), 141.9, 134.8, 132.8, 129.8, 129.6, 127.4 (aromatics), 94.4 (C-1), 80.3 (C-4), 73.9 (C-3), 68.3 (C-5), 66.3 (C-2), 63.9 (C-6), 18.8 (CH_3). Anal. Calcd for $C_{14}H_{17}ClN_2O_4S$: C, 48.77; H, 4.97; N, 8.12; S, 9.30. Found: C, 48.98; H, 5.11; N, 7.99; S, 8.93.

4.1.19. 1-(2,6-Dichlorophenyl)-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-thione (43). A solution of **40** (1.0 g, 2.61 mmol) in aqueous acetic acid (30%, 33 mL), was heated at 100 °C (external bath) for 30 min. The solution was then evaporated to dryness and the white residue obtained was crystallized from 96% aqueous ethanol (0.67 g, 70%). An analytic sample obtained by recrystallization from 96% aqueous ethanol showed mp 245–246 °C, $[\alpha]_D$ +151.2 (*c* 0.5, DMF), ν_{max} 3400–3000 (OH, NH), 1560, 1295 (thioamide), 1440 (NH), 1500, 770 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H, NH), 7.61–7.42 (m, 3H, Ar), 5.91 (d, $J_{1,2}$= 6.6 Hz, 1H, H-1), 5.38 (d, $J_{3,OH}$=5.0 Hz, 1H, C3–OH), 4.77 (d, $J_{5,OH}$=5.9 Hz, 1H, C5–OH), 4.45 (t, $J_{6,OH}$=$J_{6'-OH}$= 5.5 Hz, 1H, C6–OH), 4.29 (d, $J_{1,2}$=6.7 Hz, 1H, H-2), 4.14 (d, $J_{3,4}$=2.4 Hz, 1H, H-3), 3.86–3.30 (m, 4H, H-4, H-5, H-6, H-6′); ^{13}C NMR (50.33 MHz, DMSO-d_6) δ 181.4 (C=S), 137.3, 134.8, 133.6, 131.0, 129.2, 128.9 (aromatics), 93.8 (C-1), 80.6 (C-4), 74.1 (C-3), 68.7 (C-5), 66.5 (C-2), 64.4 (C-6). Anal. Calcd for $C_{13}H_{14}Cl_2N_2O_4S$: C, 42.75; H, 3.86; N, 7.67; S, 8.78. Found: C, 42.68; H, 3.75; N, 7.74; S, 8.72.

4.1.20. 3,5,6-Tri-*O*-acetyl-1-(2-chloro-6-methylphenyl)-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-thione (44). From **42** and following the procedure described for **28**, compound **44** was obtained (85%) as a mixture of rotamers in a ~1:4 (*M*:*P*) ratio. From a fraction of this mixture (1.3 g) both rotamers were separated by flash chromatography (ethyl acetate–hexane 1:2).

Compound **44***P*. R_f=0.6, (1.0 g, 78%). Recrystallized from 96% aqueous ethanol, mp 173–175 °C, $[\alpha]_D$ +125.4 (*c* 0.5, $CHCl_3$), ν_{max} 3310 (NH), 1740 (C=O), 1230 (C–O–C), 1050, 1030 (C–O), 1480, 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 4H, Ar and NH), 5.97 (d, $J_{1,2}$=6.7 Hz, 1H, H-1), 5.36 (d, $J_{3,4}$=2.9 Hz, 1H, H-3), 5.27 (m, 1H, H-5), 4.72 (dd, $J_{3,4}$=2.9, $J_{4,5}$=9.3 Hz, 1H, H-4), 4.60 (dd, $J_{5,6}$=2.4 Hz, $J_{6,6'}$=12.3 Hz, 1H, H-6), 4.44 (dd, $J_{1,2}$=6.6 Hz, $J_{2,3}$=1.0 Hz, 1H, H-2), 4.03 (dd, $J_{5,6'}$= 5.5 Hz, $J_{6,6'}$=12.4 Hz, 1H, H-6′), 2.25 (s, 3H, CH_3), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9 (C=S), 170.6 (CH_3–*C*O), 169.8 (CH_3–*C*O), 169.6 (CH_3–*C*O), 138.5, 135.6, 133.4, 129.9, 129.5, 128.2 (aromatics), 94.7 (C-1), 76.7 (C-3), 75.4 (C-4), 67.5 (C-5), 64.3 (C-2), 62.9 (C-6), 20.7 (2C, *C*H_3–CO), 20.6 (*C*H_3–CO), 18.1 (CH_3). Anal. Calcd for $C_{20}H_{23}ClN_2O_7S$: C, 51.01; H, 4.92; N, 5.95; S, 6.81. Found: C, 51.33; H, 4.81; N, 5.96; S, 6.86. HRMS: *m*/*z* found 471.1001. M+H$^+$ for $C_{20}H_{23}ClN_2O_7S$ required 471.0993.

Compound **44***M*. R_f=0.7, (0.20 g, 16%), mp 88 °C, $[\alpha]_D$ +182 (*c* 0.5, $CHCl_3$), ν_{max} 3320 (NH), 1740 (C=O), 1230 (C–O–C), 1030, (C–O), 1470, 770, 730 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 4H, Ar and NH), 6.18 (d, $J_{1,2}$=6.7 Hz, 1H, H-1), 5.44 (d, $J_{3,4}$=2.9 Hz, 1H, H-3), 5.31 (m, 1H, H-5), 4.68 (dd, $J_{5,6}$=2.3 Hz, $J_{6,6'}$= 12.4 Hz, 1H, H-6), 4.61 (dd, $J_{3,4}$=2.9 Hz, $J_{4,5}$=9.2 Hz, 1H, H-4), 4.55 (d, $J_{1,2}$=6.7 Hz, 1H, H-2), 4.09 (dd, $J_{5,6'}$= 4.3 Hz, $J_{6,6'}$=12.4 Hz, 1H, H-6′), 2.45 (s, 3H, CH_3), 2.15 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.09 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6 (C=S), 170.5 (CH_3–*C*O), 169.7 (CH_3–*C*O), 169.5 (CH_3–*C*O), 141.2, 133.9, 133.0, 129.9, 129.5, 127.7 (aromatics), 95.4 (C-1), 76.4 (C-3), 75.1 (C-4), 67.4 (C-5), 64.5 (C-2), 62.7 (C-6), 20.6 (2C, *C*H_3–CO), 20.5 (*C*H_3–CO), 18.6 (CH_3). HRMS: *m*/*z* found 471.0987. M+H$^+$ required for $C_{20}H_{23}ClN_2O_7S$ 471.0993.

4.1.21. 3,5,6-Tri-*O*-acetyl-1-(2,6-dichlorophenyl)-(1,2-dideoxy-α-D-glucofurano)[2,1-*d*]imidazolidine-2-thione (45). From **43** and following the procedure described for **28**, compound **45** was obtained (100%), mp 102–105 °C, $[\alpha]_D$ +152.6 (*c* 0.5, $CHCl_3$), ν_{max} 3300 (NH), 1740 (C=O), 1230 (C–O–C), 1040 (C–O), 1470, 1440, 780 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.27 (m, 4H, Ar, NH), 6.17 (d, $J_{1,2}$=6.8 Hz, 1H, H-1), 5.35 (d, $J_{3,4}$= 3.0 Hz, 1H, H-3), 5.30 (m, 1H, H-5), 4.68 (dd, $J_{3,4}$=3.0 Hz, $J_{4,5}$=9.3 Hz, 1H, H-4), 4.60 (dd, $J_{5,6}$=2.4 Hz, $J_{6,6'}$= 12.4 Hz, 1H, H-6), 4.47 (dd, $J_{2,NH}$=1.5 Hz, $J_{1,2}$=6.9 Hz, 1H, H-2), 4.02 (dd, $J_{5,6'}$=5.5 Hz, $J_{6,6'}$=12.4 Hz, 1H, H-6′), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (50.33 MHz, $CDCl_3$) δ 182.6 (C=S), 170.6 (CH_3–*C*O), 169.8 (CH_3–*C*O), 169.6 (CH_3–*C*O), 137.3, 134.8, 132.6, 130.6, 129.0, 128.7 (aromatics), 94.4 (C-1), 76.6 (C-3), 76.3 (C-4), 67.4 (C-5), 64.6 (C-2), 62.9 (C-6), 20.8 (*C*H_3–CO), 20.7 (*C*H_3–CO), 20.6 (*C*H_3–CO). Anal. Calcd for $C_{19}H_{20}Cl_2N_2O_7S$: C, 46.45; H, 4.10; N, 5.70; S, 6.52. Found: C, 46.25; H, 3.96; N, 5.63; S, 6.38.

4.1.22. 1-Acetyl-3-(2,6-dichlorophenyl)-(3,5,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucofurano)[1,2-*d*]imidazolidine-2-thione (46). A solution of **45** (0.13 g, 0.27 mmol) in pyridine (0.8 mL) and acetic anhydride (0.8 mL) was heated at 40 °C for 2 h. The reaction mixture was then poured over ice-water and a white solid was formed. This product was filtered and washed with cold water, (0.12 g, 86%), and then recrystallized from 96% aqueous ethanol, mp 202–204 °C, $[\alpha]_D$ +124.4 (*c* 0.5, $CHCl_3$), ν_{max} 3600–3100 (crystallization H_2O)[15], 1735, 1715 (C=O), 1675 (C=O), 1240, 1220 (C–O–C), 775 cm^{-1} (aromatics); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.27 (m, 3H, Ar), 6.06 (d, $J_{1,2}$=7.0 Hz, 1H, H-1), 5.79 (d, $J_{3,4}$=3.1 Hz, 1H, H-3), 5.21 (m, 1H, H-5), 4.96 (d, $J_{1,2}$=7.0 Hz, 1H, H-2), 4.55 (m, 2H, H-4, H-6), 3.99 (dd, $J_{5,6}$=5.5 Hz, $J_{6,6'}$=12.3 Hz, 1H, H-6′), 2.92 (s, 3H, N–Ac), 2.10 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.65 (bs, crystallization H_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 (C=S), 171.5 (CH_3–*C*O), 170.6 (CH_3–*C*O), 169.8 (CH_3–*C*O), 168.5 (CH_3–*C*O), 136.9, 134.2, 132.6, 130.9, 129.2, 129.0 (aromatics), 90.0 (C-1), 76.9 (C-4), 73.9 (C-3), 67.0 (2C, C-2, C-5), 63.0 (C-6), 27.1 (N–Ac), 20.8 (2C, *C*H_3–CO), 20.7 (*C*H_3–CO). Anal. Calcd for $C_{21}H_{22}Cl_2N_2O_8S\cdot 2H_2O$: C, 44.30; H, 4.60; N, 4.92; S, 5.63. Found: C, 44.29; H, 4.41; N, 4.67; S, 5.92.

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