

Synthesis and Evaluation of Isoorea-Type Glycomimetics Related to the Indolizidine and Trehazolin Glycosidase Inhibitor Families

M. Isabel García-Moreno,[†] Paula Díaz-Pérez,[†] Carmen Ortiz Mellet,^{*,†} and José M. García Fernández^{*,‡}

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, E-41071 Sevilla, Spain, and Instituto de Investigaciones Químicas, CSIC, Américo Vespucio s/n, Isla de la Cartuja, E-41092 Sevilla, Spain

jogarcia@cica.es; mellet@us.es

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A practical synthesis of reducing isourea-derived azasugar glycomimetics related to the indolizidine and trehazolin glycosidase inhibitor families with different pK_a values is disclosed. The polyhydroxylated bicyclic system was built from readily accessible hexofuranose derivatives through a synthetic scheme that involves the preparation of a 5-deoxy-5-carbodiimido adduct by triphenylphosphine-mediated tandem Staudinger–aza-Wittig-type coupling of azide and isothiocyanate precursors, intramolecular cyclization of a transient *vic*-hydroxycarbodiimide derivative, and nucleophilic addition of the endocyclic nitrogen atom of the generated 2-amino-2-oxazoline intermediate, with a pseudo-*C*-nucleoside structure, to the masked aldehyde group of the monosaccharide. The last step is pH-dependent so that the final compounds can pivot between the furanose and the 2-oxaindolizidine forms. Nevertheless, the indolizidine tautomer having the *R* configuration at the aminoacetalic center, fitting the anomeric effect, was the only species detected in solution at neutral or slightly acidic pH when starting from solutions at basic pH. Glycosidase inhibition tests (K_i values down to 1.9 μ M) showed a marked dependence of the selectivity and potency toward α - and β -glucosidases upon the nature of the substituent at the exocyclic isourea nitrogen, shifting from α - to β -selectivity when going from hydrophilic to hydrophobic substituents. Enzyme inhibition is also pH dependent, supporting a dominant role for the uncharged form of the polyhydroxyiminoindolizidine system in the inhibition of β -glucosidases.

Introduction

Naturally occurring and synthetic polyhydroxylated alkaloids with glycosidase inhibitory properties¹ have been receiving a great deal of attention both as useful biochemical tools for studies on glycoconjugate function, targeting, and turnover² and as potential chemotherapeutic agents for the treatment of viral infections,³ cancer,⁴ autoimmune pathologies,⁵ and diabetes and other metabolic disorders.⁶ Indolizidine alkaloids, of which (+)-castanospermine (**1**) is one of the more prominent derivatives,⁷ rank among the most interesting

members of this class of compounds, termed generically iminosugars ("azasugars").⁸ Their pronounced biological activity has been ascribed to their ability to mimic the transition state involved in enzymatic glycoside hydrolysis. Thus, **1** can be regarded as a stereochemical mimic

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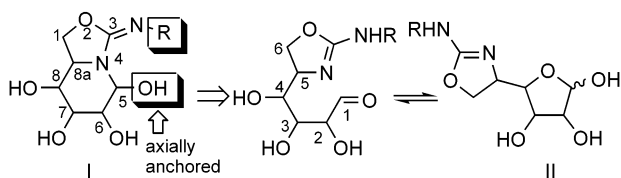


FIGURE 1. Retrosynthesis of reducing 2-oxa-3-iminoindolizidine derivatives (I) from aldohexofuranose-derived 2-aminooxazoline precursors (II).

tionally restricted monosaccharide analogue that retains the hydroxylation profile of the parent hexose. It also incorporates an aminoacetalic hydroxy group, anchored in the axial orientation, like the natural aglycons in α -glucopyranosides. In addition, incorporation of different substituents at the exocyclic nitrogen could be used to modulate the enzyme specificity, as is the case for trehazolin-type glycomimetics. Herein, we report a full account on the preparation of indolizidine-trehazolin hybrids structurally related to (+)-castanospermine (**1**) and (+)-6-epicastanospermine **2** as well as of the key intermediates. The scope and limitations of the methods and the structure, glycosidase inhibitory selectivities and potency relationships, are also discussed.

Results

Retrosynthesis. Assembly of the bicyclic skeleton of isourea-type indolizidine glycomimetics from carbohydrate precursors represents a very interesting challenge. A retrosynthetic analysis revealed that the 2-oxa-3-iminoindolizidine framework can be constructed by intramolecular nucleophilic addition of the endocyclic nitrogen atom of 2-aminooxazoline intermediates to a suitably located carbonyl group with simultaneous generation of the aminoacetal function (Figure 1). A key feature in the synthetic planning will be to introduce the five-membered cyclic isourea segment onto an aldohexofuranose template. Our synthetic strategy relies on the ability of the masked aldehyde group of the monosaccharide to act as the electrophilic target for the nitrogen atom of azole heterocycles with a pseudo-*C*-nucleoside structure through the open-chain tautomeric form. Hydroxylation profiles analogous to those of **1** and **2** in the final compounds (Figure 1, structure I) imply D-glucopyranose and D-manno configurations, respectively, of the 2-aminooxazoline precursors (Figure 1, structure II).

Isourea-Type (+)-Castanospermine-Related Glycomimetics. The initial synthetic objective of this research was the preparation of reducing 2-oxa-3-imino-(+)-castanospermine analogues, that is, 2-amino-2-oxazoline-piperidine bicyclic derivatives with an orientational pattern for the hydroxy groups at the six-membered ring analogous to that of α -D-glucopyranose. A new methodology has been developed for the construction of the cyclic isourea ring that exploits the reactivity of sugar carbodiimides, avoiding the use of hazardous reagents, such as mercury salts or isocyanates, generally employed in the reported syntheses of trehazolin analogues from thiourea¹⁸ or urea¹⁹ intermediates. Conventional acetylation of 5-azido-5-deoxy-1,2-isopropylidene-6-*O*-tetrahydropyranyl- α -D-glucopyranose **7**,²⁰ available in multigram scale from commercial D-glucurono-6,3-lactone, followed by hydrolysis of the tetrahydropyranyl

group and trimethylsilylation of the primary alcohol function led to the selectively protected azide intermediate **8**. Attempts to generate the corresponding triphenylphosphinimine (iminophosphorane, λ^5 -phosphazene, $R-N=PPh_3$) by the Staudinger reaction²¹ of **8** with triphenylphosphine required long reaction times and temperatures, leading to the formation of several byproducts. Nevertheless, when the reaction was effected in the presence of *n*-butyl, *n*-octyl, or phenyl isothiocyanate, the tandem Staudinger-aza-Wittig type transformation²¹ proceeded smoothly to give the carbodiimide adducts **11–13**. Probably the reaction occurs in this case through a transient phosphazide (triazaphosphazene, $R-N=N-N=PPh_3$), a known intermediate in the Staudinger reaction,²² instead of the phosphinimine. Similar trends have previously been observed in the preparation of other sugar carbodiimides.²³ Analogously, reaction of azide **8** with triphenylphosphine and in situ coupling with 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate²⁴ (**9**, rt) or methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato- α -D-glucopyranoside²⁵ (**10**, 80 °C) yielded the (1 \rightarrow 5) and (6 \rightarrow 5) carbodiimide-bridged pseudodisaccharides **14** and **15**, respectively (Scheme 1). The isolated yields varied from 70 to 75% for isothiocyanate reagents bearing electron-withdrawing groups (i.e., phenyl and glucopyranosyl) to 40–60% for alkyl-type isothiocyanates.

Further removal of the silyl ether group in **11–15** with tetra-*n*-butylammonium fluoride proceeded with spontaneous intramolecular nucleophilic addition of the generated hydroxyl group to the vicinal heterocumulene functionality, to give the required (4*R*)-4-(L-threofuranos-4'-yl)-2-amino-2-oxazoline pseudo-*C*-nucleoside derivatives **16–20**. In the case of the glucosyl derivative **14**, buffering the reaction mixture with acetic acid was necessary to avoid partial epimerization of the resulting glucosylamino-oxazoline at the anomeric position²⁶ (Scheme 2, a and b).

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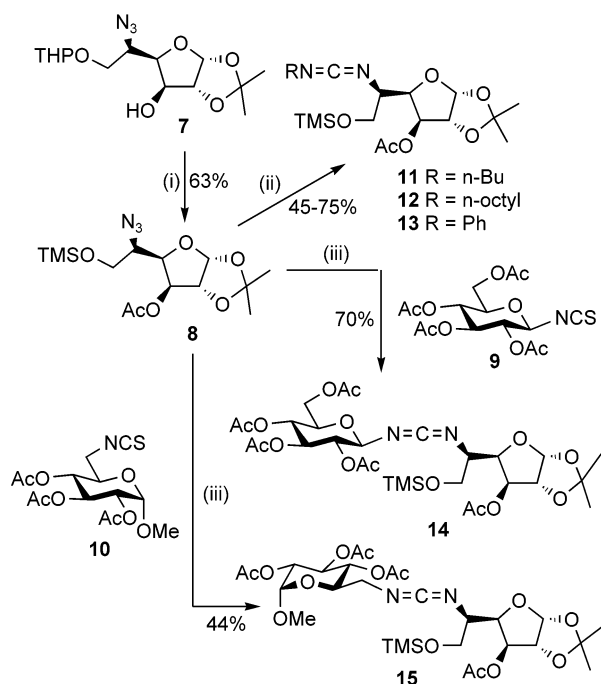
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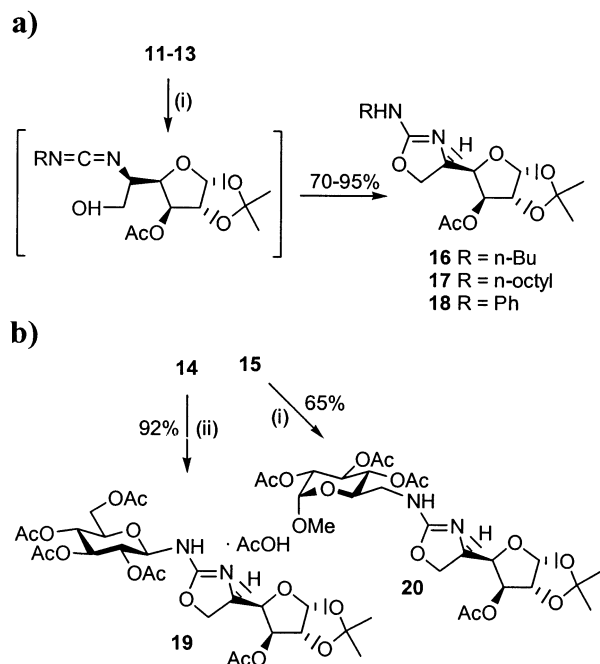
SCHEME 1^a

^a Reagents and conditions: (i) (a) Ac₂O–pyridine, (b) *p*-toluenesulfonic acid, (c) Me₃SiCl, hexamethyldisilazane, pyridine; (ii) PPh₃, RNCS (R = *n*-Bu, *n*-octyl, Ph), toluene, 80 °C (R = *n*-Bu, *n*-octyl) or rt (R = Ph), 2.5–24 h; (iii) toluene, rt (24 h) or 80 °C (8 h)

Conventional deacetylation and hydrolysis of the acetal protecting group in **16–20** with TFA–water led, initially, to α,β -anomeric mixtures of the corresponding D-glucopyranose oxazolinium trifluoroacetate salt derivatives, as seen from the ¹³C NMR and FABMS spectra of the crude reaction mixtures.²⁷ In the case of **16–19**, the equilibrium was spontaneously shifted toward the target 2-oxa-3-iminoindolizidines **21–24** upon neutralization with Amberlite IRA 68 (OH⁻) ion-exchange resin (Scheme 3). The fused bicyclic form (charged and neutral species) was the only one detected by NMR under several pH conditions. However, the (C-6)-linked methyl α -D-glucopyranoside derivative **25** existed in water solution as either the hemiacetal or the hemiaminal isomer depending not only on the final pH but also on the starting pH value. Thus, the product arising from the treatment of the amino-oxazoline precursor **20** with trifluoroacetic acid and further neutralization contained exclusively the mixture of glucopyranose anomers. Only the indolizidine form was, however, observed at pH 9, while reversion to the furanose form occurred at pHs below 4.²⁸

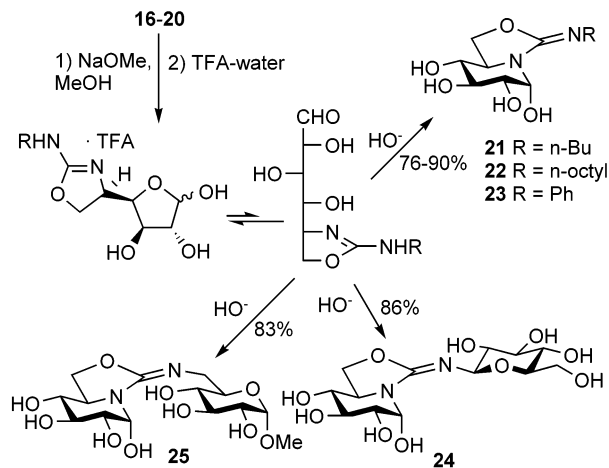
(26) Partial anomerization of the *N*- β -D-glucopyranosyl substituent in the presence of fluoride anion has also been observed during the preparation of the β -anomer of trehalosin. See: Kobayashi, Y.; Shiozaki, M. *J. Antibiot.* **1994**, *47*, 243.

(27) The ¹³C NMR spectra of the crude reaction mixtures in D₂O showed signals at 102.1–101.8 and 96.1–95.9 ppm, with similar intensities, for the C-1 resonances of the α - and β -hexofuranose anomers, respectively. See: Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27. Upon addition of 0.1 M NaOD to the solution in the NMR tube until a neutral to slightly basic pH was achieved, an instantaneous, virtually quantitative transformation into the final bicyclic compound was observed. The pseudomolecular peaks in the FABMS spectra of the crude reaction mixtures before neutralization showed an 18 *m/z* unit increase compared to those of the final compounds, in agreement with the proposed reaction pathway.

SCHEME 2^a

^a Reagents and conditions: (i) TBAF in THF, 0 °C, 25 min; (ii) TBAF in THF, AcOH (pH 7), 0 °C, 25 min

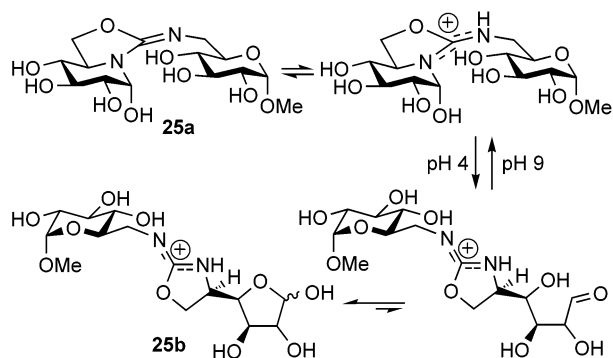
SCHEME 3



To better understand this pH-dependent behavior, the *pK_a* values of the 2-oxa-3-iminoindolizidines **21–25** were potentiometrically determined. The obtained values, 4.9 (**23**) and 5.2 (**24**) for derivatives with electron-withdrawing substituents and 6.9 (**21**), 7.0 (**22**), and 6.8 (**25**) for derivatives with alkyl-type substituents, indicated that the basicity of the isourea group for the isourea-type castanospermine related glycomimetics is lower as compared with trehalosin analogues (*a pK_a* value in the range

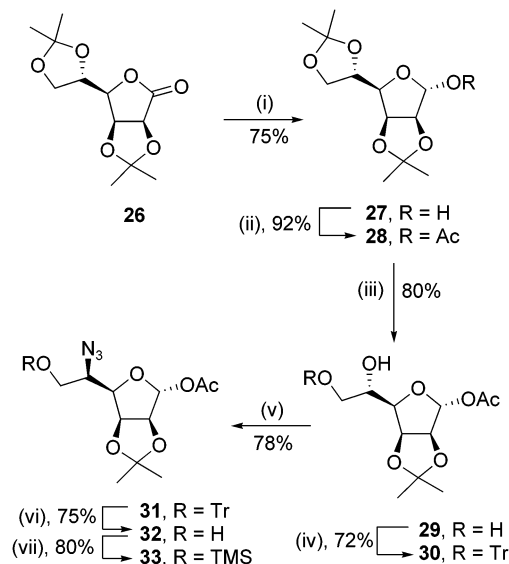
(28) A similar hemiacetal-hemiaminal equilibrium has been previously reported for cyclic guanidine-type glycomimetics. For these systems, it was observed that the interconversion rate between the two forms was slow enough to allow assuming that the species present in solution during determination of glycosidase inhibitor constants was that dictated by the initial pH. See: Jeong, J.-H.; Murray, B. W.; Takayama, S.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 4227. In our case, the interconversion rate seems to be extremely slow in a wide range of pHs (pH 9–4 in the case of **25**) and virtually instantaneous when the limit pH values are reached.

SCHEME 4



of 7.59–9.74 has been reported²⁹ for **6**). In the furanose form, protonation probably takes place at the endocyclic imino nitrogen,³⁰ thus preventing its participation in nucleophilic addition to the carbonyl group. At a critical pH value (between pH 5.5 and 6.5), the proportion of the neutral form is sufficient to promote rearrangement to the indolizidine system, probably protonated at the imino exocyclic nitrogen. We believe that the driving force for this process is the gain in stabilization due to the anomeric effect in the O-5–C-5–N fragment. Noteworthy, further lowering of the pH did not cause reversion to the furanose form in compounds **21–24**, probably because the positive charge is rather localized at the imino nitrogen atom in the iminoindolizidine species. The different behavior observed for the *N*-saccharidyl derivative **25**, with a pK_a value virtually identical to those measured for the *N*-butyl and *N*-octyl derivatives, may arise from differences in charge distribution within the amidine segment due to steric and/or solvation reasons. Thus, a higher positive charge density at the endocyclic nitrogen would result in the loss of the anomeric effect at the aminoacetal center, destabilizing the six-membered ring. Under the basic conditions, the noncharged iminoindolizidine form **25a** is favored, while under strong acidic conditions, the protonated 2-aminooxazoline-furanose form **25b** is the only species present in the solution (Scheme 4). It is noteworthy that the tautomeric form of **25** at a given pH between 4 and 9 is dictated by the initial pH of the preparation. In the evaluation of the glycosidase inhibitory properties of these compounds (see hereinafter), we have in all cases started from preparations at basic or neutral pH, containing exclusively the iminoindolizidine form. Since the determination of inhibition constants has been effected at pH 7.3–4.5, we can assume that we have only the ratio of neutral and uncharged isourea-type indolizidine glycomimetics dictated for the corresponding pK_a value and the new pH.

In the indolizidine form, compounds **21–25** existed in D₂O solutions as single diastereomers. The high field shift of the C-5 resonance, as compared with the corresponding values for the anomeric carbon C-1 in the furanose form, confirmed the aminoacetal structure, whereas the vicinal $^3J_{\text{HH}}$ values around the piperidine

SCHEME 5^a

^a Reagents and conditions: (i) DIBAL, toluene, $-78\text{ }^\circ\text{C} \rightarrow \text{rt}$, 2 h; (ii) Ac₂O, pyridine; (iii) 50% aq AcOH, $40\text{ }^\circ\text{C}$, 2 h; (iv) TrCl, pyridine, rt, 36 h; (v) (a) Tf₂O, pyridine, CH₂Cl₂, $-25\text{ }^\circ\text{C} \rightarrow 25\text{ }^\circ\text{C}$, 1 h, (b) NaN₃, DMF, rt, 18 h; (vi) BF₃·Et₂O, CH₂Cl₂, $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 2 h; (vii) TMSCl, hexamethyldisilazane, pyridine, rt, 2 h.

ring unambiguously pointed to the 5*R* configuration for the new stereocenter, with the pseudoanomeric hydroxy group in axial position, fitting the anomeric effect.

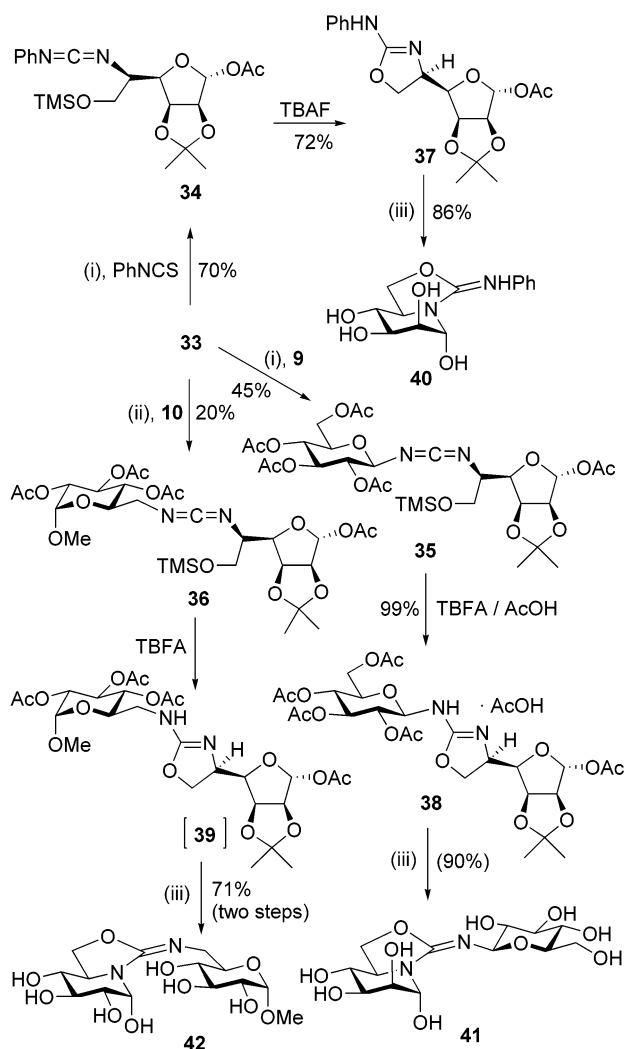
Isourea-Type (+)-6-Epicastanospermine-Related Glycomimetics. To implement the above strategy of accessing reducing 2-oxa-3-iminoindolizidines in order to synthesize (+)-6-epicastanospermine analogues, the preparation of D-mannofuranose-derived 2-amino-2-oxazolines was required. Our approach started from 2,3,5,6-di-*O*-isopropylidene-L-gulono- γ -lactone (**26**),³¹ prepared by acetonation of commercial L-gulono- γ -lactone. Reduction of the carbonyl group with DIBAL and acetylation of the resulting lactol **27** afforded the corresponding 1-*O*-acetyl- β -L-gulofuranose diacetonide **28**. Removal of the 5,6-isopropylidene protecting group (\rightarrow **29**), selective protection of the primary alcohol function as the corresponding triphenylmethyl ether (\rightarrow **30**), and inversion of the configuration at C-5 by azide anion, via trifluoromethanesulfonate ester, led to the 5-azido-5-deoxy- α -D-mannofuranose derivative **31**. The trityl group was then replaced by trimethylsilyl through a two-step reaction sequence involving selective removal by treatment with boron trifluoride–diethyl ether complex (\rightarrow **32**) and further reaction with trimethylsilyl chloride–hexamethyldisilazane to give the key selectively protected azide precursor **33** (Scheme 5).

The reaction pathway followed for preparation of the fused piperidine, oxazolidine derivatives **40–42**, mimicking the topography of (+)-6-epicastanospermine, paralleled that above commented for the synthesis of (+)-castanospermine related compounds. Thus, tandem Staudinger–aza-Wittig-type reaction of the selectively protected azide **33** with triphenylphosphine and phenyl isothiocyanate or the sugar isothiocyanates **9** or **10**

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SCHEME 6^a

^a Reagents and conditions: (i) PPh_3 , toluene, rt, 24 h; (ii) PPh_3 , toluene, 40 °C, 24 h; (iii) (a) NaOMe, MeOH, (b) 90% aq TFA, (c) OH^- .

yielded the carbodiimide adducts **34**–**36**, respectively. The coupling yields (20–70%) were significantly lower as compared with the D-gluco series, probably due to the steric hindrance imposed by the cis-oriented isopropylidene group. Removal of the silyl ether functionality using tetra-*n*-butylammonium fluoride provided the requested L-erythrofuranose-derived 2-amino-2-oxazolines **37**–**39**. Partial deacetylation was observed at this step in the case of compound **39**. Nevertheless, upon full deacetylation, acid treatment, and neutralization (or base treatment in the case of **39**), the furanose intermediates rearranged into the target 2-oxa-3-iminoindolizidines **40**–**42** (Scheme 6). As previously observed in the (+)-castanospermine series, the C-6-linked methyl α -D-glucopyranoside derivative **42** exhibited a distinct pH-dependent reversibility between the hemiaminal indolizidine form and the hemiacetal furanose form. Nevertheless, once generated from the furanose precursor (pH 9), the indolizidine species, in either neutral or charged form, remains stable in water solution at basic or moderately acidic pH (up to pH 4).

Indolizidines **40**–**42** existed in D_2O solution as single diastereomers. The absence of NOE contacts between the pseudoanomeric proton H-5 and the α -oriented piperidine protons H-6 and H-8a is indicative of the axial disposition of the aminoacetalic hydroxy group, in agreement with the existence of a very strong and stabilizing interaction between the π -type lone pair of the endocyclic nitrogen of the isourea grouping and the σ^* antibonding orbital of the contiguous C–O bond. To the best of our knowledge, compounds **21**–**25** and **40**–**42** represent the first examples of ring-modified indolizidine glycomimetics bearing exocyclic substituents.

Biological Activity. The inhibitory activities of the isourea type indolizidine glycomimetics **21**–**25** and **40**–**42** for α -glucosidase (yeast), β -glucosidase (almonds), β -glucosidase (bovine liver, cytosolic), trehalase (pig kidney), α -galactosidase (green coffee beans), amyloglucosidase (*Aspegillus niger*), α -mannosidase (jack beans), and α -fucosidase (bovine kidney) are summarized in Table 1. The presence of a pseudoanomeric hydroxy group anchored in the axial position was expected to be translated into an increased selectivity toward α -glycosidases. Actually, the (+)-castanospermine pseudodisaccharide analogue **24** showed inhibition constants (K_i) against yeast α -glucosidase (17 μM) and almond β -glucosidase (212 μM) at their optimal pH (6.8 and 5.5, respectively), indicative of a reverse selectivity as compared to **1** (>1500 and 1.5 μM , respectively).⁹ Yet, a strong influence of the nature of the exocyclic substituent on the inhibition constant was observed. Thus, the C-6-linked methyl α -D-glucopyranoside derivative **25** was a weak inhibitor for both enzymes ($K_i = 463$ and 336 μM , respectively), whereas compounds **21**–**23**, bearing lipophilic substituents, inhibited β -glucosidase more potently than α -glucosidase. The *N*-octyl derivative **22** ($K_i = 3.2$ μM) was about 10-fold a more potent inhibitor of this enzyme than the *N*-phenyl **23** and *N*-butyl **21** counterparts ($K_i = 23$ and 30 μM , respectively). Interestingly, the inhibitory potency of **22** doubled on going from pH 5.5 to pH 7.3 ($K_i = 1.9$ μM), and it additionally behaved as a strong competitive inhibitor of the mammalian β -glucosidase ($K_i = 2.7$ μM) at the latter pH value, the optimal for this particular enzyme. Compounds **21**–**23** also were weak inhibitors of trehalase. In all cases, the enzyme inhibition mode was found to be of the competitive type.

The stereochemical complementarity of the polyhydroxylated piperidine ring and the putative substrate seems to be a major requirement for glycosidase inhibition by this family of glycomimetics. Thus, in the diastereoisomeric (+)-6-epicastanospermine series, the glucosidase inhibitory activity was drastically diminished. No inhibition of α -mannosidase was observed for **40**–**42**, despite the apparent structural similarity with α -mannosides, as is the case for the natural compound **2**.⁹ Neither **21**–**25** nor **40**–**42** inhibited α -galactosidase, in agreement with the configurational specificity of the parent indolizidine alkaloids.

The higher selectivity of **1** toward some α -glucosidases as compared with the piperidine analogue **3** 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 orientation of the oxygen substituent at the position equivalent to C-6 to fully interact

TABLE 1. Glycosidase Inhibitory Activities (K_i , μM) for Indolizidine–Trehazolin Hybrids **21–25 and **40–42****

enzyme	21	22	23	24	25	40	41	42
α -glucosidase (yeast) ^a	57	168	57	17	463	179	282	378
β -glucosidase (almonds) ^b	30	3.2	23	212	336	188	213	222
	15 ^c	1.9 ^c						
β -glucosidase (bovine liver) ^c	27	2.7	244	157	n.i. ^d	1380	565	349
trehalase (pig kidney) ^e	189	182	244	n.i.	n.i.	n.i.	n.i.	n.i.
α -galactosidase (coffee beans) ^a	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
α -mannosidase (jack beans) ^b	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
α -fucosidase (bovine kidney) ^b	240	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
amyloglucosidase (<i>Aspergillus niger</i>) ^f	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.

^a pH 6.8. ^b pH 5.5. ^c pH 7.3. ^d No inhibition detected. ^e pH 6.0. ^f pH 4.5.

with the binding site of the enzyme. We had previously observed that replacing the 1-hydroxyindolizidine structure into a 2-oxaindolizidine skeleton, which is formally equivalent to a rotation of 120° about the above bond, results in a shift of the α -glucosidase selectivity.¹⁴ Thus, **1** and **2** do not inhibit yeast α -glucosidase and are good inhibitors of amyloglucosidase ($K_i = 8 \mu\text{M}$ for **1**, $\text{IC}_{50} = 7.4 \mu\text{M}$ for **2**),⁹ while 2-oxacastanospermine analogues exhibited the reverse selectivity.¹⁴ Similar trends are observed for the new castanospermine–trehazolin hybrids when considering this pair of enzymes.

The competitive inhibition of β -glucosidases by compounds **21–23**, bearing lipophilic substituents, is noteworthy. These results underline the importance of secondary interactions in glycosidase binding, even overpowering other effects related to the glyconic binding site. Moreover, the increase in the inhibition potency toward β -glucosidase upon shifting from pH 5.5 to pH 7.3 points to the neutral iminoindolizidine form (see, e.g., **25a**) as the active species, which is probably protonated from one of the catalytic carboxylic groups of the enzyme to form a tight complex. A similar observation has been reported for the inhibition of green coffee bean α -galactosidase by cyclic guanidine glycomimetics.²⁸

Conclusions

We have described here an effective synthetic route to a new family of sp²-azasugar glycomimetics that combine the essential structural features of indolizidines and trehazolins. Starting from D-glucose and L-gulose precursors, reducing analogues of (+)-castanospermine and its 6-epi diastereoisomer, respectively, were prepared by a reaction sequence that involves (i) tandem Staudiger–aza-Wittig-type coupling reaction of an azido sugar with an isothiocyanate, (ii) transformation of the resulting carbodiimide adduct into a 2-amino-1,3-oxazoline pseudo-C-nucleoside derivative, and (iii) rearrangement of the furanose intermediate through the open chain aldehyde form to give the bicyclic 3-imino-2-oxaindolizidine skeleton. The glycosidase inhibition studies evidenced a remarkable influence of the nature of the exocyclic substituent in the inhibitory properties, as well as a pH dependence of the inhibition constant. Although the inhibition potency described in this study is moderate (K_i values in the micromolar range), the prepared indolizidine–trehazolin hybrids provide a new direction to the synthesis of highly specific inhibitors and new insights into the mechanism of inhibition of glycosidases.

Experimental Section

Materials. 5-Azido-5-deoxy-1,2-*O*-isopropylidene-6-*O*-tetrahydropyranyl- α -D-glucofuranose (**7**) was prepared from com-

mmercial D-glucofuranurono-6,3-lactone in four steps as reported by Dax et al.²⁰ 2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate (**9**) was synthesized from the corresponding per-*O*-acetyl glucopyranosyl bromide by treatment with potassium thiocyanate and tetra-*n*-butylammonium hydrogensulfate in acetonitrile, following the procedure of Camarasa et al.²⁴ Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato- α -D-glucopyranoside (**10**) was obtained by isothiocyanation of the corresponding 6-amino-6-deoxysugar using thiophosgene as reported.²⁵ 2,3,5,6-Di-*O*-isopropylidene-L-gulonolactone was obtained by isopropylation of commercial L-gulonolactone.³¹ Reagents and solvents were commercial grade and were used as supplied, with the following exceptions: Potassium thiocyanate was dried with heating under vacuum at 80 °C. DMF was distilled from BaO, methanol was distilled from methylmagnesium iodide, pyridine was distilled from KOH, and acetic anhydride was distilled from freshly melted sodium acetate.

3-*O*-Acetyl-5-azido-5-deoxy-1,2-*O*-isopropylidene-6-*O*-trimethylsilyl- α -D-glucofuranose (8**).** To a solution of 5-azido-5-deoxy-1,2-*O*-isopropylidene-6-*O*-tetrahydropyranyl- α -D-glucofuranose²⁰ **7** (1.71 g, 5.2 mmol) in pyridine (8.5 mL) at rt, Ac₂O (8.5 mL) was added and the reaction mixture was stirred for 2 h. After conventional workup, the crude acetate product was dissolved in CH₂Cl₂–MeOH (1:1, 60 mL) and *p*-toluenesulfonic acid (168 mg) was added. The reaction mixture was stirred at rt for 2 h, and then diluted with CH₂Cl₂ (60 mL), washed with saturated aqueous NaHCO₃ (2 × 100 mL), dried (MgSO₄), filtered, and concentrated. The resulting residue was purified by column chromatography using 1:6 → 1:1 EtOAc–petroleum ether as eluent. Trimethylsilylation of the generated primary hydroxyl group was effected by treatment with trimethylsilyl chloride (5.3 mL) and hexamethyldisilazane (10.6 mL) in pyridine (22 mL) at rt for 2 h. The solvents were eliminated, and the residue was extracted with petroleum ether and concentrated to give **3** (1.17 g, 63% overall) as an amorphous solid. $[\alpha]_D -35.3$ (*c* 1.1, CH₂Cl₂). R_f 0.38 (1:6 EtOAc–petroleum ether). IR (KBr): ν_{max} 2988, 2101, 1751, 1651, 1454, 1377, 1258, 1094 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.88 (d, 1 H, $J = 3.7$ Hz), 5.25 (d, 1 H, $J = 3.0$ Hz), 4.50 (d, 1 H, $J = 3.7$ Hz), 4.13 (dd, 1 H, $J = 3.0, 9.8$ Hz), 4.02 (dd, 1 H, $J = 2.7, 10.8$ Hz), 3.73 (dd, 1 H, $J = 7.2, 10.8$ Hz), 3.63 (ddd, 1 H, $J = 2.7, 7.2, 9.8$ Hz), 2.12 (s, 3 H), 1.49, 1.30 (2 s, 6 H), 0.14 (s, 9 H). ¹³C NMR (125.7 MHz, CDCl₃): δ 169.4, 112.3, 104.9, 82.9, 76.8, 76.1, 63.6, 60.7, 26.5, 26.1, 20.7, –0.80. FABMS: m/z 360 (30, $[M + H]^+$). Anal. Calcd for C₁₄H₂₅N₃O₆–Si: C, 76.78; H, 7.01; N, 11.69. Found: C, 76.68; H, 6.99; N, 11.66.

General Procedure for the Preparation of 5-Carbodiimido-5-deoxy-D-glucofuranoses (11–15**).** To a solution of azide **8** (500 mg, 1.39 mmol) and the corresponding isothiocyanate (*n*-butyl, *n*-octyl, phenyl, **9**, or **10**) in toluene (8 mL) under Ar, a solution of triphenylphosphine (400 mg, 1.53 mmol, 1.1 equiv) in toluene (4 mL) was dropwise added at rt. The reaction mixture was stirred at rt (**13** and **14**) or at 80 °C (**11**, **12**, and **15**) for 2.5–24 h (TLC) and concentrated. The resulting residue was purified by column chromatography using the solvent indicated in each case to afford the carbodiimide adducts as amorphous solids.

3-*O*-Acetyl-5-(3-butylcarbodiimido)-5-deoxy-1,2-*O*-isopropylidene-6-*O*-trimethylsilyl- α -D-glucofuranose (11). Column chromatography, eluent toluene and then 1:10 \rightarrow 1:8 EtOAc–toluene; yield 298 mg (52%). $[\alpha]_D -34.0$ (*c* 1.0, CH₂Cl₂). *R*_f 0.45 (1:7 EtOAc–toluene). IR (KBr): ν_{\max} 2957, 2131, 1751, 1375, 1223, 1101 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.85 (d, 1 H, *J* = 3.7 Hz), 5.25 (d, 1 H, *J* = 3.0 Hz), 4.47 (d, 1 H, *J* = 3.7 Hz), 4.13 (dd, 1 H, *J* = 3.0, 9.7 Hz), 3.91 (dd, 1 H, *J* = 2.6, 10.3 Hz), 3.63 (dd, 1 H, *J* = 6.8, 10.3 Hz), 3.56 (ddd, 1 H, *J* = 2.6, 6.8, 9.7 Hz), 3.19 (t, 2 H, *J* = 7.0 Hz), 2.09 (s, 3 H), 1.52 (m, 2 H), 1.48, 1.29 (2 s, 6 H), 1.36 (m, 2 H), 0.90 (t, 3 H, *J* = 7.0 Hz), 0.14–0.12 (s, 9 H). ¹³C NMR (125.7 MHz, CDCl₃): δ 169.6, 139.9, 112.1, 105.0, 82.9, 78.1, 76.2, 63.7, 57.0, 46.2, 33.0, 26.6, 26.2, 20.8, 19.9, 13.5, –0.60. FABMS: *m/z* 415 (100, [M + H]⁺). Anal. Calcd for C₁₉H₃₄N₂O₆Si: C, 55.04; H, 8.26; N, 6.75. Found: C, 54.87; H, 8.21; N, 6.95.

3-*O*-Acetyl-5-deoxy-1,2-*O*-isopropylidene-5-(3-octylcarbodiimido)-6-*O*-trimethylsilyl- α -D-glucofuranose (12). Column chromatography, eluent toluene and then 1:10 EtOAc–toluene; yield 293 mg (45%). $[\alpha]_D -24.0$ (*c* 1.0, CH₂Cl₂). *R*_f 0.57 (1:7 EtOAc–toluene). IR (KBr): ν_{\max} 2930, 2131, 1759, 1381, 1223, 1101 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.87 (d, 1 H, *J* = 3.7 Hz), 5.27 (d, 1 H, *J* = 3.0 Hz), 4.48 (d, 1 H, *J* = 3.7 Hz), 4.14 (dd, 1 H, *J* = 3.0, 9.5 Hz), 3.92 (dd, 1 H, *J* = 2.4, 9.9 Hz), 3.64 (dd, 1 H, *J* = 6.8, 9.9 Hz), 3.57 (ddd, 1 H, *J* = 2.4, 6.8, 9.5 Hz), 3.19 (t, 2 H, *J* = 7.0 Hz), 2.10 (s, 3 H), 1.56 (q, 2 H, *J* = 7.0 Hz), 1.49, 1.29 (2 s, 6 H), 1.26 (m, 10 H), 0.87 (t, 3 H, *J* = 7.0 Hz), 0.14–0.12 (s, 9 H). ¹³C NMR (125.7 MHz, CDCl₃): δ 169.5, 139.9, 112.0, 104.9, 82.8, 78.0, 76.1, 63.7, 56.9, 46.5, 31.6, 30.9, 26.7, 26.1, 29.0, 26.5, 22.5, 20.7, 13.9, –0.60. FABMS: *m/z* 493 (70, [M + Na]⁺), 471 (100, [M + H]⁺). Anal. Calcd for C₂₃H₄₂N₂O₆Si: C, 58.69; H, 8.99; N, 5.95. Found: C, 58.45; H, 8.93; N, 5.84.

3-*O*-Acetyl-5-deoxy-1,2-*O*-isopropylidene-5-(3-phenylcarbodiimido)-6-*O*-trimethylsilyl- α -D-glucofuranose (13). Column chromatography, eluent toluene and then 1:7 EtOAc–toluene; yield 452 mg (75%). $[\alpha]_D -38.2$ (*c* 1.0, CH₂Cl₂). *R*_f 0.56 (1:7 EtOAc–toluene). IR (KBr): ν_{\max} 2999, 2959, 2133, 1752, 1379, 1228, 1100, 1021, 846 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.27–7.09 (m, 5 H), 5.89 (d, 1 H, *J* = 3.7 Hz), 5.32 (d, 1 H, *J* = 3.0 Hz), 4.51 (d, 1 H, *J* = 3.7 Hz), 4.25 (dd, 1 H, *J* = 2.1, 6.8, 9.4 Hz), 3.99 (dd, 1 H, *J* = 2.1, 9.9 Hz), 3.82 (ddd, 1 H, *J* = 2.1, 6.8, 9.4 Hz), 3.74 (dd, 1 H, *J* = 6.8, 9.9 Hz), 2.09 (s, 3 H), 1.51, 1.31 (2 s, 6 H), 0.06 (s, 9 H). ¹³C NMR (75.5 MHz, CDCl₃): δ 169.5, 139.6, 138.2–123.8, 112.2, 105.0, 82.8, 77.7, 76.1, 63.4, 57.7, 26.5, 26.1, 20.7, –0.87. FABMS: *m/z* 435 (100, [M + H]⁺). Anal. Calcd for C₂₁H₃₀N₂O₆Si: C, 58.04; H, 6.96; N, 6.45. Found: C, 57.85; H, 6.85; N, 6.44.

3-*O*-Acetyl-5-deoxy-1,2-*O*-isopropylidene-5-[3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)carbodiimido]-6-*O*-trimethylsilyl- α -D-glucofuranose (14). Column chromatography, eluent toluene and then 1:4 \rightarrow 1:2 EtOAc–petroleum ether; yield 669 mg (70%). $[\alpha]_D -24.1$ (*c* 1.0, CH₂Cl₂). *R*_f 0.28 (1:3 EtOAc–petroleum ether, two elutions). IR (KBr): ν_{\max} 2986, 2955, 2143, 1751, 1454, 1373, 1227, 1094 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 5.83 (d, 1 H, *J* = 3.7 Hz), 5.25 (d, 1 H, *J* = 3.0 Hz), 5.15 (t, 1 H, *J* = 9.5 Hz), 5.06 (t, 1 H, *J* = 9.5 Hz), 4.87 (t, 1 H, *J* = 9.5 Hz), 4.68 (d, 1 H, *J* = 9.5 Hz), 4.44 (d, 1 H, *J* = 3.7 Hz), 4.22 (dd, 1 H, *J* = 4.8, 12.4 Hz), 4.16 (dd, 1 H, *J* = 3.0, 9.5 Hz), 4.10 (dd, 1 H, *J* = 2.5, 12.4 Hz), 3.88 (dd, 1 H, *J* = 2.1, 9.8 Hz), 3.73 (ddd, 1 H, *J* = 2.5, 4.8, 9.5 Hz), 3.66 (dd, 1 H, *J* = 6.1, 9.8 Hz), 3.63 (ddd, 1 H, *J* = 2.1, 6.1, 9.5 Hz), 2.08, 2.07, 2.04, 2.01, 2.00 (5 s, 15 H), 1.47, 1.26 (2 s, 6 H), 0.12 (s, 9 H). ¹³C NMR (75.5 MHz, CDCl₃): δ 170.5, 170.1, 169.7, 169.1, 168.9, 138.2, 112.2, 104.9, 84.7, 82.7, 77.5, 75.8, 73.7, 72.9, 72.4, 67.9, 63.0, 61.7, 56.9, 26.4, 26.0, 21.1, 20.8, 20.5, 20.4, 20.3, –0.80. CIMS: *m/z* 689 (95%, [M + H]⁺). Anal. Calcd for C₂₉H₄₄N₂O₁₅Si: C, 50.57; H, 6.44; N, 4.07. Found: C, 50.30; H, 6.33; N, 3.85.

3-*O*-Acetyl-5-deoxy-1,2-*O*-isopropylidene-5-[3-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy- α -D-glucopyranosyl-6-yl)-carbodiimido]-6-*O*-trimethylsilyl- α -D-glucofuranose (15).

Column chromatography, eluent toluene and then 1:5 \rightarrow 1:3 EtOAc–petroleum ether; yield 404 mg (44%). $[\alpha]_D +55.8$ (*c* 0.8, CH₂Cl₂). *R*_f 0.25 (1:2 EtOAc–petroleum ether). IR (KBr): ν_{\max} 2953, 2876, 2137, 1751, 1373, 1225, 1045 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.76 (d, 1 H, *J* = 3.7 Hz), 5.34 (dd, 1 H, *J* = 9.4, 10.0 Hz), 5.16 (d, 1 H, *J* = 2.8 Hz), 4.86 (t, 1 H, *J* = 9.4 Hz), 4.85 (d, 1 H, *J* = 3.6 Hz), 4.76 (dd, 1 H, *J* = 3.6 Hz), 4.38 (d, 1 H, *J* = 3.7 Hz), 4.05 (dd, 1 H, *J* = 2.8, 9.6 Hz), 3.79 (dd, 1 H, *J* = 2.5, 10.1 Hz), 3.74 (dt, 1 H, *J* = 4.8, 9.4 Hz), 3.55 (dd, 1 H, *J* = 4.8, 10.0 Hz), 3.51 (dd, 1 H, *J* = 4.8, 10.0 Hz), 3.50 (m, 2 H), 3.30 (s, 3 H), 2.02, 1.96, 1.92, 1.90 (4 s, 12 H), 1.40, 1.20 (2 s, 6 H), 0.05 (s, 9 H). ¹³C NMR (125.7 MHz, CDCl₃): δ 169.8, 169.7, 169.4, 169.3, 139.9, 112.1, 104.9, 96.4, 82.8, 77.8, 75.9, 70.7, 70.0, 69.8, 68.2, 63.4, 56.8, 55.4, 46.9, 26.5, 26.1, 20.8, 20.6, 20.4, 20.3, –0.67. CIMS: *m/z* 661 (100, [M + H]⁺). HRCIMS: *m/z* 661.264475 (calcd 661.264008). Anal. Calcd for C₂₈H₄₄N₂O₁₄Si: C, 50.89; H, 6.71; N, 4.24. Found: C, 50.85; H, 6.64; N, 4.20.

General Procedure for the Preparation of 4-(L-Threo-furanos-4'-yl)-2-amino-2-oxazolines (16–20). To a solution of the corresponding carbodiimide **11–15** (0.5 mmol) in THF (10 mL) at 0 °C under Ar, TBAF (1 M in THF, 0.55 mL, 1.1 equiv) was added. In the case of **14**, the reaction mixture was adjusted at pH 7 using glacial AcOH. The solution was stirred at 0 °C until the disappearance of the starting material (25 min), then diluted with Et₂O (5 mL), washed with water (2 \times 3 mL), dried (MgSO₄), filtered, and concentrated. The residue was purified by column chromatography using the eluent indicated in each case.

(4*R*)-4-[(4*R*)-3'-*O*-Acetyl-1,2'-*O*-isopropylidene- β -L-threo-furanos-4'-yl]-2-butylamino-2-oxazoline (16). Column chromatography, eluent EtOAc and then 45:5:3 EtOAc–EtOH–H₂O; yield 159 mg (95%). $[\alpha]_D -24.4$ (*c* 0.98, CH₂Cl₂). *R*_f 0.30 (45:5:3 EtOAc–EtOH–H₂O). IR (KBr): ν_{\max} 3389, 2959, 1748, 1543, 1456, 1375, 1225, 1074 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.87 (d, 1 H, *J* = 3.7 Hz), 5.18 (d, 1 H, *J* = 2.6 Hz), 4.51 (d, 1 H, *J* = 3.7 Hz), 4.50 (dd, 1 H, *J* = 5.5, 8.4 Hz), 4.42 (t, 1 H, *J* = 8.4 Hz), 4.26 (ddd, 1 H, *J* = 5.5, 7.4, 8.4 Hz), 4.25 (dd, 1 H, *J* = 2.6, 7.4 Hz), 3.19 (td, 3 H, *J* = 3.0, 7.1 Hz), 2.10 (s, 3 H), 1.50 (q, 2 H, *J* = 7.0 Hz), 1.49, 1.28 (2 s, 6 H), 1.33 (m, 2 H, *J* = 7.0 Hz), 0.90 (t, 3 H). ¹³C NMR (125.7 MHz, CDCl₃): δ 169.7, 162.1, 112.4, 104.9, 83.3, 80.8, 73.5, 71.6, 59.7, 42.6, 31.7, 26.7, 26.2, 21.0, 19.8, 13.6. FABMS: *m/z* 343 (100, [M + H]⁺). Anal. Calcd for C₁₆H₂₆N₂O₆: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.96; H, 7.47; N, 8.06.

(4*R*)-4-[(4*R*)-3'-*O*-Acetyl-1,2'-*O*-isopropylidene- β -L-threo-furanos-4'-yl]-2-octylamino-2-oxazoline (17). Column chromatography, eluent EtOAc and then 45:5:3 EtOAc–EtOH–H₂O; yield 139 mg (70%). $[\alpha]_D -33.3$ (*c* 1.0, CH₂Cl₂). *R*_f 0.36 (45:5:3 EtOAc–EtOH–H₂O). IR (KBr): ν_{\max} 3350, 2930, 1757, 1589, 1375, 1223, 1101 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.86 (d, 1 H, *J* = 3.7 Hz), 5.07 (d, 1 H, *J* = 3.0 Hz), 4.59 (dd, 1 H, *J* = 5.0, 8.8 Hz), 4.53 (t, 1 H, *J* = 7.0 Hz), 4.52 (d, 1 H, *J* = 3.7 Hz), 4.28 (dt, 1 H, *J* = 5.0, 7.0 Hz), 4.25 (dd, 1 H, *J* = 3.4, 7.0 Hz), 3.15 (td, 2 H, *J* = 1.4, 7.0 Hz), 2.10 (s, 3 H), 1.53 (q, 2 H, *J* = 7.0 Hz), 1.49, 1.28 (2 s, 6 H), 1.24 (m, 2 H), 0.87 (t, 3 H, *J* = 7.0 Hz). ¹³C NMR (75.5 MHz, CDCl₃): δ 169.6, 162.7, 112.3, 104.9, 83.1, 79.9, 76.4, 71.8, 55.8, 42.1, 31.6, 29.5, 26.5, 25.9, 22.4, 20.8, 13.9. FABMS: *m/z* 421 (30, [M + Na]⁺), 399 (100, [M + H]⁺). Anal. Calcd for C₂₂H₃₈N₂O₈: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.17; H, 8.32; N, 6.93.

(4*R*)-4-[(4*R*)-3'-*O*-Acetyl-1,2'-*O*-isopropylidene- β -L-threo-furanos-4'-yl]-2-phenylamino-2-oxazoline (18). Column chromatography, eluent 100:1 CH₂Cl₂–MeOH; yield 136 mg (75%). $[\alpha]_D -6.5$ (*c* 1.0, CH₂Cl₂). *R*_f 0.30 (20:1 CH₂Cl₂–MeOH). IR (KBr): ν_{\max} 3349, 2991, 1752, 1553, 1379, 1236, 1077 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.36–7.25 (m, 5 H), 7.00 (m, 1 H), 5.91 (d, 1 H, *J* = 3.7 Hz), 5.34 (d, 1 H, *J* = 2.9 Hz), 4.53 (d, 1 H, *J* = 3.7 Hz), 4.40 (m, 2 H), 4.31 (m, 1 H), 4.23 (dd, 1 H, *J* = 2.9, 7.6 Hz), 2.11 (s, 3 H), 1.51, 1.31 (2 s, 6 H). ¹³C NMR (75.5 MHz, CDCl₃): δ 169.7, 157.3, 129.1–118.5, 112.1, 104.8, 83.2, 81.4, 76.1, 69.6, 56.0, 26.5, 26.0, 20.8; FABMS: *m/z* 363

(100%, [M + H]⁺). Anal. Calcd for C₁₈H₂₂N₂O₆: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.69; H, 6.07; N, 7.75.

(4R)-4-[(4R)-3'-O-Acetyl-1',2'-O-isopropylidene-β-L-threofuranos-4'-yl]-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)amino-2-oxazolium Acetate (19). Column chromatography, eluent 100:1 → 20:1 CH₂Cl₂-MeOH; yield 310 mg (92%). [α]_D -20.0 (c 1.0, CH₂Cl₂). R_f 0.53 (20:1 CH₂Cl₂-MeOH). IR (KBr): ν_{max} 3443, 2961, 1750, 1559, 1514, 1377, 1258, 1094 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 5.86 (d, 1 H, J = 3.7 Hz), 5.65 (bs, 1 H, NH), 5.22 (t, 1 H, J = 9.3 Hz), 5.13 (d, 1 H, J = 3.0 Hz), 5.06 (t, 1 H, J = 9.3 Hz), 4.98 (t, 1 H, J = 9.3 Hz), 4.89 (d, 1 H, J = 9.3 Hz), 4.51 (d, 1 H, J = 3.7 Hz), 4.45 (m, 2 H), 4.26 (m, 1 H), 4.25 (dd, 1 H, J = 4.8, 12.4 Hz), 4.17 (dd, 1 H, J = 3.0, 7.8 Hz), 4.10 (dd, 1 H, J = 2.2, 12.4 Hz), 3.77 (ddd, 1 H, J = 2.2, 4.8, 9.3 Hz), 2.09, 2.05, 2.01, 2.00, 1.99, 1.92 (6 s, 18 H), 1.50, 1.29 (2 s, 6 H). ¹³C NMR (75.5 MHz, CDCl₃): δ 178.0, 170.6, 169.9, 169.6, 169.3, 168.9, 161.2, 112.1, 104.7, 83.1, 82.2, 80.7, 76.2, 73.1, 72.8, 71.5, 70.4, 68.0, 61.6, 59.9, 26.5, 25.9, 22.8, 21.1, 20.8, 20.6, 20.5, 20.4. FABMS: m/z 639 (100, [M - AcOH + Na]⁺), 617 (50%, [M - AcO]⁻). Anal. Calcd for C₂₈H₄₀N₂O₁₇: C, 49.70; H, 5.96; N, 4.14. Found: C, 49.83; H, 5.90; N, 3.92.

(4R)-4-[(4R)-3'-O-Acetyl-1',2'-O-isopropylidene-β-L-threofuranos-4'-yl]-2-(methyl 2,3,4-tri-O-acetyl-α-D-glucopyranosyl-6-yl)amino-2-oxazoline (20). Column chromatography, eluent 100:1 → 20:1 CH₂Cl₂-MeOH; yield 191 mg (65%). [α]_D +38.5 (c 1.0, CH₂Cl₂). R_f 0.43 (45:5:3 EtOAc-EtOH-H₂O). IR (KBr): ν_{max} 3443, 2984, 1751, 1565, 1373, 1225, 1101 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.82 (d, 1 H, J = 3.7 Hz), 5.40 (dd, 1 H, J = 9.5, 10.1 Hz), 5.15 (d, 1 H, J = 2.9 Hz), 4.87 (d, 1 H, J = 3.6 Hz), 4.80 (dd, 1 H, J = 3.6 Hz), 4.44 (d, 1 H, J = 3.7 Hz), 4.40 (t, 1 H, J = 9.5 Hz), 4.29 (m, 3 H), 4.09 (dd, 1 H, J = 2.9, 7.9 Hz), 3.82 (ddd, 1 H, J = 2.9, 5.4, 9.5 Hz), 3.36 (dd, 1 H, J = 2.9, 11.9 Hz), 3.30 (dd, 1 H, J = 5.4, 11.9 Hz), 3.34 (s, 3 H), 2.10, 2.02, 2.01, 1.99 (4 s, 12 H), 1.48, 1.26 (2 s, 6 H). ¹³C NMR (125.7 MHz, CDCl₃): δ 170.1, 169.9, 169.8, 168.7, 161.8, 112.1, 104.8, 96.6, 83.3, 81.4, 76.2, 70.8, 69.9, 69.1, 67.6, 61.5, 55.3, 42.7, 26.5, 26.1, 20.9, 20.8, 20.6, 20.5. FABMS: m/z 589 (100, [M + H]⁺). Anal. Calcd for C₂₅H₃₆N₂O₁₄: C, 51.02; H, 6.16; N, 4.76. Found: C, 50.97; H, 5.98; N, 4.80.

General Procedure for the Preparation of Isoarea-Type (+)-Castanospermine Analogues (21–25). To a solution of the corresponding 2-amino-2-oxazoline precursor **16–20** (0.43 mmol) in dry MeOH (4 mL), methanolic NaMeO (1 M, 0.1 equiv per mol of acetate) was added. The reaction mixture was stirred at rt for 30 min, then neutralized with solid CO₂, and concentrated. The residue was treated with TFA-H₂O (9:1, 2 mL) for 15 min, concentrated under reduced pressure, coevaporated several times with water, neutralized with Amberlite IRA-68 (OH⁻) ion-exchange resin, and subjected to column chromatography with the eluent indicated in each case. The bicyclic 2-iminoindolizidine derivatives **21–24** were thus obtained from **16–19** as white lyophilizates. However, the methyl α-D-glucopyranosid-6-ylimino derivative **25** was shown to exist under such conditions as an anomeric mixture of the furanose form **25a** (NMR). Shifts at pH 9 (0.1 M NaOH) and further neutralization (0.1 M HCl) provided the indolizidine tautomer **25b** as the only detectable form (NMR). In all cases, the fully deprotected compounds were further purified by GPC (Sephadex G-10, 1:1 MeOH-H₂O).

(5R,6S,7R,8R,8aR)-3-Butylimino-5,6,7,8-tetrahydroxy-2-oxaindolizidine (21). Column chromatography, eluent 15:1 MeCN-H₂O; yield 101 mg (90%). [α]_D -2.0 (c 1.0, H₂O). R_f 0.38 (10:1:1 MeCN-H₂O-NH₄OH). ¹H NMR (300 MHz, D₂O): δ 5.53 (d, 1 H, J = 3.9 Hz), 5.01 (t, 1 H, J = 8.8 Hz), 4.67 (t, 1 H, J = 8.8 Hz), 4.24 (dt, 1 H, J = 8.8, 9.4 Hz), 3.74 (t, 1 H, J = 9.4 Hz), 3.62 (dd, 1 H, J = 3.9, 9.4 Hz), 3.61 (t, 1 H, J = 9.4 Hz), 3.36 (td, 2 H, J = 2.1, 7.1 Hz), 1.55 (q, 2 H, J = 7.1 Hz), 1.30 (m, 2 H), 0.87 (t, 3 H, J = 7.1 Hz). ¹³C NMR (75.5 MHz, D₂O): δ 158.7, 74.9, 73.9, 73.0, 71.9, 70.9, 56.2, 42.9, 30.4, 19.2, 12.9. FABMS: m/z 261 (100, [M + H]⁺). Anal.

Calcd for C₁₁H₂₀N₂O₅: C, 50.78; H, 7.69; N, 10.77. Found: C, 50.73; H, 7.80; N, 10.60.

(5R,6S,7R,8R,8aR)-5,6,7,8-Tetrahydroxy-3-octylimino-2-oxaindolizidine (22). Column chromatography, eluent 15:1 MeCN-H₂O; yield 122 mg (90%). [α]_D -5.0 (c 1.0, H₂O). R_f 0.39 (10:1:1 MeCN-H₂O-NH₄OH). ¹H NMR (500 MHz, D₂O): δ 5.74 (d, 1 H, J = 3.8 Hz), 5.22 (t, 1 H, J = 8.9 Hz), 4.90 (t, 1 H, J = 8.9 Hz), 4.45 (dt, 1 H, J = 8.8, 9.5 Hz), 3.95 (t, 1 H, J = 9.5 Hz), 3.83 (dd, 1 H, J = 3.8, 9.5 Hz), 3.80 (t, 1 H, J = 9.5 Hz), 3.57 (td, 2 H, J = 4.2, 7.1 Hz), 1.53 (m, 2 H), 1.24 (m, 10 H), 0.87 (t, 3 H, J = 7.1 Hz). ¹³C NMR (75.5 MHz, D₂O): δ 158.7, 74.9, 73.9, 73.0, 71.9, 70.9, 56.2, 43.2, 31.2, 28.4, 28.2, 25.8, 28.3, 22.1, 13.5. FABMS: m/z 317 (100, [M + H]⁺). Anal. Calcd for C₁₅H₂₈N₂O₅: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.67; H, 8.88; N, 8.74.

(5R,6S,7R,8R,8aR)-5,6,7,8-Tetrahydroxy-2-oxa-3-phenyliminoindolizidine (23). Column chromatography, eluent 20:1 CH₂Cl₂-MeOH; yield 76 mg (63%). [α]_D -26.7 (c 0.75, pyridine). R_f 0.15 (9:1 CH₂Cl₂-MeOH). ¹H NMR (500 MHz, D₂O): δ 7.44–7.27 (m, 5 H), 5.73 (bs, 1 H), 4.96 (t, 1 H, J = 8.8 Hz), 4.69 (t, 1 H, J = 8.8 Hz), 4.28 (dt, 1 H, J = 8.8, 9.4 Hz), 3.81 (t, 1 H, J = 9.4 Hz), 3.73 (dd, 1 H, J = 3.7, 9.4 Hz), 3.66 (t, 1 H, J = 9.4 Hz). ¹³C NMR (75.5 MHz, D₂O): δ 157.4, 129.7–123.9, 75.3, 74.1, 73.0, 71.9, 70.9, 56.1. FABMS: m/z 281 (100, [M + H]⁺). Anal. Calcd for C₁₃H₁₆N₂O₅: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.70; H, 5.81; N, 9.97.

(5R,6S,7R,8R,8aR)-3-β-D-Glucopyranosylimino-5,6,7,8-tetrahydroxy-2-oxaindolizidine (24). Column chromatography, eluent 4:1 MeCN-H₂O; yield 135 mg (86%). [α]_D +5.9 (c 1.0, H₂O). R_f 0.26 (6:3:1 MeCN-H₂O-NH₄OH). ¹H NMR (500 MHz, D₂O): δ 5.34 (d, 1 H, J = 4.0 Hz), 4.65 (d, 1 H, J = 8.7 Hz), 4.52 (t, 1 H, J = 8.0 Hz), 4.18 (t, 1 H, J = 8.0 Hz), 3.99 (dt, 1 H, J = 8.0, 9.5 Hz), 3.73 (dd, 1 H, J = 4.7, 12.2 Hz), 3.61 (dd, 1 H, J = 1.7, 12.2 Hz), 3.60 (t, 1 H, J = 9.5 Hz), 3.51 (dd, 1 H, J = 4.0, 9.5 Hz), 3.39 (t, 1 H, J = 9.5 Hz), 3.55 (m, 2 H), 3.38 (t, 1 H, J = 8.7 Hz), 3.09 (t, 1 H, J = 8.7 Hz). ¹³C NMR (125.7 MHz, D₂O): δ 156.9, 86.6, 77.4, 76.3, 74.6, 74.5, 73.1, 72.6, 71.1, 69.9, 69.6, 60.7, 54.4. FABMS: m/z 389 (25, [M + Na]⁺), 367 (10, [M + H]⁺). Anal. Calcd for C₁₃H₂₂N₂O₁₀: C, 42.62; H, 6.05; N, 7.65. Found: C, 42.75; H, 6.13; N, 7.69.

(5R,6S,7R,8R,8aR)-5,6,7,8-Tetrahydroxy-3-(methyl α-D-glucopyranosyl-6-yl)imino-2-oxa-indolizidine (25). Column chromatography, eluent 7:1 MeCN-H₂O; yield 55 mg (83%). [α]_D +99.0 (c 1.0, H₂O). R_f 0.71 (6:3:1 MeCN-H₂O-NH₄OH). ¹H NMR (500 MHz, D₂O): δ 5.58 (bs, 1 H), 4.78 (d, 1 H, J = 3.8 Hz), 4.70 (m, 1 H), 4.67 (t, 1 H, J = 9.5 Hz), 4.48 (d, 1 H, J = 9.5 Hz), 4.21 (m, 1 H), 3.98 (t, 1 H, J = 7.8 Hz), 3.82 (d, 1 H, J = 9.5 Hz), 3.63 (t, 1 H, J = 9.5 Hz), 3.57 (dd, 1 H, J = 3.0, 13.8 Hz), 3.56 (dd, 1 H, J = 3.8, 9.5 Hz), 3.52 (m, 1 H), 3.37 (s, 3 H), 3.29 (dd, 1 H, J = 7.0, 13.8 Hz), 3.28 (t, 1 H, J = 9.5 Hz). ¹³C NMR (125.7 MHz, D₂O): δ 161.4, 100.5, 74.3, 72.6, 72.4, 71.8, 56.2, 53.8, 42.0. FABMS: m/z 403 (100, [M + Na]⁺). Anal. Calcd for C₁₄H₂₄N₂O₁₀: C, 44.21; H, 6.36; N, 7.36. Found: C, 44.29; H, 6.32; N, 7.29.

2,3,5,6-Di-O-isopropylidene-β-L-gulofuranose (27). To a solution of 2,3,5,6-di-O-isopropylidene-L-gulonolactone³¹ (**26**) (2 g, 7.74 mmol) in toluene (70 mL) at -78 °C under Ar, DIBAL (1 M in hexanes, 19 mL, 2.5 equiv) was added and the reaction mixture was allowed to reach rt. After 2 h, the reaction was quenched by addition of MeOH until gas evolution ceased, and saturated aqueous sodium potassium tartrate (20 mL) was added. The mixture was partitioned between H₂O and EtOAc (50 mL each), the aqueous phase was washed with EtOAc (3 × 20 mL), and the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The resulting residue was purified by column chromatography using 1:3 → 1:1 EtOAc-petroleum ether as the eluent to give **27** (1.50 g, 75% as an amorphous solid. [α]_D +3.6 (c 1.0, CH₂Cl₂). R_f 0.43 (1:1 EtOAc-toluene). IR (KBr): ν_{max} 3459, 2986, 1454, 1379, 1260, 1092 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 5.44 (s, 1 H), 4.68 (dd, 1 H, J = 3.8, 5.9 Hz), 4.60 (d, 1 H, J = 5.9 Hz), 4.33 (dt, 1 H, J = 6.8, 8.4 Hz), 4.19 (dd, 1 H, J = 6.8, 8.4 Hz),

4.10 (dd, 1 H, $J = 3.8, 8.4$ Hz), 3.71 (dd, 1 H, $J = 6.8, 8.4$ Hz), 3.60 (bs, 1 H), 1.42, 1.36, 1.27 (3 s, 12 H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 112.7, 109.7, 101.1, 85.5, 81.9, 79.7, 75.3, 65.8, 26.5, 25.8, 25.2, 24.6. FABMS: m/z 261 (40, $[\text{M} + \text{H}]^+$). Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_6$: C, 55.37; H, 7.75. Found: C, 55.31; H, 7.83.

1-*O*-Acetyl-2,3,5,6-di-*O*-isopropylidene- β -*L*-gulofuranose (28). Conventional acetylation of **27** (2 g, 7.70 mmol) with Ac_2O -pyridine (1:1, 15 mL) yielded **28** (2.15 g, 75%). $[\alpha]_{\text{D}} +44.0$ (c 1.0, CH_2Cl_2). R_f 0.53 (1:3 EtOAc-petroleum ether). IR (KBr): ν_{max} 2988, 1746, 1454, 1377, 1213, 1094 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.93 (s, 1 H), 5.14 (dd, 1 H, $J = 4.7, 7.0$ Hz), 5.09 (d, 1 H, $J = 7.0$ Hz), 4.73 (td, 1 H, $J = 7.7, 9.5$ Hz), 4.56 (dd, 1 H, $J = 7.7, 9.6$ Hz), 4.41 (dd, 1 H, $J = 4.7, 9.5$ Hz), 3.96 (t, 1 H, $J = 9.6$ Hz), 2.02 (s, 3 H), 1.33, 1.32, 1.24, 1.13 (4 s, 12 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 169.3, 113.3, 109.8, 101.1, 85.1, 81.9, 79.7, 75.3, 65.2, 26.5, 25.8, 25.2, 24.6, 20.9. FABMS: m/z 325 (30, $[\text{M} + \text{Na}]^+$), 303 (20, $[\text{M} + \text{H}]^+$). Anal. Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_7$: C, 55.62; H, 7.34. Found: C, 55.48; H, 7.24.

1-*O*-Acetyl-2,3-*O*-isopropylidene- β -*L*-gulofuranose (29). The diacetone derivative **28** (2.0 g, 6.62 mmol) was suspended in 50% aqueous AcOH (6 mL) and heated at 40 °C for 2 h. The resulting solution was concentrated and coevaporated several times with water and toluene, and the residue was purified by column chromatography (2:1 EtOAc-petroleum ether \rightarrow EtOAc) to give **29** (1.40 g, 80%) as an amorphous solid. $[\alpha]_{\text{D}} +61.8$ (c 1.0, CH_2Cl_2). R_f 0.34 (3:1 EtOAc-petroleum ether). IR (KBr): ν_{max} 3352, 2984, 1748, 1375, 1238, 1103 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.18 (s, 1 H), 4.83 (dd, 1 H, $J = 3.6, 5.9$ Hz), 4.72 (d, 1 H, $J = 5.9$ Hz), 4.14 (dd, 1 H, $J = 3.6, 6.8$ Hz), 4.10 (ddd, 1 H, $J = 3.7, 4.7, 6.8$ Hz), 3.82 (dd, 1 H, $J = 3.7, 11.6$ Hz), 3.75 (dd, 1 H, $J = 4.7, 11.6$ Hz), 2.78, 2.08 (2 bs, 2 H), 2.06 (s, 3 H), 1.48, 1.32 (2 s, 6 H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 169.4, 113.2, 100.1, 85.3, 82.1, 79.2, 70.6, 62.9, 25.8, 24.5, 20.9. FABMS: m/z 285 (100, $[\text{M} + \text{Na}]^+$). Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_7$: C, 50.38; H, 6.92. Found: C, 50.47; H, 6.84.

1-*O*-Acetyl-2,3-*O*-isopropylidene-6-*O*-trityl- β -*L*-gulofuranose (30). Trityl chloride (1.9 g, 6.8 mmol, 1.5 equiv) was added to a solution of **29** (1.25 g, 4.59 mmol) in pyridine (8 mL), and the resulting mixture was stirred at rt for 36 h. The reaction mixture was poured into ice-water (80 mL) to give a solid that was dissolved in toluene (40 mL), which was washed successively with iced 10% aqueous AcOH (10 mL) and saturated aqueous NaHCO_3 (10 mL), dried (MgSO_4), and concentrated. The resulting residue was purified by column chromatography using 1:3 EtOAc-petroleum ether as eluent to give **30** (1.70 g, 72%) as an amorphous solid. $[\alpha]_{\text{D}} +24.7$ (c 1.0, CH_2Cl_2). R_f 0.58 (1:1 EtOAc-petroleum ether). IR (KBr): ν_{max} 3492, 2943, 1752, 1450, 1379, 1236, 1013 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 7.48–7.24 (m, 15 H), 6.20 (s, 1 H), 4.67 (d, 1 H, $J = 5.9$ Hz), 4.61 (dd, 1 H, $J = 3.3, 5.9$ Hz), 4.28 (dd, 1 H, $J = 3.3, 6.2$ Hz), 4.18 (ddd, 1 H, $J = 2.3, 4.8, 5.2$ Hz), 3.94 (dd, 1 H, $J = 5.2, 9.5$ Hz), 3.26 (dd, 1 H, $J = 4.8, 9.5$ Hz), 2.81 (d, 1 H), 2.05 (s, 3 H), 1.44, 1.25 (2 s, 6 H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 169.2, 146.7–126.9, 112.9, 100.3, 86.6, 85.3, 82.0, 79.8, 69.6, 63.8, 25.8, 24.4, 20.9. FABMS: m/z 527 (50, $[\text{M} + \text{Na}]^+$). Anal. Calcd for $\text{C}_{30}\text{H}_{32}\text{O}_7$: C, 71.41; H, 6.39. Found: C, 71.43; H, 6.47.

1-*O*-Acetyl-5-azido-5-deoxy-2,3-*O*-isopropylidene-6-*O*-trityl- α -*D*-mannofuranose (31). To a solution of **30** (2.3 g, 4.59 mmol) in CH_2Cl_2 (20 mL) at -25 °C under Ar, pyridine (0.72 mL) and trifluoromethanesulfonic anhydride (1.05 mL, 6.36 mmol) were added. The reaction mixture was allowed to reach rt, stirred for 1 h, then diluted with CH_2Cl_2 (15 mL), washed with saturated aqueous NaHCO_3 (15 mL), dried (MgSO_4), and concentrated. The resulting triflate ester was dissolved in DMF (18 mL), NaN_3 (3.04 g, 32.13 mmol, 7 equiv) was added, and the reaction mixture was stirred at rt for 18 h. The solvent was removed under reduced pressure, and the resulting residue was dissolved in CH_2Cl_2 (50 mL) and washed with water. The organic phase was dried (MgSO_4) and concentrated to give a solid, which was purified by column

chromatography (1:5 EtOAc-petroleum ether) to afford **31** (1.87 g, 78%) as an amorphous solid. $[\alpha]_{\text{D}} +2.5$ (c 1.0, CH_2Cl_2). R_f 0.54 (1:2 EtOAc-petroleum ether). IR (KBr): ν_{max} 2986, 2099, 1750, 1381, 1260, 1211, 1111 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.46–7.18 (m, 15 H), 6.15 (s, 1 H), 4.88 (dd, 1 H, $J = 3.5, 5.8$ Hz), 4.69 (d, 1 H, $J = 5.8$ Hz), 4.23 (dd, 1 H, $J = 3.5, 9.8$ Hz), 3.76 (ddd, 1 H, $J = 2.8, 5.6, 9.8$ Hz), 3.46 (dd, 1 H, $J = 2.8, 10.1$ Hz), 3.43 (dd, 1 H, $J = 5.6, 10.1$ Hz), 1.98 (s, 3 H), 1.45, 1.30 (2 s, 6 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 169.1, 143.7–126.8, 113.3, 100.4, 86.9, 84.6, 79.7, 79.4, 63.2, 59.4, 26.0, 24.9, 20.8. FABMS: m/z 552 (100, $[\text{M} + \text{Na}]^+$). Anal. Calcd for $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_6$: C, 68.04; H, 5.90; N, 7.94. Found: C, 68.02; H, 5.95; N, 7.82.

1-*O*-Acetyl-5-azido-5-deoxy-2,3-*O*-isopropylidene- α -*D*-mannofuranose (32). To a solution of the tritylated azido derivative **31** (1.5 g, 2.8 mmol) in CH_2Cl_2 (19 mL) at 0 °C under Ar, $\text{BF}_3\text{-Et}_2\text{O}$ (391 μL) and MeOH (1 mL) were added. The reaction mixture was allowed to reach rt and was stirred for 2 h, then washed with saturated aqueous NaHCO_3 (2×10 mL), dried (MgSO_4), and concentrated. The resulting residue was purified by column chromatography (1:4 \rightarrow 1:1 EtOAc-petroleum ether) to give **32** (603 mg, 75%) as an amorphous solid. $[\alpha]_{\text{D}} +30.5$ (c 0.99, CH_2Cl_2). R_f 0.24 (1:2 EtOAc-petroleum ether). IR (KBr): ν_{max} 2957, 2097, 1742, 1379, 1262, 1094 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.13 (d, 1 H, $J = 1.9$ Hz), 4.86 (dd, 1 H, $J = 3.6, 5.8$ Hz), 4.69 (dd, 1 H, $J = 1.9, 5.8$ Hz), 4.03 (dd, 1 H, $J = 3.6, 9.5$ Hz), 3.85 (ddd, 1 H, $J = 3.2, 5.6, 9.5$ Hz), 3.94 (dd, 1 H, $J = 3.2, 11.5$ Hz), 3.75 (dd, 1 H, $J = 5.6, 11.5$ Hz), 2.04 (s, 3 H), 1.48, 1.35 (2 s, 6 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 169.1, 113.4, 100.6, 84.7, 80.5, 79.4, 63.0, 61.4, 25.9, 24.8, 20.8. FABMS: m/z 310 (100, $[\text{M} + \text{Na}]^+$). Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_6$: C, 45.99; H, 5.96; N, 14.63. Found: C, 45.92; H, 5.91; N, 14.43.

1-*O*-Acetyl-5-azido-5-deoxy-2,3-*O*-isopropylidene-6-*O*-trimethylsilyl- α -*D*-mannofuranose (33). To a solution of **32** (212 mg, 0.74 mmol) in pyridine (5.4 mL), a mixture of trimethylsilyl chloride and hexamethyldisilazane (1:2, 3.76 mL) was added and the reaction mixture was stirred at rt for 2 h. The solvents were concentrated under reduced pressure, and the resulting residue was extracted with petroleum ether, concentrated, and purified by column chromatography (1:6 EtOAc-petroleum ether) to give **33** (213 mg, 80%) as an amorphous solid. $[\alpha]_{\text{D}} +29.0$ (c 1.0, CH_2Cl_2). R_f 0.41 (1:6 EtOAc-petroleum ether). IR (KBr): ν_{max} 2951, 2101, 1752, 1625, 1458, 1386, 1236, 1100 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.12 (s, 1 H), 4.84 (dd, 1 H, $J = 3.6, 5.9$ Hz), 4.68 (d, 1 H, $J = 5.9$ Hz), 3.99 (dd, 1 H, $J = 3.6, 9.1$ Hz), 3.97 (dd, 1 H, $J = 2.2, 9.1$ Hz), 3.75 (dd, 1 H, $J = 6.2, 9.1$ Hz), 3.71 (ddd, 1 H, $J = 2.2, 6.2, 9.1$ Hz), 2.05 (s, 3 H), 1.47, 1.35 (s, 3 H), 0.13, 0.12 (2 s, 9 H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 169.1, 113.1, 100.4, 84.4, 79.4, 79.3, 63.0, 60.5, 25.9, 24.7, 20.8, -0.59 . FABMS: m/z 382 (95, $[\text{M} + \text{Na}]^+$). Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{N}_3\text{O}_6\text{-Si}$: C, 46.78; H, 7.01; N, 11.69. Found: C, 46.78; H, 6.90; N, 11.69.

General Procedure for the Preparation of 5-Carbodiimido-5-deoxy- α -*D*-mannofuranoses (34–36). To a solution of azide **33** (500 mg, 1.39 mmol) and the corresponding isothiocyanate (phenyl, **9** or **10**) in toluene (8 mL) under Ar, a solution of triphenylphosphine (400 mg, 1.53 mmol, 1.1 equiv) in toluene (4 mL) was dropwise added at rt. The reaction mixture was stirred at rt (**34** and **35**) or at 40 °C (**36**) for 24 h (TLC) and was concentrated. The resulting residue was purified by column chromatography using the solvent indicated in each case to afford the carbodiimide adducts as amorphous solids.

1-*O*-Acetyl-5-deoxy-2,3-*O*-isopropylidene-5-(3-phenyl-carbodiimido)-6-*O*-trimethylsilyl- α -*D*-mannofuranose (34). Column chromatography, eluent toluene and then 1:7 EtOAc-toluene; yield 422 mg (70%). $[\alpha]_{\text{D}} -23.7$ (c 1.0, CH_2Cl_2). R_f 0.37 (1:5 EtOAc-petroleum ether). IR (KBr): ν_{max} 2959, 2133, 1752, 1386, 1267, 1093 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.29–7.09 (m, 5 H), 6.14 (d, 1 H, $J = 2.0$ Hz), 4.92 (dd, 1 H, $J = 3.5,$

5.9 Hz), 4.70 (dd, 1 H, $J = 2.0, 5.9$ Hz), 4.14 (dd, 1 H, $J = 3.5, 9.5$ Hz), 3.93 (dd, 1 H, $J = 2.3, 10.2$ Hz), 3.85 (ddd, 1 H, $J = 5.0, 9.5, 10.2$ Hz), 3.80 (dd, 1 H, $J = 5.0, 10.2$ Hz), 2.05 (s, 3 H), 1.48, 1.34 (2 s, 6 H), 0.41 (s, 9 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 169.2, 140.0, 138.3–123.9, 113.2, 100.6, 84.6, 80.3, 79.4, 62.5, 57.6, 26.0, 24.8, 20.9, –0.80. FABMS: m/z 457 (75, $[\text{M} + \text{Na}]^+$). Anal. Calcd for $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_6\text{Si}$: C, 58.04; H, 6.96; N, 6.45. Found: C, 58.01; H, 6.69; N, 6.47.

1-O-Acetyl-5-deoxy-2,3-O-isopropylidene-5-[3-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)carbodiimidol]-6-O-trimethylsilyl- α -D-mannofuranose (35). Column chromatography, eluent toluene and then 1:5 \rightarrow 1:2 EtOAc–petroleum ether; yield 430 mg (45%). $[\alpha]_{\text{D}} +3.0$ (c 1.0, CH_2Cl_2). R_f 0.22 (1:3 EtOAc–petroleum ether, two elutions). IR (KBr): ν_{max} 2959, 2880, 2149, 1760, 1379, 1236, 1108 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.08 (s, 1 H), 5.16 (t, 1 H, $J = 9.4$ Hz), 5.07 (t, 1 H, $J = 9.4$ Hz), 4.93 (dd, 1 H, $J = 8.7, 9.4$ Hz), 4.82 (dd, 1 H, $J = 3.5, 5.8$ Hz), 4.72 (d, 1 H, $J = 8.7$ Hz), 4.64 (d, 1 H, $J = 5.8$ Hz), 4.21 (dd, 1 H, $J = 4.7, 12.3$ Hz), 4.12 (dd, 1 H, $J = 2.1, 12.3$ Hz), 3.98 (dd, 1 H, $J = 3.5, 9.4$ Hz), 3.84 (dd, 1 H, $J = 1.8, 10.0$ Hz), 3.68 (ddd, 1 H, $J = 2.1, 4.7, 9.4$ Hz), 3.67 (m, 2 H), 2.05, 2.02, 2.00, 1.99, 1.97, 1.92 (6 s, 18 H), 1.43, 1.31 (2 s, 6 H), 0.11 (s, 9 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 170.4, 170.3, 170.2, 169.5, 169.0, 138.1, 113.1, 100.7, 84.9, 84.7, 80.3, 79.4, 73.7, 73.1, 72.8, 68.1, 62.6, 61.9, 57.1, 26.0, 24.9, 22.8, 20.8, 20.7, 20.6, 20.4, 20.2, –0.65. FABMS: m/z 711 (80, $[\text{M} + \text{Na}]^+$). Anal. Calcd for $\text{C}_{22}\text{H}_{44}\text{N}_2\text{O}_{15}\text{Si}$: C, 50.57; H, 6.44; N, 4.07. Found: C, 50.56; H, 6.35; N, 3.93.

1-O-Acetyl-5-deoxy-2,3-O-isopropylidene-5-[3-(methyl-2,3,4-tri-O-acetyl-6-deoxy- α -D-glucopyranosyl-6-yl)-carbodiimidol]-6-O-trimethylsilyl- β -L-mannofuranose (36). Column chromatography, eluent toluene and then 1:3 EtOAc–petroleum ether; yield 183 mg (20%). $[\alpha]_{\text{D}} +72.4$ (c 1.0, CH_2Cl_2). R_f 0.20 (1:3 EtOAc–petroleum ether, two elutions). IR (KBr): ν_{max} 2951, 2133, 1752, 1371, 1228, 1100 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.07 (s, 1 H), 5.41 (t, 1 H, $J = 9.7$ Hz), 4.93 (t, 1 H, $J = 9.7$ Hz), 4.89 (d, 1 H, $J = 3.6$ Hz), 4.82 (dd, 1 H, $J = 3.6, 6.9$ Hz), 4.80 (dd, 1 H, $J = 3.6, 9.7$ Hz), 4.63 (d, 1 H, $J = 6.9$ Hz), 3.99 (dd, 1 H, $J = 3.6, 9.5$ Hz), 3.81 (m, 1 H), 3.80 (dd, 1 H, $J = 2.5, 10.4$ Hz), 3.67 (dd, 1 H, $J = 5.1, 10.4$ Hz), 3.63 (ddd, 1 H, $J = 2.5, 5.1, 9.5$ Hz), 3.34 (d, 2 H, $J = 4.9$ Hz), 3.38 (s, 3 H), 2.02, 2.00, 1.98, 1.95 (4 s, 12 H), 1.41, 1.30 (2 s, 6 H), 0.08, 0.07 (2 s, 9 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 170.1, 170.0, 169.6, 169.3, 141.1, 113.1, 100.8, 96.6, 84.7, 80.5, 79.5, 70.9, 70.1, 70.0, 63.4, 62.8, 56.9, 55.5, 47.1, 26.1, 25.0, 21.0, 20.7, 20.6, 20.5, –0.50. FABMS: m/z 683 (30, $[\text{M} + \text{Na}]^+$), 661 (100, $[\text{M} + \text{H}]^+$). Anal. Calcd for $\text{C}_{28}\text{H}_{44}\text{N}_2\text{O}_{13}\text{Si}$: C, 50.89; H, 6.71; N, 4.24. Found: C, 50.80; H, 6.81; N, 4.26.

General Procedure for the Preparation of 4-(L-Erythrofuranos-4'-yl)-2-amino-2-oxazolines (37–39). To a solution of the corresponding carbodiimide **34–36** (0.5 mmol) in THF (10 mL) at 0 °C under Ar, TBAF (1 M in THF, 0.55 mL, 1.1 equiv) was added. In the case of **35**, the reaction mixture was adjusted at pH 7 using glacial AcOH. The solution was stirred at 0 °C until the disappearance of the starting material (25 min), then diluted with Et_2O (5 mL), washed with water (2 \times 3 mL), dried (MgSO_4), filtered, and concentrated. For the phenyl and β -D-glucopyranosyl derivatives **34** and **35**, column chromatography of the residue using the eluent indicated in each case afforded the corresponding 2-amino-2-oxazoline derivatives **37** and **38**, respectively, as amorphous solids. In the case of the (6 \rightarrow 5)-carbodiimide linked pseudodisaccharide **36**, partial deacetylation of the reaction product **39** was observed under the stated reaction conditions. The mixture was directly used in the next reaction step without further purification.

(4R)-4-[(4R)-1'-O-Acetyl-2',3'-O-isopropylidene-L-erythrofuranos-4'-yl]-2-phenylamino-2-oxazoline (37). Column chromatography, eluent CH_2Cl_2 and then 100:1 CH_2Cl_2 –MeOH; yield 130 mg (72%). $[\alpha]_{\text{D}} +85.1$ (c 0.7, CH_2Cl_2). R_f 0.30 (20:1 CH_2Cl_2 –MeOH). IR (KBr): ν_{max} 3428, 2975, 1752, 1680, 1553, 1386, 1243, 1013 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ

7.31–7.23 (m, 5 H), 6.97 (bs, 1 H), 6.17 (s, 1 H), 4.86 (dd, 1 H, $J = 5.9$ Hz, $J = 3.7$ Hz), 4.69 (d, 1 H, $J = 5.9$ Hz), 4.29 (m, 3 H), 4.19 (dd, $J = 3.7, 5.6$ Hz), 2.00 (s, 3 H), 1.47, 1.30 (2 s, 6 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 169.3, 128.8–119.1, 157.8, 113.0, 100.7, 84.9, 83.9, 79.4, 77.0, 69.4, 25.8, 24.4, 20.9. FABMS: m/z 385 (95, $[\text{M} + \text{Na}]^+$), 363 (100, $[\text{M} + \text{H}]^+$). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.61; H, 6.13; N, 7.74.

(4R)-4-[(4R)-1'-O-Acetyl-2',3'-O-isopropylidene-L-erythrofuranos-4'-yl]-2-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)amino-2-oxazolium Acetate (38). Column chromatography, eluent CH_2Cl_2 and then 100:1 \rightarrow 9:1 CH_2Cl_2 –MeOH; yield 305 mg (99%). $[\alpha]_{\text{D}} +24.3$ (c 1.0, CH_2Cl_2). R_f 0.35 (20:1 CH_2Cl_2 –MeOH). IR (KBr): ν_{max} 3452, 2973, 1752, 1612, 1386, 1236, 1093 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.11 (s, 1 H, H-1), 5.23 (t, 1 H, $J = 9.5$ Hz), 5.05 (t, 1 H, $J = 9.5$ Hz), 4.96 (d, 1 H, $J = 9.5$ Hz), 4.91 (t, 1 H, $J = 9.5$ Hz), 4.79 (dd, 1 H, $J = 3.5, 6.0$ Hz), 4.65 (d, 1 H, $J = 6.0$ Hz), 4.38 (dd, 1 H, $J = 4.5, 10.5$ Hz), 4.37 (m, 1 H), 4.36 (dd, 1 H, $J = 5.0, 10.5$ Hz), 4.24 (dd, 1 H, $J = 12.5$ Hz, $J = 4.5$ Hz), 4.09 (dd, 1 H, $J = 3.5, 9.4$ Hz), 4.08 (dd, 1 H, $J = 2.5, 12.5$ Hz), 3.77 (ddd, 1 H, $J = 2.5, 4.5, 12.5$ Hz), 2.06, 2.04, 2.02, 2.00, 1.98, 1.92 (6 s, 18 H), 1.41, 1.27 (2 s, 6 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 178.2, 170.6, 170.4, 169.9, 169.5, 169.4, 160.2, 113.2, 100.5, 84.9, 83.5, 82.4, 79.3, 73.1, 72.9, 70.7, 70.6, 68.2, 61.8, 61.4, 25.8, 24.4, 21.0, 20.7, 20.6, 20.5. FABMS: m/z 639 (40, $[\text{M} - \text{AcOH} + \text{Na}]^+$), 617 (100, $[\text{M} - \text{AcO}]^+$). Anal. Calcd for $\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_{17}$: C, 49.70; H, 5.96; N, 4.14. Found: C, 49.63; H, 5.73; N, 4.10.

General Procedure for the Preparation of Isoarea-Type (+)-6-Epicastanospermine Analogues (40–42). To a solution of the corresponding 2-amino-2-oxazoline precursor **37, 38** (0.43 mmol), or of the partially deacetylated product **39** (see above) in dry MeOH (4 mL), methanolic NaMeO (1 M, 0.1 equiv per mol of acetate) was added. The reaction mixture was stirred at rt for 30 min, then neutralized with solid CO_2 and concentrated. The residue was treated with TFA– H_2O (9:1, 2 mL) for 15 min, concentrated under reduced pressure, coevaporated several times with water, neutralized with Amberlite IRA-68 (OH^-) ion-exchange resin, and subjected to column chromatography with the eluent indicated in each case. The bicyclic 2-iminoindolizidine derivatives **40** and **41** were thus obtained from **37** and **38**, respectively, as white lyophilizates. The methyl α -D-glucopyranosid-6-ylimino derivative **42** was obtained after adjusting an aqueous solution of the crude reaction product at pH 9 (0.1 M NaOH) and further neutralization (0.1 M NaOH), as reported for the preparation of the C-6 epimer **25**. In all cases, the fully deprotected compounds were further purified by GPC (Sephadex G-10, 1:1 MeOH– H_2O).

(5R,6R,7R,8R,8aR)-5,6,7,8-Tetrahydroxy-2-oxa-3-phenyliminoindolizidine (40). Column chromatography, eluent CH_2Cl_2 and then 50:1 \rightarrow 9:1 CH_2Cl_2 –MeOH; yield 104 mg (86%). R_f 0.28 (9:1 CH_2Cl_2 –MeOH). $[\alpha]_{\text{D}} -19.1$ (c 2.2, MeOH). ^1H NMR (500 MHz, D_2O): δ 7.36–7.05 (m, 5 H), 5.47 (bs, 1 H, H-1), 4.64 (t, 1 H, $J = 8.3$ Hz), 4.27 (t, 1 H, $J = 8.3$ Hz), 4.12 (d, 1 H, $J = 2.8$ Hz), 3.94 (dt, 1 H, $J = 8.3, 9.6$ Hz), 3.90 (dd, 1 H, $J = 2.8, 9.6$ Hz), 3.78 (t, 1 H, $J = 9.6$ Hz). ^{13}C NMR (125.7 MHz, D_2O): δ 155.2, 146.6, 130.3, 124.9, 124.6, 78.1, 72.2, 71.5, 71.4, 56.2. FABMS: m/z 303 (30, $[\text{M} + \text{Na}]^+$), 281 (80, $[\text{M} + \text{H}]^+$). Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.53; H, 5.75; N, 9.81.

(5R,6R,7R,8R,8aR)-3- β -D-Glucopyranosylimino-5,6,7,8-tetrahydroxy-2-oxaindolizidine (41). Column chromatography, eluent 3:1 MeCN– H_2O ; yield 142 mg (90%). $[\alpha]_{\text{D}} -26.8$ (c 1.0, H_2O). R_f 0.31 (6:3:1 MeCN– H_2O – NH_4OH). ^1H NMR (500 MHz, D_2O): δ 5.49 (d, 1 H, $J = 2.5$ Hz), 5.00 (t, 1 H, $J = 9.0$ Hz), 4.87 (d, 1 H, $J = 9.0$ Hz), 4.76 (t, 1 H, $J = 6.5$ Hz), 4.25 (dt, 1 H, $J = 6.5, 9.0$ Hz), 4.05 (t, 1 H, $J = 2.5$ Hz), 3.78 (m, 2 H), 3.76 (dd, 1 H, $J = 2.0, 12.4$ Hz), 3.62 (dd, 1 H, $J = 5.2, 12.4$ Hz), 3.43 (t, 1 H, $J = 9.0$ Hz), 3.42 (ddd, 1 H, $J = 2.0, 5.2, 12.4$ Hz), 3.37 (t, 1 H, $J = 9.0$ Hz), 3.32 (t, 1 H, $J = 9.0$ Hz). ^{13}C NMR (125.7 MHz, D_2O): δ 160.2, 82.7, 78.2, 77.9, 76.0,

74.0, 71.8, 70.7, 69.7, 69.4, 68.9, 60.3, 57.1. FABMS: m/z 389 (20, $[M + Na]^+$), 367 (10, $[M + H]^+$). Anal. Calcd for $C_{13}H_{22}N_2O_{10}$: C, 42.62; H, 6.05; N, 7.65. Found: C, 42.46; H, 5.89; N, 7.49.

(5*R*,6*R*,7*R*,8*R*,8*aR*)-5,6,7,8-Tetrahydroxy-3-(methyl 6-deoxy- β -D-glucopyranosyl-imino-2-oxaindolizidine (42). Column chromatography, eluent 7:1 MeCN-H₂O; yield 67 mg (70% over two steps). $[\alpha]_D -22.0$ (c 1.0, H₂O). R_f 0.42 (6:3:1 MeCN-H₂O-NH₄OH). ¹H NMR (500 MHz, D₂O): δ 5.67 (d, 1 H, $J = 2.8$ Hz), 5.07 (t, 1 H, $J = 8.4$ Hz), 5.02 (d, 1 H, $J = 3.8$ Hz), 4.74 (bt, 1 H, $J = 8.4$ Hz), 4.36 (t, 1 H, $J = 2.8$ Hz), 4.26 (m, 1 H), 4.12 (dd, 1 H, $J = 2.8, 9.6$ Hz), 4.04 (t, 1 H, $J = 9.6$ Hz), 3.93 (ddd, 1 H, $J = 3.0, 7.5, 9.5$ Hz), 3.91 (dd, 1 H, $J = 3.0, 13.8$ Hz), 3.90 (t, 1 H, $J = 9.5$ Hz), 3.63 (s, 3 H), 3.62 (dd, 1 H, $J = 7.5, 13.8$ Hz), 3.59 (t, 1 H, $J = 9.5$ Hz), 3.37 (t, 1 H, $J = 9.5$ Hz). ¹³C NMR (75.5 MHz, D₂O): δ 157.2, 99.1, 77.2, 73.0, 70.6, 70.0, 71.1, 70.9, 55.9, 55.0, 45.0. FABMS: m/z

403 (40, $[M + Na]^+$), 381 (100, $[M + H]^+$). Anal. Calcd for $C_{14}H_{24}O_{10}N_2$: C, 44.21; H, 6.36; N, 7.36. Found: C, 44.05; H, 6.22; N, 7.21.

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Supporting Information Available: General methods and experimental procedure for determination of glycosidase inhibition constants (K_i), as well as fully assigned ¹H and ¹³C NMR data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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