Generalized Anomeric Effect in Action: Synthesis and Evaluation of Stable Reducing Indolizidine Glycomimetics as Glycosidase Inhibitors

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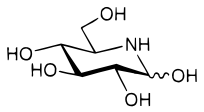
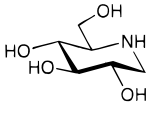
A series of aminoketalic castanospermine analogues incorporating a stereoelectronically anchored axial hydroxy group at the pseudoanomeric stereocenter (C-5) have been synthesized to satisfy the need for glucosidase inhibitors that are highly selective for α-glucosidases. The polyhydroxylated bicyclic system was built from readily available hexofuranose derivatives through a synthetic scheme that involved (i) the construction of a five-membered cyclic (thio)carbamate or (thio)urea moiety at the nonreducing end and (ii) the intramolecular nucleophilic addition of the heterocyclic thiocarbamic nitrogen atom to the masked aldehyde group of the monosaccharide. A biological screening of the resulting reducing 2-oxa- and 2-azaindolizidines against several glycosidase enzymes is reported.

Introduction

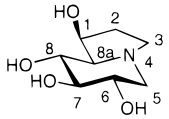
Natural and synthetic polyhydroxylated alkaloids with glycosidase inhibitory properties have been receiving a great deal of attention both as useful biological tools for studies on glycoconjugate function, targeting, and turnover[1] and as potential chemotherapeutic agents for the treatment of viral infections,[2] cancer,[3] and metabolic disorders such as diabetes.[4] Most of the biologically interesting members of this class of compounds, termed generically iminosugars ("azasugars"),[5] are related to nojirimycin (NJ, **1**) or 1-deoxynojirimycin (DNJ, **2**),[6] nitrogenous-ringed stereochemical mimics of D-glucose, or to the indolizidine alkaloid glucomimetic castanospermine (CS, **3**).[7] Neither **1**−**3** nor most of the plethora of synthetic analogues reported so far possess a defined configuration at the pseudoanomeric center.[8] It is therefore not surprising that **1**−**3** simultaneously inhibit several α- and β-glucosidases, which may be particularly problematic for clinical applications.[4a]



NJ, 1



DNJ, 2



CS, 3

One approach to improving the selectivity of iminosugar glycosidase ligands would be to exploit the stereocomplementarity of the scissile aglyconic oxygen atom with the key bilateral carboxylic groups, crucial for the α- or β-glycosidic bond specificity, in the active site of the enzyme.[9] Yet, the development of aza-*O*-glycoside glycomimetics is limited by the lability of the O/N acetal

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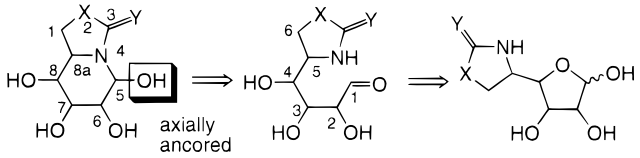

I, X = O; Y = S, O
II, X = NH; Y = S, O

III

Figure 1. Structures I, reducing 2-oxaindolizidine; II, reducing 2-azaindolizidine; III, aldohexofuranose.

function under hydrolytic conditions.[10] Although the anomeric hydroxyl group in **1** can be seen as an universal surrogate for natural glycosidic links, reducing azasugars suffer likewise from low stability, and moreover, rapid anomerization occurs in aqueous solution. This paper describes a novel approach that obviates these problems based on the assumption that replacement of the imino sp^3 nitrogen by a (thio)carbamic-type nitrogen would substantiate sp^2 character[11] and hence increases the orbitalic contribution to the generalized anomeric effect[12] in aminoketalic centers.[13] The resulting *N*-(thio)carbonyl iminosugars exhibit a much higher stability as well as configurational integrity in water.[14] This principle has been translated into a practical synthesis of reducing 2-oxa- and 2-azaindolizidine glycomimetics (Figure 1, structures I and II, respectively), a hitherto unknown class of compounds, from cyclic (thio)carbamate and cyclic (thio)urea carbohydrate precursors. Like **3**, structures I and II can be seen as conformationally restricted monosaccharide analogues: 2-oxaindolizidines retain the hydroxylation profile of the parent hexose, whereas 2-azaindolizidines are, formerly, mimics of 6-amino-6-deoxy sugars. Both share the reducing character with **1**, but they also have the aminoketalic hydroxy group, anchored in the axial position, like the natural aglycons in α-glycopyranosides. The preparation of the key intermediates, the scope and limitation of the methods, and the structural glycosidase inhibitory selectivities and potency relationships are discussed.

Results

A retrosynthetic analysis revealed that the bicyclic skeleton of 2-oxa- and 2-azaindolizidines can be constructed by the intramolecular nucleophilic addition of the nitrogen atom of five-membered cyclic (thio)carbamate or (thio)urea intermediates to a suitably located carbonyl group, with simultaneous generation of the aminoketal function (Figure 1). Our synthetic strategy centers on the use of aldohexofuranose-derived azole heterocycles with pseudo-*C*-nucleoside structure (III) as precursors because the masked aldehyde group of the monosaccharide can actually act as the electrophilic target through the open-chain tautomeric form.

Synthesis and Structure of 5-Hydroxy-2-oxaindolizidines. The initial synthetic objective of this research was the preparation of reducing 2-oxacastanospermine analogues, that is, oxazolidine−piperidine bicyclic derivatives with a hydroxylation profile at the six-membered ring identical to that of D-glucose. The thiocarbonylation reaction of 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[15] (**4**) with carbon disulfide−DCC at −10 °C afforded the required 6,5-(cyclic thiocarbamate) **6** in a regioselective manner (Scheme 1).[16] Because the epimeric amino sugar **5**, with L-ido configuration, was readily accessible with minor modification of the syntetic route leading to **4**,[15] it was of interest to contemplate a parallel study on the reactivity and structural properties for both sugar series to assess the scope and limitations of the approach. Thus, compound **5** was subjected to thiocarbonylation with the same reagent as that used with **4** to give **7** in 85% yield. Carbonylation of **4** and **5** with bis(trichloromethyl)-carbonate (triphosgene)[17] and diisopropyl ethylamine (DIPEA) led to the corresponding 2-oxazolidinone heterocycles **8** and **9**, respectively, in virtually quantitative yields (Scheme 1).[18] The relative proportion of reactants was found to have a strong influence on the outcome of the latter reaction. Higher concentrations of triphosgene resulted in further intra- and intermolecular carbonylation, thereby producing a subsequent loss of product purity.

(8) The exceptions correspond to compounds having the exocyclic glycosidic oxygen replaced by other atom or group of atoms. Noteworthy examples are aza-*C*-glycosides and aza-*S*-glycosides. See: (a) Leewenburgh, M. A.; Picasso, S.; Overkleeft, H. S.; van der Marel, G. A.; Vogel, P.; van Boom, J. H. *Eur. J. Org. Chem.* **1999**, *1185*, 5. (b) Zhu, Y.-H.; Vogel, P. *J. Org. Chem.* **1999**, *64*, 666. (c) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R.; *J. Am. Chem. Soc.* **1997**, *119*, 4856. (d) Fuchss, T.; Streicher, H.; Schmidt, R. R. *Liebigs Ann./Recl.* **1997**, 1315. (e) Asano, N.; Nishida, M.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60*, 98. (f) Wong, C.-H.; Proveacher, L.; Porco, Jr., J. A.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492. (g) Suzuki, K.; Hashimoto, H. *Tetrahedron Lett.* **1994**, 4119.

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(12) For reviews on the generalized anomeric effect, see: (a) Tvaroska, I.; Bleha, T. *Adv. Carbohydr. Chem. Biochem.* **1989**, *47*, 45. (b) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, 1995. For recent papers on the controversial subject of the relative contribution of orbitalic and electrostatic interactions to the generalized anomeric effect in azaheterocycles, see: (c) Perrin, C. L.; Armstrong, K. B.; Fabian, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 715. (d) Salzner, U. *J. Org. Chem.* **1995**, *60*, 986. (e) Ritter, J.; Gleiter, R.; Irngartinger, H.; Oeser, T. *J. Am. Chem. Soc.* **1997**, *119*, 10599.

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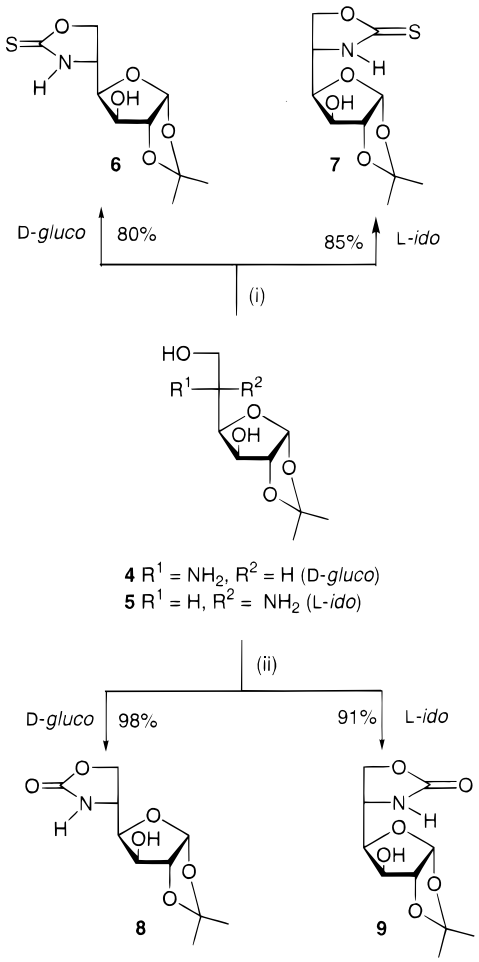
(16) Previous work on the synthesis of 2-thioxo-1,3-*O*,*N*-heterocycles from amino sugar templates had shown that β-amino alcohol segments undergo regioselective cyclization to the corresponding oxazolidine-2-thiones upon reaction with thiophosgene, provided that a cis relationship of the reactive groups is allowed. See: (a) García Fernández, J. M.; Ortiz Mellet, C.; Fuentes, J. *J. Org. Chem.* **1993**, *58*, 5192. (b) García Fernández, J. M.; Ortiz Mellet, C.; Jiménez Blanco, J. L.; Fuentes, J. *J. Org. Chem.* **1994**, *59*, 5565. In the present case, this procedure proved unsatisfactory, affording a rather modest 28% yield. Simultaneous formation of oligomeric material was observed. Using 1,1-thiocarbonyldiimidazole as the thiocarbonylating reagent likewise resulted in low yields.

(17) For a review on the synthetic applications of triphosgene, see: Cotarca, L.; Delogu, P.; Nardelli, A.; Sunjic, V. *Synthesis* **1996**, 553.

Scheme 1[a]

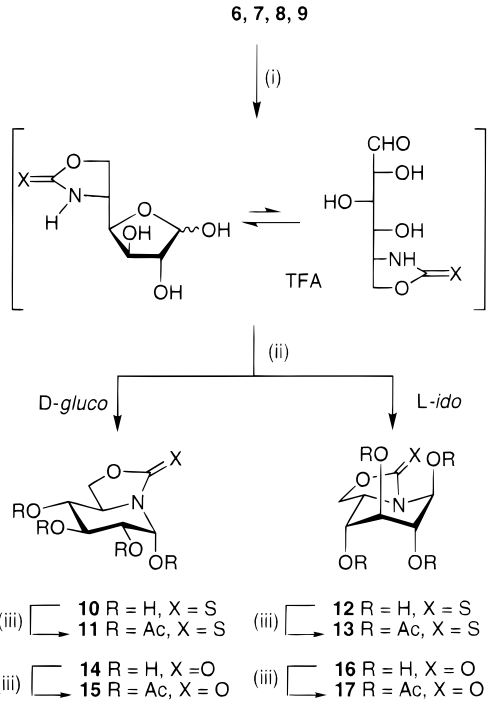


[a] Reagents: (i) CS_2, DCC, CH_2Cl_2, 6−7 h; (ii) triphosgene (1.5 equiv), DIPEA (10 equiv); CH_2Cl_2, 5 min.

Acid hydrolysis of the acetal protecting group in **6**−**9** with TFA−water led, initially, to α,β anomeric mixtures of the corresponding furanoses, with the (thio)carbamate group probably being protonated, as seen from ^{13}C NMR spectra of the crude reaction mixtures. After neutralization, the equilibrium was spontaneously shifted toward the target 2-oxaindolizidines (Scheme 2).

The castanospermine analogues **10** and **14** existed in D_2O solution as single diastereomers. The high field shift of the C-1 resonance[19] (77.4 and 77.0 ppm, respectively) confirmed the aminoketalic bicyclic structure, whereas the vicinal $^3J_{H,H}$ values around the piperidine ring unambiguosly pointed to the 5*R* configuration for the new stereocenter, with the pseudoanomeric hydroxy group in axial position, fitting the anomeric effect. No traces, either of the 5*S* epimer or of the furanose forms, were detected even after conventional acetylation (→**11** and **15**, respectively). For the L-idose derived indolizidines,

Scheme 2[a]



[a] Reagents: (i) 90% TFA−water; (ii) Amberlite IRA-68 (OH^-) (87−96%); (iii) 1:1 Ac_2O/pyridine (85−97%).

the all-axial 5*S* diastereomer was detected exclusively for the fully unprotected compounds (**12** and **16**) and the tetra-*O*-acetates (**13** and **17**, respectively). The configurational assignment was confirmed by the existence of a long-range coupling constant between protons in W arrangement and the lack of NOE contact between H-5 and H-8a.

Synthesis and Structure of 5-Hydroxy-2-azaindolizidines. To implement this strategy of accessing reducing 2-azacastanospermine analogues, the preparation of 5,6-diamino-5,6-dideoxyaldohexofuranose derivatives was required. The reported methods for the synthesis of these compounds are very scarce and suffer from either low overall yields or formation of epimeric mixtures.[20] Because the introduction of a first azido substituent at C-5 can be effected very efficiently, and with total stereocontrol in the multigram scale in both D-gluco and L-ido series (**18** and **19**, respectively), we decided to introduce the second nitrogen substituent in a stepwise manner: (i) first, we accomplished the tosylation of the primary hydroxyl group and the in situ acetylation of the remaining 3-OH (→**20** and **21**, respectively), and (ii) then we effected the nucleophilic displacement of tosylate by azide anion (→**22** and **23**) (Scheme 3). Deacetylation and Staudinger reduction of the diazides **24** and **25** afforded the corresponding diamines **26** and **27**, in quantitative yield[21] (^{13}C NMR monitoring), as hygroscopic solids which were directly thiocarbonylated (→**28** and **30**) or carbonylated (→**29** and **31**, respectively) following the protocols previously optimized in the preparation of the cyclic (thio)carbamate counterparts (Scheme 4).

(18) An alternative synthetic approach based on the aza-Wittig-type reaction of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose, or the L-ido epimer, with triphenylphosphine and CO_2, proved unsuccessful. When 1,1-carbonyldiimidazole was used as the carbonylating reagent, the corresponding cyclic thiocarbamates were isolated in 50% yield.

(19) For clarity of presentation, the authors choose not to use the numbers resulting from the heterocyclic compounds (see the Experimental Section) in the notation of atoms for NMR data. Instead, the notation is kept consistent with the parent carbohydrate compounds. See Figure 1 for atom notation equivalency.

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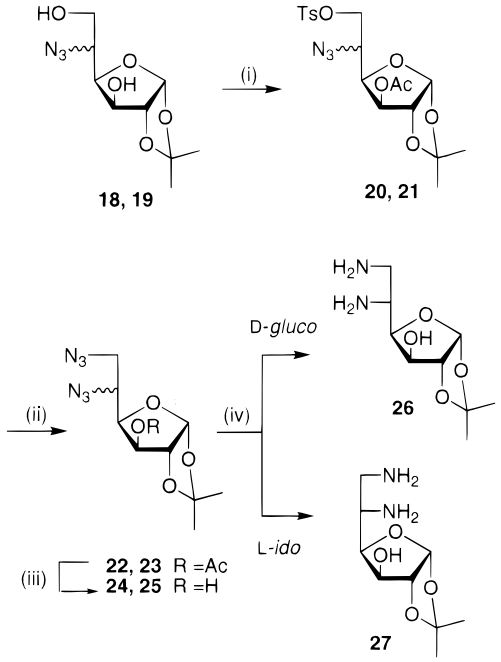
(21) The acetylation/deacetylation step was found to be necessary to avoid extensive formation of 3,6-anhydro derivatives, resulting from intramolecular nucleophilic displacement of the tosylate group by 3-OH.

Scheme 3[a]

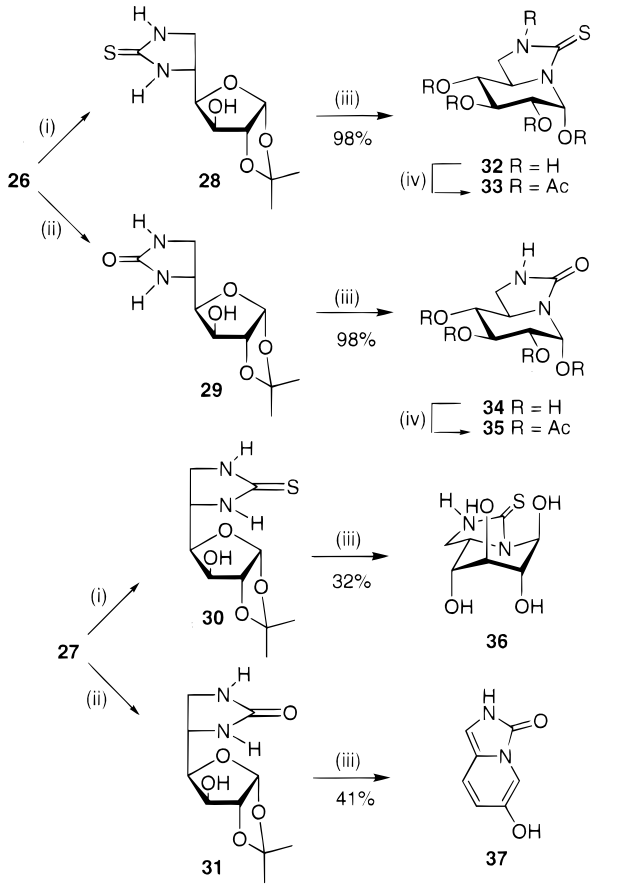


[a] Reagents: (i) TsCl (1.1 equiv), pyridine, 0 (D-gluco) and −30 °C (L-ido), respectively, 1:1 Ac_2O/pyridine (69−87%); (ii) NaN_3, DMF, 70 °C (86−98%); (iii) NaOMe, MeOH (97−98%), (iv) Ph_3P, dioxane/MeOH, aqueous NH_4OH (quant).

The tendency of the cyclic (thio)ureas **28** and **29** toward acid hydrolysis of the acetal protecting group was analogous to that previously observed for the configurationally related oxazolidines **6** and **8**. Upon neutralization of the reaction mixtures, the corresponding fused imidazolidine−piperidine bicyclic glucomimetics **32** and **34** were isolated in high yield (Scheme 4). Conventional acetylation of the thioxo derivative **32** afforded the penta-*O,N*-acetyl compound **33**, whereas the oxo analogue **34** was transformed into the tetra-*O*-acetate **35** under identical reaction conditions. Both the fully unprotected and the acetylation products showed coupling constant values around the six-membered ring, indicative of a conformation close to a chair with the pseudoanomeric hydroxy or acetoxy group in axial position. In the case of the imidazoline derivatives of L-idose **30** and **31**, the outcome of the reaction was radically different. Although the thioxo compound **30** led to the expected all-axial polyhydroxy 2-azaindolizidine **36** with 5*S* configuration, albeit in low yield, the analogous 3-oxo diazabicycle could not be isolated and experienced further dehydration to give a product for which structure **37** was proposed, on the basis of microanalytical, MS, and NMR data (Scheme 4).

Evaluation of the Inhibitory Selectivities and Potencies of Reducing Indolizidines. First, 2-oxa-3-thioxoindolizidines **10** and **12** were screened against yeast α-glucosidase and sweet almond *β*-glucosidase. Both enzymes have been widely used to check the α- versus *β*-glucosidase selectivity for different inhibitors. The conventional reducing iminosugar glucomimetic NJ (**1**) inhibits *β*-glucosidase more potently (K_i = 0.89 *μ*M) than α-glucosidase (K_i = 6.3 *μ*M).[1f] In stark contrast, the inhibition constants for **10** (>100 000 and 40 *μ*M, respectively) indicated a reverse linkage specificity. Although the inhibition potency for α-glucosidase is about 1 order of magnitude lower as compared with **1**, the selectivity ratio is inverted, by a factor of above 10^4, for this

Scheme 4[a]



[a] Reagents: (i) CS_2, DCC (73−79%); (ii) triphosgene (1.5 equiv), DIPEA (10 equiv) (61−70%); (iii) 90% TFA−water, Amberlite IRA-68 (OH^-); (iv) 1:1 AC_2O/pyridine (85−98%).

Table 1. Comparison of Inhibitory Activities (K_i, *μ*M) for 2-Oxa (10 and 14) and 2-Azacastanospermines (32 and 34)

	compound			
enzyme	10	14	32	34
β-glucosidase (almonds)	150 000	n.i.[a]	n.i.	n.i.
α-glucosidase (yeast)	40	2.2	4 200	5 700
α-glucosidase (rice)	1 600	1600	n.i.	4 300
amiloglucosidase (*Aspergillus niger*)	22 000	8 200	15 000	1 600
trehalasa (pig kidney)	2 000	n.d.[b]	n.d.	n.d.
intestinal lactase (newborn lamb)	30 000	n.d.	n.d.	n.d.

[a] No inbition detected. [b] Not determined.

particular pair of enzymes. The α-linkage selectivity is even much higher than that of DNJ (**2**), considered to be a selective inhibitor of α-glucosidase (K_i = 47 and 12.3 *μ*M for *β*- and α-glucosidase, respectively),[1f] or CS (**3**; K_i = 1.5 and >1500 *μ*M).[1f] The L-idose derived diastereomer **12** did not inhibit any of these two glycosidases, discarding the possibility of any significant contribution of inspecific interactions with the cyclic thiocarbamate portion to the K_i values.

We have further evaluated the ability of **10** to inhibit a series of other glycosidases: α-glucosidase (rice), amiloglucosidase (*Aspergillus niger*), trehalase (pig kidney), and intestinal *β*-glycosidase complex (intestinal lactase purified from lamb). The K_i values obtained are collected in Table 1. None of these enzymes were strongly inhibited, having K_i values in the mM range. It may be

concluded that **10** can discriminate not only between sweet almond β-glucosidase and yeast α-glucosidase but also between the latter and other α-glucosidases. This effect was found to be more pronounced for the 3-oxo analogue **14**, which was 18-fold more potent as an inhibitor of yeast α-glucosidase (K_i = 2.2 μM) than **10** and, likewise, a very poor inhibitor of rice α-glucosidase and amiloglucosidase. The replacement of the endocyclic oxygen atom by nitrogen dramatically weakened the inhibitory potency against yeast α-glucosidase and abolished selectivity. Thus, **32** and **34** were found to be very weak inhibitors of the above three α-glucosidases.

Discussion

We have designed and synthesized a new class of glycosidase inhibitors, reducing polyhydroxyindolizidines incorporating a (thio)carbamic segment in the bicyclic skeleton. The synthetic scheme is straightforward and employs readily available monosaccharide precursors. The two configurations considered in this study, D-glucose and L-idose, are limit cases regarding steric constraints. In the first series, the nonanomeric substituents are in the equatorial position in the final bicyclic glycomimetics, whereas in the latter they are axially oriented. Nevertheless, the diastereomer having the aminoketalic hydroxy group in axial arrangement was exclusively detected in water solution in all cases. This result is in agreement with the existence of a very strong and stabilizing interaction between the π-type lone-pair orbital of the nitrogen atom in the ground state of (thio)carbamic functionalities and the σ^* antibonding orbital of the contiguous C−O bond, which is fully operative in polar solvents. To the best of our knowledge, these are the first examples of configurationally and conformationally stable reducing glycomimetics.

Because the double-bond character of the N−C(Y)X bond decreases in the sense thiocarbamate > carbamate > thiourea > urea,[11] a parallel abatement of the contribution of the above orbitalic interaction to the generalized anomeric effect on going from 2-oxa-3-thioxoindolizidines to 2-aza-3-oxoindolizidines was expected. This probably explains the lower stability of L-idose derived 2-azaindolizidines, for which steric repulsions balance or overcome the anomeric effect stabilization. With the exception of this particular case, all compounds here reported were found to be stable for months as solids or as aqueous solution in a refrigerator, which is notably different than was found to be the case for NJ-type reducing iminosugars.[22]

Iminosugars are thought to be good, but rather nonspecific, inhibitors of glycosidases because they mimic the glycosyl cation, a proposed intermediate in the mechanism of action for both α- and β-glycosidases, as a result of the heterocyclic nitrogen atom being protonated at physiological pH.[1g] In *N*-(thio)carbonyl compounds, the basicity at the nitrogen center is drastically decreased (by 14 p*K* units) as compared with the corresponding amine,[11,23] while keeping a positive charge density resulting from delocalization of the lone electron pair into the (thio)carbonyl group. This scenario is probably closer to that encountered in the transition state of enzymatic glycoside hydrolysis at the endocyclic oxygen atom region.[24] In agreement with that assumption, the 2-oxacastanospermine glycomimetics **10** and **14** exhibited K_i values against yeast α-glucosidase that are comparable to those of the classical iminosugars **1** and **2**; compound **14** was a stronger inhibitor by 3-fold and 6-fold, respectively. In sharp contrast, they practically did not inhibit β-glucosidases at all, which is in agreement with the decisive role of anomeric stereochemistry in enzyme specificity.

Indolizidine glycomimetics, such as castanospermine (**3**), are known to be more potent and selective inhibitors of some α-glucosidases than their related piperidine analogues. This has been ascribed to the rigidity of the bicyclic structure, which locks the homologous bond to C-5−C-6 in hexopyranosides, thereby fixing the hydroxy group equivalent to 6-OH in the correct position to fully interact with the binding site of the enzyme.[25] A comparative analysis of the topographical characteristics of **3**, **10**, and **14** at this region[26] showed that the result of replacing the 1-hydroxyindolizidine structure into a 2-oxaindolizidine skeleton is formally equivalent to a rotation of ~120° about the above bond. This brings the oxygen atom equivalent to O-6 in hexoses from a gauche arrangement into the anti position with respect to the piperidine carbon atom C-8. This structural change is probably responsible for the dramatic differences observed in the glycosidase inhibitory properties: Although castanospermine does not inhibit yeast α-glucosidase and is a very strong inhibitor of rice α-glucosidase (K_i = 0.015 μM)[1f] and amiloglucosidase (K_i = 8 μM),[27] the 2-oxacastanospermine analogues **10** and **14** have the reverse selectivity (Table 1). These results strongly support the notion that the prochiral O-6 in D-glucopyranosides binds to α-glucosidases in a specific manner. Therefore, the results suggest a way to discriminate the bound conformation: those glucosidases that are inhibited by castanospermine require a disposition close to gauche−gauche about C-5−C-6, whereas those that are inhibited by 2-oxacastanospermine derivatives bind in a gauche−trans arrangement (Figure 2).[28] Although differences in the pK_b of the inhibitors may also have an influence in the α-glucosidase selectivity, the orientational properties of the O-6 equivalent atom seem to be the major structural requirement. Thus, replacement of this key oxygen atom (e.g., with 1-deoxycastanospermine[25] or 2-azacastanospermines **32** and **34**), which does not

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(26) Molecular mechanics calculations for **3**, **10**, and **14** were performed using MM2* as integrated in MACROMODEL 6.0 and the GB/SA continuum solvent model for water. The three-dimensional geometries obtained were in agreement with the discussed NMR data.

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(28) For the nomenclature used to denote the staggered rotamers about the C-5−C-6 bond in hexopyranoses, see: Bock, K.; Duus, J. Ø. *J. Carbohydr. Chem*. **1994**, *13*, 513.

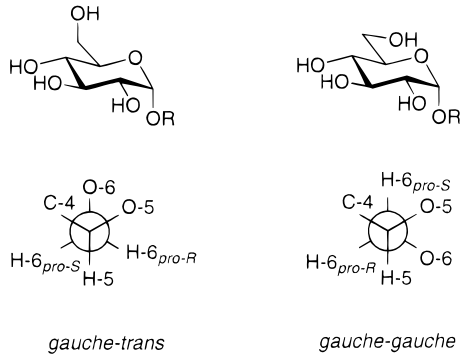

Figure 2. Major staggered rotamers about C-5—C-6 in the conformational equilibrium of α-glucopyranosides.

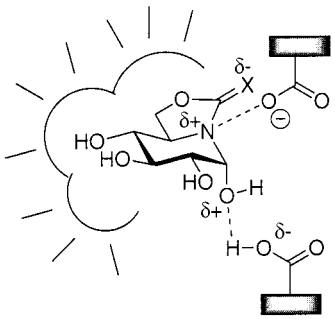

Figure 3. Probable mode of interaction between reducing 2-oxacastanospermine analogs and yeast α-glucosidase.

significantly affect the basicity at the nitrogen center, abolishes strong inhibition in both series.

Further work is necessary to determine the exact mode of interaction of reducing indolizidines with glycosidases. Kinetic studies for **10** and **14** against yeast α-glucosidase indicate fast and competitive inhibition. Most probably, the bicyclic glucomimetics are bound in a ground-state-like conformation, with the axial anomeric oxygen in the necessary position to interact with the general acid at the active site and the thiocarbamic nitrogen in position to interact with the general base carboxylate (Figure 3). Whether the enzyme is able to transform these potential substrates into transition-state structures and, eventually, glycosyl-cation-like intermediates is still under investigation. In any case, our work provides a new tool for designing selective α-glycosidase inhibitors by exploiting orbitalic interactions in bicyclic aminoketalic systems.

Conclusions

The concept, demonstrated herein, of stereoelectronically controlling the stereochemistry at aminoketalic centers in aqueous solution, through the use of *N*-(thio)-carbonyl functionalities, indicates a new design strategy for the development of selective inhibitors of α-glycosidases. By taking advantage of the capability of *N*-(thio)-carbonyl functionalities to undergo nucleophilic attack on the masked aldehydo group of reducing monosaccharide derivatives, an efficient synthesis of reducing 2-oxa- and 2-azaindolizidine glycomimetics has been achieved. The observed α versus *β* linkage specificity is ascribable to the presence of an axially anchored pseudoanomeric hydroxy group. The selectivity for yeast α-glucosidase, among other α-glucosidases, is probably due to the ridigity of the bicyclic skeleton that fixes an anti position between C-8 and O-2 that is equivalent to a gauche—trans conformation about C-5—C-6 in glucopyranosides.

Experimental Section

General Procedures. Optical rotations were measured at room temperature in either 1-cm or 1-dm tubes. IR spectra were recorded on an FT-IR instrument. UV spectra were recorded with a Philips PU 8710 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 500 (125.7) and 300 (75.5) MHz. In the FABMS spectra, the primary beam consisted of Xe atoms with a maximum energy of 8 keV. The samples were dissolved in the matrices *m*-nitrobenzyl alcohol or thioglycerol and the positive ions were separated and accelerated over a potential of 7 keV. 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. Fully deprotected compounds were purified by GPC. Acetylations were effected conventionally with 1:1 pyridine/Ac_2O (10 mL per 1 g of sample). Microanalyses were performed by the Instituto de Investigaciones Químicas (Sevilla, Spain).

Materials. 5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**18**) was prepared from commercial D-glucofuranurono 6,3-lactone in four steps, as reported.[15] The L-ido epimer **19** was obtained in three steps from the same lactone (50% overall yield) by triflation at O-5, nucleophilic displacement by an azide anion, and reduction of the lactone group with lithium borohydride. Staudinger reduction[29] of the 5-azido derivatives with triphenylphosphine in dioxane—MeOH followed by in situ hydrolysis of the resulting iminophosphoranes (R—N=PPh_3) with ammonium hydroxide afforded the corresponding 5-amino-5-deoxy sugars with D-gluco (**4**) and L-ido configuration (**5**). The 5,6-diamino-5,6-dideoxy-1,2-*O*-isopropylidenehexofuranoses **26** and **27** were prepared from the monoazides **18** and **19** by replacement of the primary OH-6 group by azide via tosylate and final Staudinger reduction (Scheme 3; see the Supporting Information).

The solvents were commercial grade and were used as supplied, with the following exceptions: DMF was distilled from BaO. Methanol was distilled from methylmagnesium iodide. Pyridine was distilled from KOH. Acetic anhydride was distilled from freshly melted sodium acetate.

General Procedure for Inhibition Assay. Inhibitory potencies of the 2-oxa- and 2-azaindolizidines were determined by spectrophotometrically measuring the residual hydrolytic activities of the glycosidases against the corresponding *p*-nitrophenyl α- or *β*-D-glucopyranoside, *o*-nitrophenyl α-D-galactopyranoside (for lactase), or trehalose in the presence of the corresponding 2-oxaindolizidine. The glycosidases used were α-glucosidase (rice), α-glucosidase (yeast), amiloglucosidase (*Aspergillus niger*), *β*-glucosidase (almond), intestinal *β*-glycosidase complex (intestinal lactase, newborn lamb), and trehalase (pig kidney). All enzymes were purchased from Sigma, except the lactase, which was isolated and purified as reported.[30]

Each assay was performed in a phosphate buffer at the optimal pH for each enzyme. The reactions were initiated by the addition of the enzyme to a solution of the substrate in the presence or absence of various concentrations of inhibitor. After the mixture was incubated for 10—30 min at 37 °C, the reaction was quenched by the addition of 1 M Na_2CO_3 or a solution of GLC-Trinder (Sigma, for trehalase). The absorbance of the resulting mixture was determined at 400 nm (for *p*-nitrophenol), 420 nm (for *o*-notrophenol), or 505 nm (for D-glucose, in the case of trehalase). The K_i values were determined with a Sigma Plot program (version 4.14, Jandel Scientific).

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5-Amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-(Cyclic thiocarbamate) (6). To a stirred solution of 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose **4** (120 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) at −10 °C were added CS_2 (0.3 mL, 4.5 mol) and DCC (114 mg, 0.55 mmol). The reaction mixture was allowed to reach room temperature and was stirred for 6−7 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (2:1 EtOAc/petroleum ether) to give **6** (115 mg, 80%) as an amorphous solid: R_f 0.38; $[\alpha]_D = -21.2$ (*c* 1.0, acetone); UV (MeOH) 242 nm (ϵ_{mM} 16.3); IR (KBr) ν_{max} 3337, 3262, 1530 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) Table 2 (Supporting Information) and δ 1.44 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 191.0, 113.0, 106.6, 86.7, 81.7, 75.4, 73.1, 56.9, 27.1, 26.4; FABMS *m*/*z* 284 (100, $[M + Na]^+$). Anal. Calcd for $C_{10}H_{15}NO_5S$: C, 45.96; H, 5.79; N, 5.36; S, 12.27. Found: C, 45.90; H, 5.62; N, 5.21; S, 12.25.

5-Amino-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose 5,6-(Cyclic thiocarbamate) (7). Thiocarbonylation of **5** (120 mg, 0.55 mmol) following the above procedure afforded **7** (122 mg, 85%) as an amorphous solid: R_f 0.38; $[\alpha]_D = +8.8$ (*c* 0.5, CH_2Cl_2); UV (MeOH) 242 nm (ϵ_{mM} 21.4); IR (KBr) ν_{max} 3360, 1651, 1516 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) Table 2 (Supporting Information) and δ 1.44 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 191.4, 113.0, 106.6, 87.1, 83.2, 75.6, 73.2, 57.8, 27.2, 26.4; FABMS *m*/*z* 284 (100, $[M + Na]^+$). Anal. Calcd for $C_{10}H_{15}NO_5S$: C, 45.96; H, 5.79; N, 5.36; S, 12.27. Found: C, 46.35; H, 5.84; N, 5.27; S, 12.49.

5-Amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-(Cyclic carbamate) (8). To a stirred solution of **4** (120 mg, 0.55 mmol) in CH_2Cl_2 (8 mL) were added diisopropyl ethylamine (DIPEA, 0.96 mL, 5.52 mmol) and triphosgene (82 mg, 0.29 mmol, 1.5 equiv). After 5 min, the solvent was removed under reduced preassure, and the residue was purified by column chromatography (1:1 toluene/acetone) to give **8** (132 mg, 98%) as an amorphous solid: R_f 0.35; $[\alpha]_D = -24.6$ (*c* 1.0, MeOH); IR (KBr) ν_{max} 3441, 3237, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Table 2 (Supporting Information) and δ 6.74 (bs, 1 H), 1.65 (bs, 1 H), 1.51 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.2 , 110.3, 104.1, 84.4, 81.8, 71.9, 66.8, 49.5, 25.8, 25.1; FABMS *m*/*z* 268 (100, $[M + Na]^+$). Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.16; N, 5.71. Found: C, 48.96; H, 6.17; N, 5.73.

5-Amino-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose 5,6-(Cyclic carbamate) (9). Carbonylation of **5** (120 mg, 0.55 mmol) following the above procedure afforded **9** (123 mg, 91%) as an amorphous solid: R_f 0.35; $[\alpha]_D = +8.1$ (*c* 0.3, CH_2Cl_2); IR (KBr) ν_{max} 3354, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Table 2 (Supporting Information) and δ 5.95 (bs, 1 H), 1.81 (bs, 1 H), 1.49, 1.32 (2 s, each 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.1, 112.0, 104.9, 85.4, 80.6, 75.6, 67.4, 52.0, 26.7, 26.0; FABMS *m*/*z* 268 (100, $[M + Na]^+$). Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.16; N, 5.71. Found: C, 48.97; H, 6.14; N, 5.71.

General Procedure for the Preparation of Reducing 2-Oxaindolizidines. A solution of the corresponding 5,6-cyclic (thio)carbamate (**6**−**9**, 0.90 mmol) in 90% TFA−H_2O (10 mL) was stirred at room temperature for 2 h monitored by TLC (45:5:3 EtOAc/EtOH/H_2O). The solvent was eliminated under reduced presure, and the residue was coevaporated with water several times. The solvent was then neutralized with Amberlite IRA-68 (OH^-) ion-exchange resin, purified by GPC (Sephadex G-10, 1:1 MeOH/H_2O), concentrated, and freeze-dried. Peracetylated derivatives were obtained by conventional acetylation in virtually quantitative yields.

(5*R*,6*S*,7*R*,8*R*,8a*R*)-5,6,7,8-Tetrahydroxy-2-oxa-3-thioxoindolizidine (10). Compound **10** was given as a white foam in 93% yield: R_f (45:5:3 AcOEt/EtOH/H_2O) 0.61; $[\alpha]_D = +0.8$ (*c* 0.8, H_2O); UV (H_2O) 245 nm (ϵ_{mM} 17.4); IR (KBr) ν_{max} 3372, 3291 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 2 (Supporting Information); ^{13}C NMR (125.5 MHz, D_2O) δ 186.4, 77.4, 72.4, 71.6, 71.4, 69.8, 56.1; FABMS *m*/*z* 244 (100, $[M + Na]^+$), 211 (40, $[M + H]^+$). Anal. Calcd for $C_7H_{11}NO_5S$: C, 38.00; H, 5.01; N, 6.33; S, 14.49. Found: C, 38.11; H, 5.16; N, 6.31; S, 14.23.

(5*R*,6*S*,7*R*,8*R*,8a*R*)-5,6,7,8-Tetraacetoxy-2-oxa-3-thioxoindolizidine (11). Compound **11** was given as an amorphous solid in 95% yield: R_f (EtOAc/petroleum ether) 0.43; $[\alpha]_D = +33.5$ (*c* 0.8, CH_2Cl_2); UV (CH_2Cl_2) 248 nm (ϵ_{mM} 27.6); IR (KBr) ν_{max} 1753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 2 (Supporting Information) and δ 2.16, 2.08, 2.05, 2.02 (4 s, each 3 H); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 187.0, 169.8, 169.7, 169.2, 168.3, 74.8, 71.6, 71.3, 68.6, 68.3, 56.1, 20.5, 20.4, 20.2 (2C); FABMS *m*/*z* 412 (100, $[M + Na]^+$). Anal. Calcd for $C_{15}H_{19}NO_9S$: C, 46.27; H, 4.92; N, 3.60. Found: C, 46.22; H, 4.82; N, 3.55.

(5*S*,6*S*,7*R*,8*R*,8a*S*)-5,6,7,8-Tetrahydroxy-2-oxa-3-thioxoindolizidine (12). Compound **12** was given as a white foam in 87% yield: R_f (45:5:3 EtOAc/EtOH/H_2O) 0.59; $[\alpha]_D = +64.0$ (*c* 0.8, H_2O); UV (H_2O) 245 nm (ϵ_{mM} 16.6); IR (KBr) ν_{max} 3584, 3324 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6 + D_2O) Table 2 (Supporting Information); ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 187.1, 80.8, 70.6, 68.8, 68.2 (2C), 53.4; FABMS *m*/*z* 244 (100, $[M + Na]^+$). Anal. Calcd for $C_7H_{11}NO_5S$: C, 38.00; H, 5.01; N, 6.33; S, 14.49. Found: C, 37.68; H, 5.02; N, 6.20; S, 14.02.

(5*S*,6*S*,7*R*,8*R*,8a*S*)-5,6,7,8-Tetraacetoxy-2-oxa-3-thioxoindolizidine (13). Compound **13** was given as an amorphous solid in 97% yield: R_f (3:1 EtOAc/petroleum ether) 0.49; $[\alpha]_D = -35.8$ (*c* 1.2, CH_2Cl_2); UV (CH_2Cl_2) 250 nm (ϵ_{mM} 15.9); IR (KBr) ν_{max} 1748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 2 (Supporting Information) and δ 2.15, 2.14, 2.12, 2.10 (4 s, each 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.8,169.6, 168.6, 168.2, 167.7, 76.5, 67.9, 66.0, 65.7, 65.4, 52.4, 20.5 (2C), 20.2 (2C); FABMS *m*/*z* 412 (100, $[M + Na]^+$). Anal. Calcd for $C_{15}H_{19}NO_9S$: C, 46.27; H, 4.92; N, 3.60. Found: C, 46.25; H, 4.88; N, 3.55.

(5*R*,6*S*,7*R*,8*R*,8a*R*)-5,6,7,8-Tetrahydroxy-2-oxa-3-oxoindolizidine (14). Compound **14** was given as a white foam in 93% yield: R_f (2:1:1 BuOH/AcOH/H_2O) 0.30; $[\alpha]_D = +43.6$ (*c* 1.1, H_2O); IR (KBr) ν_{max} 3414, 3148, 1748 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 2 (Supporting Information); ^{13}C NMR (125.5 MHz, D_2O) δ 160.1, 77.0, 76.0, 74.8, 73.5, 70.0, 55.6; FABMS *m*/*z* 228 (50, $[M + Na]^+$). Anal. Calcd for $C_7H_{11}NO_6$: C, 40.98; H, 5.40; N, 6.82. Found: C, 40.69; H, 5.48; N, 6.82.

(5*R*,6*S*,7*R*,8*R*,8a*R*)-5,6,7,8-Tetraacetoxy-2-oxa-3-oxoindolizidine (15). Compound **15** was given as an amorphous solid in 95% yield: R_f (2:1 EtOAc/petroleum ether) 0.42; $[\alpha]_D = +38.3$ (*c* 0.6, CH_2Cl_2); IR (KBr) ν_{max} 1778, 1751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 2 (Supporting Information) and δ 2.12, 2.05, 2.03, 1.98 (4 s, each 3 H); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 169.9, 169.7, 169.2, 168.5, 154.1, 72.2, 72.1, 68.9 (2C), 66.8, 52.5, 20.5, 20.4, 20.3, 20.2; FABMS *m*/*z* 396 (100, $[M + Na]^+$). Anal. Calcd for $C_{15}H_{19}NO_{10}$: C, 48.26; H, 5.13; N, 3.75. Found: C, 48.25; H, 5.09; N, 3.76.

(5*S*,6*S*,7*R*,8*R*,8a*S*)-5,6,7,8-Tetrahydroxy-2-oxa-3-oxoindolizidine (16). Compound **16** was given as a white foam in 96% yield: R_f (2:1:1 BuOH/AcOH/H_2O) 0.28; $[\alpha]_D = +4.0$ (*c* 1.1, H_2O); IR (KBr) ν_{max} 3351, 1734 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 2 (Supporting Information); ^{13}C NMR (125.5 MHz, D_2O) δ 159.0, 76.8, 69.7, 69.5, 67.8, 64.2, 49.2; FABMS *m*/*z* 228 (100, $[M + Na]^+$). Anal. Calcd for $C_7H_{11}NO_6$: C, 40.98; H, 5.40; N, 6.82. Found: C, 41.00; H, 5.35; N, 6.82.

(5*S*,6*S*,7*R*,8*R*,8a*S*)-5,6,7,8-Tetraacetoxy-2-oxa-3-oxoindolizidine (17). Compound **17** was given as an amorphous solid in 85% yield: R_f (2:1 EtOAc/petroleum ether) 0.51; $[\alpha]_D = -17.3$ (*c* 0.9, CH_2Cl_2); IR (KBr) ν_{max} 1767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 2 (Supporting Information) and δ 2.13, 2.12, 2.08, 2.07 (4 s, each 3 H); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 168.6, 168.3 (2C), 168.0, 155.2, 74.4, 65.7 (2C), 65.4, 63.2, 48.4, 20.6, 20.5; FABMS *m*/*z* 396 (100, $[M + Na]^+$). Anal. Calcd for $C_{15}H_{19}NO_{10}$: C, 48.26; H, 5.13; N, 3.75. Found: C, 48.30; H, 5.19; N, 3.75.

5,6-Diamino-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-(Cyclic thiourea) (28). To a solution of diamine **26** (290 mg, 1.33 mmol) in CH_2Cl_2 (15 mL) were added CS_2 (0.64 mL) and DCC (290 mg, 1.40 mmol). The reaction mixture was stirred for 1 h and then concentrated. The resulting residue was chromatographed on a silica gel column (45:5:3 EtOAc/EtOH/H_2O) to give **26** (273 mg, 79%) as an amorphous solid: R_f 0.67; $[\alpha]_D = -41.8$ (*c* 0.9, MeOH); UV

(MeOH) 240 nm (ϵ_{mM} 14.6); IR (KBr) ν_{max} 3374, 3247, 1528 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) Table 3 (Supporting Information) and δ 1.45, 1.29 (2 s, each 3 H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 184.6, 112.9, 106.4, 86.8, 82.7, 75.1, 56.6, 49.2, 27.0, 26.4; CIMS *m/z* 261 (50, $[M + H]^+$). Anal. Calcd for $C_{10}H_{16}N_2O_4S$: C, 46.14; H, 6.20; N, 10.76. Found: C, 46.11; H, 5.94; N, 10.62.

5,6-Diamino-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-(Cyclic urea) (29). A solution of triphosgene (0.45 mmol) in CH_2Cl_2 (8 mL) was added dropwise to a stirred solution of diamine **26** (295 mg, 1.35 mmol) and DIPEA (13.5 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature and monitored by TLC (45:5:3 EtOAc/EtOH/H_2O) until total consumption of the starting diamine resulted (1 h). The mixture was then concentrated, and the crude product was purified by column chromatography using the same solvent to give **29** (229 mg, 70%) as an amorphous solid: R_f 0.42; $[\alpha]_D = -31.7$ (*c* 0.2, MeOH); IR (KBr) ν_{max} 3441, 3393, 1686 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) Table 3 (Supporting Information) and δ 1.44, 1.29 (2 s, each 3 H); ^{13}C NMR (125.5 MHz, CD_3OD) δ 166.3, 112.8, 106.5, 86.9, 83.8, 75.2, 52.2, 45.1, 27.1, 26.4; FABMS *m/z* 267 (100, $[M + Na]^+$). Anal. Calcd for $C_{10}H_{16}N_2O_5$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.14; H, 6.66; N, 11.44.

5,6-Diamino-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose 5,6-(Cyclic thiourea) (30). Thiocarbonylation of **27** (290 mg, 1.33 mmol), following the procedure above decribed for the preparation of **28** from **26**, and purification by column chromatography (45:5:3 EtOAc/EtOH/H_2O) yielded **30** (252 mg, 73%) as an amophous solid: R_f 0.64; $[\alpha]_D = +10.3$ (*c* 0.5, MeOH); UV (MeOH) 241.6 nm (ϵ_{mM} 7.1); IR (KBr) ν_{max} 3125, 1516 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) Table 3 (Supporting Information) and δ 1.43, 1.28 (2 s, each 3 H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 184.3, 111.8, 106.5, 87.0, 83.6, 75.6, 57.9, 47.9, 27.1, 26.4; FABMS *m/z* 283 (100, $[M + Na]^+$), 261 (25, $[M + H]^+$). Anal. Calcd for $C_{10}H_{16}N_2O_4S$: C, 46.14; H, 6.20; N, 10.76. Found: C, 45.88; H, 6.22; N, 10.50.

5,6-Diamino-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose 5,6-(Cyclic urea) (31). Thiocarbonylation of **27**(295 mg, 1.35 mmol), following the procedure above decribed for the preparation of **29** from **26**, and purification by column chromatography (45:5:3 EtOAc/EtOH/H_2O) yielded **31** (197 mg, 61%): R_f 0.37; $[\alpha]_D = +10.9$ (*c* 0.7, MeOH); IR (KBr) ν_{max} 3383, 1694 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 313 K) Table 3 (Supporting Information) and δ 1.44, 1.30 (2 s, each 3 H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 166.4, 112.8, 106.5, 87.1, 84.4, 75.6, 53.6, 44.1, 27.1, 26.4; FABMS *m/z* 267 (100, $[M + Na]^+$). Anal. Calcd for $C_{10}H_{16}N_2O_5$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.17; H, 6.55; N, 11.23.

General Procedure for the Preparation of Reducing 2-Azaindolizidines. Deacetalation of the cyclic (thio)ureas **28**−**30** (0.40 mmol) with 90% TFA-water, as above-described for the preparation of reducing 2-oxaindolizidines, and purification by GPC (Sephadex G-10, 1:1 MeOH−H_2O) afforded the corresponding 2-azaindolizidines **32**, **34**, and **36**, respectively. When the cyclic urea derivative of L-idofuranose **31** was subjected to identical reaction conditions, the 2-azaindolizine derivative **37** was obtained. Conventional acetylation of **32** and **34** afforded the penta- and tetraacetates **33** and **35**, respectively.

(5*R*,6*S*,7*R*,8*R*,8a*R*)-5,6,7,8-Tetrahydroxy-2-aza-3-thioxoindolizidine (32). Compound **32** was given as a white foam in 98% yield: R_f (MeOH) 0.48; $[\alpha]_D = -3.6$ (*c* 1.1, H_2O); UV (H_2O) 238 nm (ϵ_{mM} 10.7); IR (KBr) ν_{max} 3452, 3237, 1645 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 3 (Supporting Information); ^{13}C NMR (125.5 MHz, D_2O) δ 183.7, 87.2, 76.2, 75.7, 73.6, 59.6, 58.6; FABMS *m/z* 221 (70, $[M + H]^+$). Anal. Calcd for $C_7H_{12}N_2O_4S$: C, 38.17; H, 5.49; N, 12.72. Found: C, 37.93; H, 5.12; N, 12.47.

(5*R*,6*S*,7*R*,8*R*,8a*R*)-2-*N*-Acetyl-5,6,7,8-tetraacetoxy-2-aza-3-thioxoindolizidine (33). Compound **33** was given as an amorphous solid in 85% yield: R_f (1:1 EtOAc/petroleum ether) 0.44; $[\alpha]_D$ +38.0 (*c* 0.8, H_2O); UV (CH_2Cl_2) 237 nm (ϵ_{mM} 14.1); IR (KBr) ν_{max} 1755, 1694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 3 (Supporting Information) and δ 2.85 (s, 3 H), 2.19, 2.12, 2.08, 2.06 (4 s, each 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.6, 171.6, 169.9, 169.5, 169.3, 168.5, 74.2, 71.7, 69.3, 68.5, 52.8, 48.3, 26.6, 20.6, 20.4, 20.2 (2 C); FABMS *m/z* 453 (100, $[M + Na]^+$). Anal. Calcd for $C_{17}H_{22}N_2O_9S$: C, 47.44; H, 5.15; N, 6.51. Found: C, 47.33; H, 5.22; N, 6.48.

(5*R*,6*S*,7*R*,8*R*,8a*R*)-5,6,7,8-Tetrahydroxy-2-aza-3-oxoindolizidine (34). Compound **34** was given as a white foam in 98% yield: $[\alpha]_D = +69.7$ (*c* 0.9, H_2O); IR (KBr) ν_{max} 3364, 1690 cm^{-1}; ^1H NMR (300 MHz, D_2O) (Table 3); ^{13}C NMR (75.5 MHz, D_2O) δ 183.7, 79.9, 74.2, 73.2, 72.0, 53.8, 42.5. Anal. Calcd for $C_7H_{12}N_2O_5$: C, 41.18; H, 5.92; N, 13.72. Found: C, 41.18; H, 5.66; N, 13.59.

(5*R*,6*S*,7*R*,8*R*,8a*R*)-5,6,7,8-Tetraacetoxy-2-aza-3-oxoindolizidine (35). Compound **35** was given as an amorphous solid in 75% yield: *Rf* (EtOAc) 0.51; $[\alpha]_D = +39.0$ (*c* 0.5, CH_2Cl_2); IR (KBr) ν_{max} 3441, 1753, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Table 3 (Supporting Information) and δ 2.12, 2.07, 2.04, 1.98 (4 s, each H); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 169.8 (2 C), 169.7 (2 C),157.4, 72.5, 72.0, 69.7, 69.5, 52.7, 42.4, 20.8, 20.5, 20.4, 20.2; FABMS *m/z* 395 (100, $[M + Na]^+$). Anal. Calcd for $C_{15}H_{20}N_2O_9$: C, 48.39; H, 5.41; N, 7.52. Found: C, 48.19; H, 5.11; N, 7.32.

(5*S*,6*S*,7*R*,8*R*,8a*S*)-5,6,7,8-Tetrahydroxy-2-aza-3-thioxoindolizidine (36). Compound **36** was given as a white foam in 32% yield: $[\alpha]_D = +59.7$ (*c* 0.8, H_2O); ^1H NMR (300 MHz, D_2O) Table 3 (Supporting Information); ^{13}C NMR (75.5 MHz, D_2O) δ 180.8, 78.1, 70.0, 69.3, 68.8, 53.1, 42.3; FABMS *m/z* 221 (40, $[M + H]^+$). Anal. Calcd for $C_7H_{12}N_2O_4S$: C, 38.17; H, 5.49; N, 12.72. Found: C, 37.99; H, 5.39; N, 12.57.

2-Aza-6-hydroxy-3-oxoindolizine (37). Compound **37** was given as a syrup in 41% yield: ^1H MNR (500 MHz, D_2O) δ 8.71 (d, 1 H, $J_{5,7} = 2.4$ Hz, H-5), 8.32 (dd, 1 H, $J_{7,8} = 8.9$ Hz, H-7), 8.19 (d, 1 H, H-8); ^{13}C NMR (75.5 MHz, D_2O) δ 156.6, 151.3, 144.2, 137.2, 124.1, 121.4, 45.2; FABMS *m/z* 173 (40%, $[M + Na]^+$), 151 (100, $[M + H]^+$); EIMS *m/z* 150 (100%, $M^{+\bullet}$). Anal. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66. Found: C, 56.19; H, 3.89; N, 18.47.

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Supporting Information Available: Tables 2−4 containing ^1H and ^{13}C NMR data for all the new compounds and the experimental details for the preparation of diamino sugars **26** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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