Synthesis and Evaluation of Calystegine B_2 Analogues as Glycosidase Inhibitors

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A practical synthesis of polyhydroxylated 6-oxa-*nor*-tropanes incorporating the essential structural features of calystegine B_2 from 5-deoxy-5-thioureido and 5-ureido-L-idofuranose precursors is presented. The methodology relies on the ability of pseudoamide-type nitrogen atoms (thiourea, urea, and carbamate) to undergo nucleophilic addition to the masked aldehyde group of the monosaccharide. The generated hemiaminal functionality may further undergo in situ intramolecular glycosidation to give the bicyclic aminoacetal compounds, the whole process being favored by the anomeric effect. A series of derivatives bearing different substituents at nitrogen has been prepared and screened against several glycosidases in comparison with xylonojirimycin-type piperidine analogues. Interestingly, strong and highly specific inhibition of bovine liver β-glucosidase was observed for 6-oxacalystegine B_2 analogues incorporating aromatic pseudoaglyconic groups. On the basis of these data, a 1-azasugar inhibition mode is proposed for this family of glycomimetics.

Introduction

Calystegines,[1] bicyclic alkaloids that possess a *nor*-tropane structure bearing hydroxyl groups varying in position and stereochemistry,[2] represent a recently discovered group of plant secondary metabolites believed to function as nutritional mediators in the plant rhizosphere.[3] Like other polyhydroxyalkaloids with structural resemblance to sugars isolated from both plants and microorganisms,[4] iminosugars ("azasugars"),[5] the calystegines exhibit strong and specific glycosyl hydrolase competitive inhibitory activity.[6] They show, therefore, considerable promise as probes for structure/function studies of enzymatic mechanisms[4,7] and as chemotherapeutic drugs for the treatment of viral infections,[8] cancer,[9] and metabolic disorders such as diabetes.[10] On the other hand, the occurrence of calystegines in the leaves, skins, and sprouts of some edible vegetables such as potatoes, egg plant, and sweet potato and their interaction with mammalian liver glycosidases have raised concerns regarding their safety in human diet.[11]

In contrast to the polyhydroxy pyrrolidine, piperidine, pyrrolizidine, and indolizidine azasugar glycosidase inhibitors, which by now have been extensively investigated, an understanding of the structural bases for glycosidase inhibition by the calystegine group of alkaloids has only been partially established. Even when they may be viewed as hybrids of piperidine and pyrrolidine

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(5) Although the term "azasugar" is widely used in the literature to refer to glycomimetics where the endocyclic oxygen atom has been replaced by nitrogen, the term is not strictly correct according to the IUPAC-IUBM nomenclature recommendations for carbohydrates. "Azahexose" would actually imply that a carbon atom has been exchanged for a nitrogen. See: McNaught, A. D. *Pure Appl. Chem.* **1996**, *68*, 1919.

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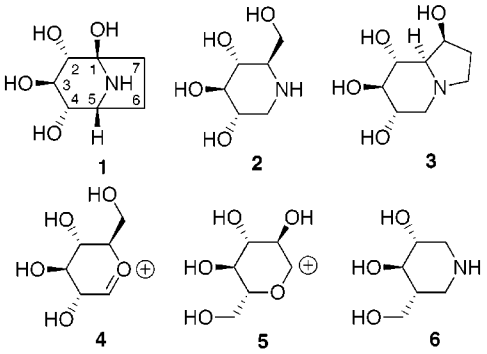
carbohydrate mimics, their enzyme specificities may be drastically different. Thus, calystegine B_2 (**1**), one of the most powerful representatives, has topographical properties similar to those of the potent α-glycosidase inhibitors 1-deoxynojirimycin (**2**) and castanospermine (**3**). Notwithstanding, compound **1** behaves instead as a potent inhibitor of *β*-glucosidases, whereas little or no inhibition is detected for α-glucosidases. A binding model has been proposed that invokes charge interactions with the catalytic carboxylic groups at the active site by analogy with the presumed glycosyl oxocarbenium cation intermediate of enzymatic glycoside cleavage (**4**).[6e,12] However, in light of recent mechanistic studies on the *β*-glucosidase reaction,[13] the remarkable *β*-anomeric selectivity would rather suggest a correspondence with an anomeric carbocation species (**5**). Calystegine B_2 might then be regarded as a rigid analogue of the strong 1-azasugar *β*-glucosidase inhibitor isofagomine (**6**),[14] a stereochemical mimic of D-glucose in which the anomeric carbon has been replaced by nitrogen.[15] Surprisingly, compound **1** is also a potent inhibitor of several α-galactosidases, suggesting that different recognition patterns may operate with different enzymes.[12] Confirmation of any inhibition model has been prevented, however, by the absence of versatile synthetic routes to calystegine analogues. The reported approaches to the preparation of polyhydroxy-*nor*-tropanes are, generally, rather long,[16,17] and no ring-modified analogues have been described so far.

We have previously reported a versatile synthesis of reducing *N*-thiocarbonyl and *N*-carbonyl azasugar glycomimetics related to castanospermine by intramolecular nucleophilic addition of (thio)carbamic-type groupings to



the masked aldehyde group of a monosaccharide.[18] The conformational properties and reactivity of the generated aminoketalic center were shown to be governed by the generalized anomeric effect. Exclusively dispositions with an axially oriented pseudoanomeric oxygen substituent are allowed, probably due to a very efficient delocalization interaction between the *π*-type lone-pair orbital of the sp^2-hybridized nitrogen atom in the ground state of *N*-(thio)carbonyl functionalities and the *σ**-antibonding orbital of the contiguous C−O bond (Figure 1). We assumed that the same orbital interactions should favor intramolecular glycosidation of the hemiaminal functionality by suitably located OH groups provided that the anomeric effect is fulfilled, giving access to bridged 1,3-*O*,*N*-heterobicyclic systems.[19] This principle was the subject of a preliminary account[20] and has now been translated into a practical synthesis of 1-deoxy-6-oxacalystegine B_2 glucomimetics (Figure 2), a hitherto unknown class of compounds, from (thio)carbamic (thiourea, urea, carbamate) carbohydrate precursors. Preparation of the key intermediates, the scope and limitations of the methods, and the structure/glycosidase inhibitory selectivities and potency relationships are discussed in comparison with data for monocyclic nojirimycin-type analogues.[21]

Results

A retrosynthetic analysis revealed that the bicyclic 6-oxa-*nor*-tropane skeleton can be constructed by intramolecular O-6-glycosylation of reducing azasugar-type intermediates (Figure 2). Our synthetic strategy relies on the ability of 5-deoxy-5-thioureido and 5-ureido aldohexofuranose derivatives (Figure 2, structure III) to undergo spontaneous rearrangement to the correspond-

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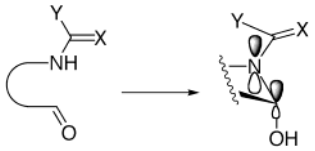


Figure 1. Stereochemical outcome of the intramolecular nucleophilic addition of (thio)carbamic-type nitrogen atoms to carbonyl groups (X = S, O).

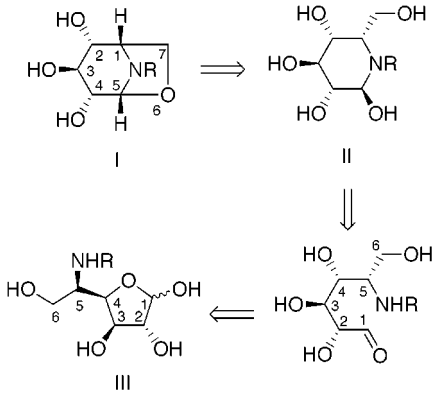


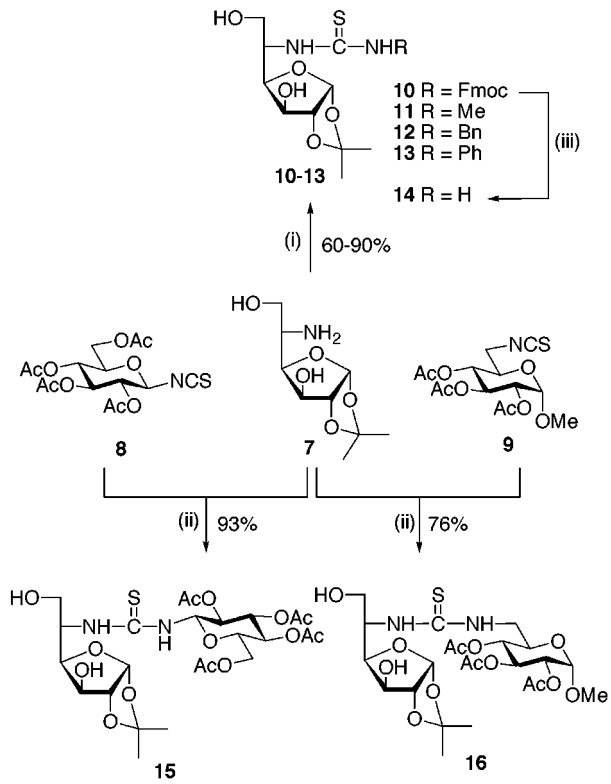
Figure 2. Structures of (I) 6-oxacalystegine, (II) polyhydroxypiperidine, and (III) aldohexofuranose.

ing polyhydroxylated *N*-(thio)carbamoyl piperidines (Figure 2, structure II) through the open-chain tautomeric form, with simultaneous generation of the reactive aminoacetal group. A hydroxylation profile analogous to that of calystegine B_2 (**1**) in the final compounds (Figure 2, structure I) implies an L-*ido* configuration of the (thio)urea precursors.

Synthesis and Structure of 6-Oxa-*nor*-tropanes. The initial synthetic objective of this research was the preparation of *N*-thiocarbamoyl and *N*-carbamoyl-6-oxacalystegine B_2 derivatives bearing different substituents at the exocyclic N′-atom. Reaction of 5-amino-5-deoxy-1,2-*O*-isopropylidene-*β*-L-idofuranose (**7**), available in a multigram scale (five steps) from commercial D-glucurono-6,3-lactone,[22] with 9-fluorenylmethoxycarbonyl (Fmoc), methyl, benzyl, and phenyl isothiocyanates afforded the required thioureas **10**−**13** with total chemoselectivity. Analogously, nucleophilic addition of amine **7** to 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl isothiocyanate (**8**)[23] and methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato-α-D-glucopyranoside (**9**)[24] yielded the (1 → 5) and (6 → 5) thiourea-bridged pseudodisaccharides **15** and **16**, respectively (Scheme 1).[25] The N-monosubstituted thiourea **14** was obtained from **10** by removal of the *N*′-Fmoc protecting group with piperidine.

For the preparation of the urea analogues, a different synthetic strategy that avoids the use of hazardous isocyanate reagents was devised. Condensation of the per-O-protected azide **17** with triphenylphosphine and further in situ aza-Wittig-type reaction with the corresponding isothiocyanate gave the carbodiimide adducts **18**−**20**. The yield varied from 80−90% for isothiocyanates bearing electron-withdrawing groups (i.e., phenyl and glucopyranosyl) to 31% for the alkyl-type isothiocyanate **9**. Acid-catalyzed nucleophilic addition of water to the carbodiimide group afforded the 5-deoxy-5-ureido-L-idofuranose derivatives **21**−**23** (Scheme 2).[26]

Scheme 1[a]



[a] Reagents: (i) RNCS (R = Fmoc, Me, Bn, Ph), pyridine, Et_3N; (ii) pyridine, Et_3N; (iii) 20% piperidine in MeOH, CH_2Cl_2 (60%).

Conventional deacetylation and/or acid hydrolysis of the acetal protecting group in **11**−**16** and **21**−**23** with TFA−water led, initially, to α,*β*-anomeric mixtures of the corresponding L-idofuranose derivatives, with the (thio)urea group probably being protonated, as seen from the ^{13}C NMR and FABMS spectra of the crude reaction mixtures. Upon neutralization with Amberlite IRA 68 (OH^-) ion-exchange resin, the formed *N*-(thio)carbamoylpiperidine derivatives underwent in situ intramolecular glycosylation reaction involving OH-6 to give the target trihydroxylated *N*-(thio)carbamoyl-6-oxa-*nor*-tropane glucomimetics **24**−**32** (Scheme 3).[27,28] A similar pH-dependent equilibrium between hemiacetal and hemi-

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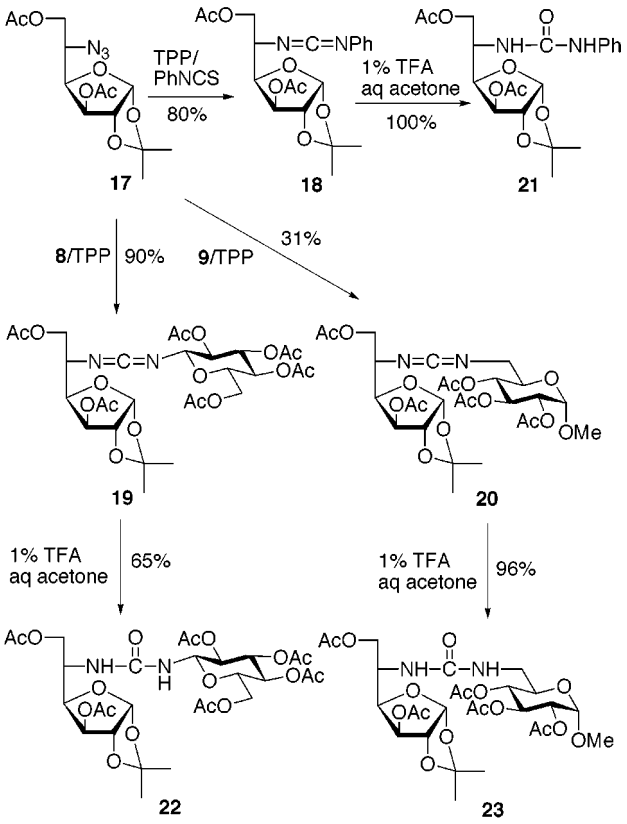
(27) The ^{13}C NMR spectra of the crude reaction mixtures in D_2O showed signals at 102.1−101.8 and 96.1−95.9 ppm, with similar intensities, for the C-1 resonances of the α- and *β*-idofuranose anomers, respectively. See: Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27. Upon 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

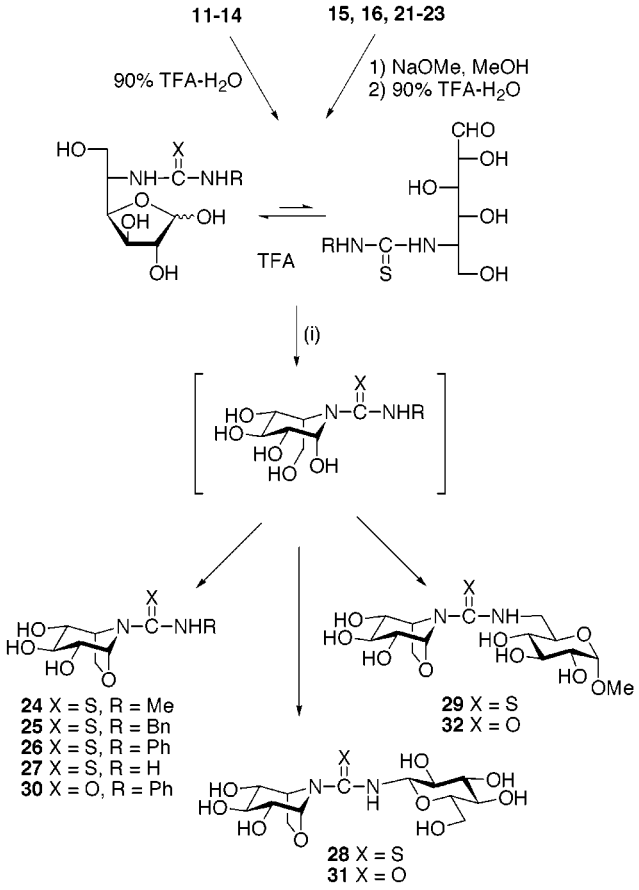


aminal forms has previously been observed for polyhydroxy-γ-oxoguanidines.[29]

To compare both the reactivity and biological properties of pseudoamide vs amine-type 6-oxacalystegine analogues, preparation of the N-unsubstituted 1-deoxy-6-oxacalystegine B_2 **35** was of interest. Attempts to obtain this compound directly from amine **7** or its *N*-Boc- or *N*-Fmoc-protected derivatives by acid treatment failed, probably due to further hydrolysis−dehydration reactions of the transient aminoacetal derivative in acidic media.[30] Instead, the benzyl carbamate **33**[31] was prepared that, after acid hydrolysis of the isopropylidene group and neutralization as described above, afforded the *N*-bezyloxycarbonyl-6-oxa-*nor*-tropane **34**.[32] Hydrogenolysis of **34** led to the target compound **35** in 60% yield (Scheme 4).

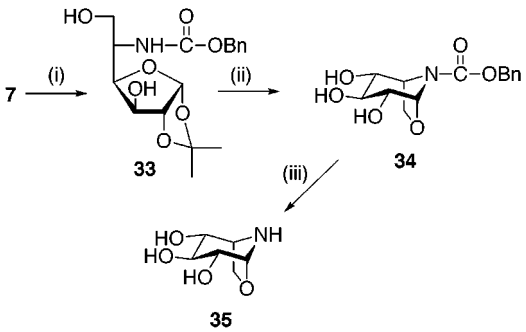
The ^{1}H NMR spectra of **24**−**32**, **34**, and **35** showed vicinal coupling constants characteristic of trans-diaxial

Scheme 3[a]



[a] Reagents: (i) Amberlite IRA 68 (OH^-) (60−96%).

Scheme 4[a]



[a] Reagents: (i) benzylchloroformate, Na_2CO_3 (85%); (ii) 90% TFA−H_2O, Amberlite IRA 68 (OH^-) (80%); (iii) H_2, 10% Pd/C (60%).

dispositions for the H-2, H-3, and H-4 protons, with the bridgehead H-1 and H-5 protons in equatorial orientations,[33] in agreement with the chair conformation for the six-membered ring. In addition, long-range $^4J_{H,H}$ coupling constants between protons in a W-arrangement, e.g., H-4/H-6_{exo} and H-1/H-5, were also observed, as expected for the rigid bicyclo[3.2.1]octane skeleton. The low-field ^{13}C chemical shift of C-6 confirmed its involvement in the oxazolidine ring closure.[33]

(28) No products arising from inter- or intramolecular addition of sulfur to the carbonyl group of the monosaccharide were detected. Although a rationalization of the sulfur vs nitrogen nucleophilicity in thioureas is problematic, from the ensemble of results available in the literature (cf. ref 24), it appears that nitrogen is generally involved in nucleophilic additions to carbonyl groups, whereas nucleophilic displacement reactions generally proceed through sulfur.

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(30) (a) Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 512. (b) Paulsen, H.; Todt, K. *Angew. Chem.* **1965**, *77*, 589.

(31) Schaller, C.; Vogel, P.; Jäger, V. *Carbohydr. Res.* **1998**, *314*, 25.

(32) The 5-benzyloxycarbonylamino-5-deoxy-β-L-idofuranose structure has been previously assigned to the product of acid hydrolysis of acetonide **33** (cf. ref 31). However, the NMR data (CD_3OD) provided by the authors are rather consistent with a piperidine derivative (low-field-shifted δ_{C-1} in agrement with the existence of an N−C-1 bond), in a chair conformation ($J_{2,3}$ = 8.0 Hz, $J_{3,4}$ = 8.1 Hz), bearing an axial anomeric substituent ($J_{1,2}$ = 1.7 Hz). The isolated compound was most likely a hydrated form of **34**.

(33) For clarity of presentation, the authors chose not to use the numbers resulting from the heterocyclic compounds (see Experimental Section) in the notation of atoms for NMR data. Instead, the notation is kept consistent with the parent carbohydrate compounds. See Figure 2 for atom notation equivalency.

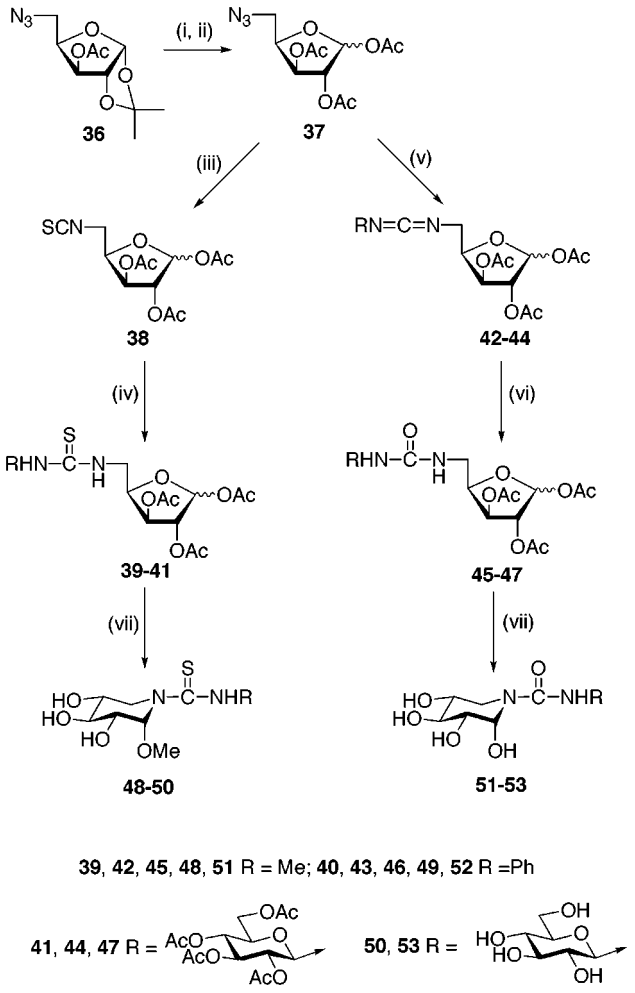
Synthesis and Structure of *N*-Thiocarbamoyl and *N*-Carbamoyl Piperidines. To determine the influence of the C-1−C-5 two-atom bridge on the inhibitory properties of this family of glycomimetics, the preparation and biological evaluation of a series of monocyclic piperidine analogues seemed intriguing. Attempts to prepare these compounds from 1,2-*O*-isopropylidene-α-D-xylofuranose precursors[34] following the above synthetic strategy failed, however, due to extensive decomposition of the products upon acid treatment. An alternative route was developed on the basis of the use of peracetylated xylofuranose templates. Replacement of the acetonide group by acetyl in the known azide **36**[35] afforded the triacetate **37** as an inseparable mixture of the α- and β-anomers. Condensation of **37** with triphenylphosphine and subsequent aza-Wittig-type reaction with either carbon disulfide or methyl, phenyl, or 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate led to the isothiocyanate **38** or carbodiimide derivatives **42**−**44**, respectively. Nucleophilic addition of methylamine, aniline, and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine[36] to **38** yielded the thiourea adducts **39**−**41**, respectively, whereas acid-catalyzed addition of water to the heteroallene group of **42**−**44** afforded the corresponding oxocompounds **45**−**47** (Scheme 5).

Deacetylation of **39**−**41** and **45**−**47** in methanol under standard NaOMe-catalyzed conditions proceeded with concomitant rearrangement to the target polyhydroxypiperidine tautomers. In the case of the thiourea derivatives, subsequent fast glycosidation at the aminoacetal center occurred, even using short reaction times and low temperatures, leading to the α-methyl glycosides **48**−**50**.[37] The later reaction was much slower for the urea analogues. The use of short reaction times allowed the reducing xylonojirimycin-type azaheterocycles **51**−**53** to be isolated in 60−70% yields (Scheme 5).

Both the *N*-thiocarbamoyl and *N*-carbamoyl compounds **48**−**50** and **51**−**53**, respectively, existed in D_2O solution as single diastereomers. The high-field shift of the C-1 resonance[33] confirmed the aminoacetal and hemiaminal structure, whereas the vicinal $^3J_{H,H}$ values around the piperidine ring unambiguously pointed to a conformation close to a chair and to the *R* configuration for the new stereocenter, with the pseudoanomeric methoxy or hydroxy group in the axial position, fitting the anomeric effect.

Biological Activity. The inhibitory activities of the oxacalystegine B_2 derivatives **24**−**32**, **34**, and **35** and of the monocyclic piperidine analogues **48**−**53** for α-glucosidase (yeast), β-glucosidase (almonds), β-glucosidase (bovine liver, cytosolic), and α-galactosidase (green coffee beans) are summarized in Table 1. None of these compounds inhibited α-glucosidase, in agreement with the linkage specificity of the parent calystegine alkaloids. The bicyclic *N*-thiocarbamoyl *nor*-tropane derivatives **25** and **26** acted as competitive inhibitors of both the almond and the cytosolic β-glucosidases, the inhibition potency being about 2−3 orders of magnitude higher for the mammalian enzyme. It may be concluded that these types of compounds can discriminate not only between α- and β-glucosidases but also between β-glucosidases of a different origin. A strong influence of the nature of the N′-substituent on the inhibition constant was observed, the potency as an inhibitor of β-glucosidase being about 100-fold higher for compounds bearing aromatic substituents than for compounds with methyl, glucosyl, or hydrogen substituents. The inhibition potency also increased by a factor of about 10 on going from *N*-carbamoyl (**30**) to *N*-thiocarbamoyl derivatives (**25** and **26**). Actually, the *N*-(*N*′-phenyl)thiocarbamoyl derivative **26** inhibits the mammalian cytosolic β-glucosidase ($K_i = 2.5\ \mu M$) 18-fold more strongly than the natural compound calystegine B_2 **1** ($K_i = 45\ \mu M$). When considering the almond β-glucosidase, we found that the corresponding K_i values (970 and 1.5 μM for **26** and **1**, respectively) indicated a reverse specificity. Conversely, the unsubstituted derivative **35**, having an amine-type endocyclic nitrogen, exhibited a behavior toward this particular pair of β-glucosidases parallel to that of calystegine B_2. The 10-fold increment in the corresponding inhibition constant values of **35** (85 and 606 μM for the almond and bovine liver enzymes,

Scheme 5[a]



[a] Reagents: (i) 50% TFA−H_2O, 5 h; (ii) 1:1 Ac_2O−pyridine, 12 h (70% overall); (iii) TPP, CS_2, dioxane (95%); (iv) RNH_2 (70−95%); (v) RNCS, TPP, toluene, 24 h (45−87%); (vi) 2:1 acetone−H_2O, 1% TFA (60−95%); (vii) NaOMe, MeOH, then Amberlite IR-120 (H^+) (54−88%).

(34) García-Moreno, M. I.; Benito, J. M.; Ortiz Mellet, C.; García Fernández, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 1331.

(35) Szarek, W. A.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 2345.

(36) Babiano Caballero, R.; Fuentes Mota, J.; Gálbis Pérez, J. A. *Carbohydr. Res.* **1986**, *154*, 280.

(37) Deacetylation of **40** was also carried out using $NaCD_3$ in CD_3OD. The corresponding NMR spectra of the mixture evidenced the formation of the corresponding deuterated methyl glycoside under these conditions, discarding an alternative acid-catalyzed mechanism during neutralization with the resin.

Table 1. Comparison of Inhibitory Activities (K_i, μM) for Bicyclic (24−32, 34, and 35) and Monocyclic Glycomimetics Related to Calystegine B_2 (48−53)

	enzyme					enzyme			
compd	α-glucosidase (yeast)	β-glucosidase (almonds)	β-glucosidase (bovine liver)	α-galactosidase (green coffee)	compd	α-glucosidase (yeast)	β-glucosidase (almonds)	β-glucosidase (bovine liver)	α-galactosidase (green coffee)
24	n.i.[a]	n.i.	300	n.i.	**34**	n.i.	n.i.	70	17800
25	n.i.	1500	5.3	163	**35**	n.i.	85	606	191
26	n.i.	970	2.5	137	**48**	n.i.	n.i.	n.i.	n.i.
27	n.i.	n.i.	n.i.	170	**49**	n.i.	1500	n.i.	400
28	n.i.	n.i.	148	n.i.	**50**	n.i.	n.i.	n.i.	n.i.
29	n.i.	118	325	n.i.	**51**	n.i.	n.i.	n.i.	n.i.
30	n.i.	1500	30	172	**52**	n.i.	1500	n.i.	550
31	n.i.	n.i.	n.i.	160	**53**	n.i.	n.i.	n.i.	n.i.
32	n.i.	n.i.	1640	175					

[a] No inhibition (n.i.) detected.

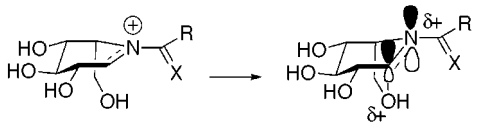


Figure 3. Anomeric-effect-driven intramolecular glycosylation in L-*ido*-configurated polyhydroxypiperidine intermediates.

respectively), in comparison with the corresponding values for the parent natural alkaloid, probably reflects the contribution of the bridgehead hydroxy group of calystegines to the binding energy. In stark contrast, the monocyclic counterparts did not significantly affect any of the glucosidases considered in this study.

The strength of inhibition of α-galactosidase by this family of compounds was, in general, much less influenced by the nature of the N′-substituent. Values in the 137−191 μM range, much higher than the reported data for calystegine B_2 (0.86 μM), were measured for derivatives bearing lipophilic or hydrophilic substituents in both the thiocarbamoyl and carbamoyl series, as well as for the unsubstituted compound **35**.

Discussion

We have designed and synthesized a new class of glycosidase inhibitors, the polyhydroxy 6-oxa-*nor*-tropanes. The synthetic scheme employs *N*-(thio)carbamic monosaccharide precursors and involves a tandem furanose → piperidine rearrangement−intramolecular glycosylation process. The L-*ido* configuration considered in this study leads to compounds that incorporate the essential structural features of the azasugar alkaloid calystegine B_2 (**1**), i.e., an 8-azabicyclo[3,2,1]octane system and an identical orientational pattern for the hydroxy groups at C-2, C-3, and C-4, with the hemiaminal functionality characteristic of the natural compound being replaced by an intramolecular aminoacetal grouping. To the best of our knowledge, these are the first examples of ring-modified calystegine analogues.

The propensity of the reducing *N*-(thio)carbamoylpiperidine intermediate to undergo glycosidation reactions is in agreement with formation of a transient azacarbenium cation and an efficient stabilization of the transition state leading to aminoacetal formation by the incipient anomeric effect, the whole pathway being favored by the π-symmetry of the lone-pair orbital of the N-atom in pseudoamide functional groups (Figure 3). Because the partial double-bond character of the N−C(X)N bond decreases on going from thiourea to urea, a parallel abatement of the contribution of orbital interactions to the generalized anomeric effect was expected.[25,38] This is probably the reason that the hemiaminal compounds **51**−**53** could be isolated in the D-xylose-derived *N*-carbamoyl piperidine series, whereas the thioxo counterparts underwent in situ glycosidation by methanol (→ **48**−**50**).[39] The anomeric effect stabilization also explains the high stability of all the *N*-(thio)carbamoyl azasugars reported here as well as their configurational and conformational integrity, which is notably different than that found for the amine derivative **35** due to the lability of the N/O acetal function.[40] Thus, whereas **26**−**32** and **48**−**53** were found to be stable for weeks as solids or as aqueous solutions in a refrigerator, compound **35** underwent extensive decomposition after 1 day.

Azasugars such as 1-deoxynojirimycin (**2**) are thought to be good but rather nonspecific inhibitors of glycosidases because they mimic the glycosyl oxocarbenium cation (e.g., **4**), a proposed intermediate in the mechanism of action of both α- and β-glycosidases, upon protonation. In contrast, 1-azasugars such as isofagomine (**6**) would be good mimics of the glycosyl carbocation (e.g., **5**), the proposed first transition state in the mechanism of β-glycosidases.[14d] In *N*-(thio)carbonyl compounds, the basicity at the nitrogen atom is drastically decreased (by 14 p*K* units) compared to that in the corresponding amine while keeping a positive charge density that results from delocalization of the lone electron pair into the (thio)carbonyl group.[38,41] This scenario is probably closer to that encountered in the transition state of enzymatic glycoside hydrolysis at the anomeric region.[12,42] One could expect that if glycomimetics of the calystegine family behave as inhibitors of the 1-azasugar type, substituents at the heterocyclic nitrogen would project into the aglycon

(38) For reviews on the comparative chemical and electronic properties of *N*-(thio)carbonyl compounds, see: (a) Molina, M. T.; Yáñez, M.; Mó, O.; Notario, R.; Abboud, J.-L. M. The Thiocarbonyl Group. In *Supplement A3, The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons: Chichester, England, 1997; Part 2, p 1355. (b) Duus, F. Thiocarbonyl Compounds. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: London, 1979; Vol. 3, p 373.

(39) The formation of the methyl glycosides **48**−**50** under basic conditions is noteworthy. Glycosylation reactions generally need acid catalysis. The observed reactivity can be rationalized assuming that the transient hemiaminal precursor is in equilibrium with the corresponding Δ^1-piperidinium cation, which undergo electrophilic adition of methylate. A similar mechanism has been put forward by other authors to explain the formation of glycosides from heterocyclic hemiaminals under neutral conditions. See: (a) Izquierdo, I.; Plaza, M. T.; Robles, R.; Mota, A. J. *Eur. J. Org. Chem*. **2000**, 2071. (b) Domínguez, M.-J.; García López, M.-T.; Herranz, R.; Martín Martínez, M.; Gozález Muñiz, R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2839. (c) Domínguez, M.-J.; García López, M.-T.; Gozález Muñiz, R. *Tetrahedron* **1993**, *49*, 8911.

(40) Johnson, C. R.; Golebiowski, A.; Sundram, H.; Miller, M. W.; Dwaihy, R. L. *Tetrahedron Lett*. **1994**, *36*, 653.

(41) Humeres, E.; Debacher, N. A.; Sierra, M. M. de S.; Franco, J. D.; Schutz, A. *J. Org. Chem*. **1998**, *63*, 1598.

binding subsite. Introduction of aglycon-mimicking groups may then result in stronger inhibition.

The high selectivity and potency observed for the oxacalystegine derivatives with aromatic substituents **25**, **26**, **30**, and **33** in the inhibition of the mammaliam cytosolic β-glucosidase, an enzyme known to possess a hydrophobic binding site and for which aromatic β-D-glucosides are good substrates,[43] confirm the above assumptions and strongly support a 1-azasugar mode of action for calystegine-type inhibitors against β-glucosidases. The reverse selectivity of the *N*-(thio)carbamoyl-6-oxacalystegines toward cytosolic and almond β-glucosidases compared with that of calystegine B_2 or the unsubstituted 6-oxacalystegine **35**, incorporating a basic nitrogen atom, probably reflects the need for a higher contribution of electrostatic interactions to achieve an efficient binding in the case of the later enzyme.

The 10-fold increase in the cytosolic β-glucosidase inhibition potency for thiocarbamoyl (e.g., **26**) compared with that for carbamoyl *nor*-tropane derivatives (e.g., **30**) is probably due to the higher positive charge density of the thiourea N-atom compared with that of urea. In any case, the rigid bicyclic structure seems to be a major requirement for β-glucosidase inhibition. Thus, replacement of the oxazolidine ring (e.g., in **26** or **30**) by an open aminoacetal center (e.g., in the xylonojirimycin analogues **49** and **52**) totally abolished inhibition in both series.

No significant influence of the nature of the pseudoaglyconic substituent on the interaction of 6-oxacalystegines with α-galactosidase was observed. The strong decrease in inhibition potency for the unsubstituted derivative **35** compared to that for calystegine B_2, more than 100-fold, indicates that the bridgehead hydroxy group of **1** is actively involved in strong binding. In contrast to the above comments for the mammalian β-glucosidase, disrupting the cyclic aminoacetal group has only a weak effect (a ca. 3-fold decrease) on the inhibition potency.

Further work is necessary to determine the exact mode of interaction of calystegine-type azasugars with glycosidases. Kinetic studies with the new oxacalystegine derivatives against both cytosolic β-glucosidase and α-galactosidase indicated fast and competitive inhibition, as reported for the natural alkaloids. The C-1−C-5 two-atom bridge seems to prevent recognition by α-glucosidase and forces a recognition mode analogous to that of 1-azasugars for β-glucosidase, the N-substituent interacting with the aglycon binding subsite. In any case, our work provides a new tool for preparing selective β-glucosidase inhibitors of the calystegine family by exploiting the reactivity of *N*-(thio)carbamoyl aminoketalic systems. A variety of structures become available by acting on the configuration of the monosaccharide template and the nature of the N-substituent.

Experimental Section

General Procedures. Optical rotations were measured at room temperature in 1 cm or 1 dm tubes. IR spectra were recorded on a FT-IR instrument. ^{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 *m*-nitrobenzyl alcohol or thioglycerol as the matrixes, and the positive ions were separated and accelerated over a potential of 7 keV. NaI was added as a cationizing agent. In the CIMS spectra, isobutane was used as the reactive gas (500 mA, 8 kV). Visualization of TLC plates was effected by UV light and by charring with 10% sulfuric acid or 0.2% w/v cerium(IV) sulfate−5% ammonium molybdate in 2 M H_2SO_4. Fully unprotected compounds were purified by GPC (Sephadex G-10, 1:1 MeOH−H_2O). Acetylations were effected conventionally with 1:1 pyridine−Ac_2O (10 mL/1 g of sample). Deacetylations were effected by treatment with methanolic NaOMe (0.1 equiv/mol of acetate) at room temperature for 3 h, followed by neutralization with Amberlite IR-120 (H^+) ion-exchange resin. Microanalyses were performed by the Instituto de Investigaciones Químicas (Sevilla, Spain).

Materials. 5-Amino-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**7**) was prepared from commercial D-glucofuranurono 6,3-lactone according to the literature.[18a,22] 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**8**) 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.[23] Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato-α-D-glucopyranoside (**9**) was obtained by isothiocyanation of the corresponding 6-amino-6-deoxysugar using thiophosgene as reported.[24] 3,6-Di-*O*-acetyl-5-azido-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**16**) was obtained by conventional acetylation of 5-azido-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose[18a,22] in quantitative yield (see Supporting Information). 5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**36**) was prepared from the corresponding 5-*O*-tosyl derivative by treatment with sodium azide.[35] TFA-catalyzed hydrolysis of the acetonide protecting group of **36** and further conventional acetylation afforded the triacetate **37** as a mixture of the α- and β-anomers (Scheme 5; see Supporting Information). 9-Fluorenylmethyloxycarbonyl isothiocyanate was prepared from commercial chloride by reaction with potassium isothiocyanate.[44] The α-glucosidase (from brewer yeast), β-glucosidase (from almonds), β-glucosidase (from bovine liver, cytosolic), and α-galactosidase (from green coffee beans) used in the inhibition studies as well as the corresponding *p*-nitrophenyl glycoside substrates were purchased from Sigma Chemical Company.

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.

General Procedure for the Inhibition Assay. Inhibitory potencies were determined by spectrophotometrically measuring the residual hydrolytic activities of the glycosidases against the respective *p*-nitrophenyl α- or β-D-glucopyranoside or *p*-nitrophenyl α-D-galactopyranoside in the presence of the corresponding 6-oxacalystegine derivative. Each assay was performed in phosphate buffer at the optimal pH for each enzyme. The reactions were initiated by addition of the enzyme to a solution of the substrate in the presence or absence of various concentrations of the inhibitor. After the mixture was incubated for 10−30 min at 37 °C, the reaction was quenched by addition of 1 M Na_2CO_3. The absorbance of the resulting mixture was determined at 400 nm. The K_i value and enzyme inhibition mode were determined from the slope of Lin-

(42) Theoretical and experimental studies indicate that true transition state analogues must be essentially neutral or zwitterionic at physiological pH to keep specificity against the target enzyme. See: (a) Jeong, J.-H.; Murray, B. W.; Takayama, S.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 4227. (b) Legler, G.; Finken, M.-T. *Carbohydr. Res.* **1996**, *292*, 103. (c) Blériot, Y.; Genre-Grandpierre, A.; Imberty, A.; Tellier, C. *J. Carbohydr. Chem.* **1996**, *15*, 985. (d) Deng, H.; Chan, A. W.-Y.; Bagdasianan, C. K.; Estupiñán, B.; Ganem, B.; Callender, R. H.; Scharam, V. L. *Biochemistry* **1996**, *35*, 6037. (e) Ernert, P.; Vasella, A.; Weber, M.; Rupitz, K.; Withers, S. G. *Carbohydr. Res.* **1993**, *250*, 113.

(43) Legler, G.; Bieberich, E. *Arch. Biochem. Biophys.* **1988**, *260*, 427.

(44) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *63*, 196.

eweaver−Burk plots and double-reciprocal analyses using a Sigma Plot program (version 4.14, Jandel Scientific).

General Procedure for the Preparation of 5-Deoxy-5-thioureido-L-idofuranoses (10−16). To a solution of 5-amino-5-deoxy-1,2-*O*-isopropylidene-*β*-L-idofuranose **7** (0.5 g, 2.29 mmol) in pyridine (15 mL) were added the corresponding 9-fluorenyloxycarbonyl, methyl, benzyl, phenyl, or sugar-derived isothiocyanate **8** or **9** (2.29 mmol) and Et_3N (0.05 mL). The mixture was stirred at room temperature for 3−24 h (TLC) and concentrated. The resulting residue was chromatographed with the indicated eluent to give the thiourea adduct **10**−**13**, **15**, or **16**, respectively, as an amorphous solid. The N-monosubstituted thiourea **14** was obtained from the *N*′-Fmoc-protected derivative **10** (195 mg, 0.39 mmol) by treatment with 20% methanolic piperidine (1 mL) in CH_2Cl_2 (1.6 mL) at room temperature for 2 h and further purification by column chromatography (45:5:3 AcOEt−EtOH−H_2O).

5-Deoxy-5-[3-(9-fluorenylmethyloxycarbonyl)thioureido]-1,2-*O*-isopropylidene-*β*-L-idofuranose (10): yield 0.92 g (80%); R_f (2:1 EtOAc−petroleum ether) 0.53; $[\alpha]_D$ −18.4 (*c* 1.0, CH_2Cl_2); UV (CH_2Cl_2) 266 nm (ϵ_{mM} 36.0); IR (KBr) ν_{max} 3275, 2986, 1723, 1537 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (see also Table 2, Supporting Information) δ 10.11 (d, 1 H, $J_{NH,5}$ = 8.0 Hz, NH), 8.58 (s, 1 H, NH), 7.74−7.30 (m, 8 H, aromatic), 4.45 (dd, 1 H, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 6.8 Hz, CH_2), 4.42 (dd, 1 H, CH_2), 4.20 (t, 1 H, CH), 1.48, 1.28 (2 s, each 3 H, Me_2C); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 179.1, 152.4, 142.9, 141.2, 127.9, 127.2, 124.9, 120.1, 111.8, 104.7, 85.1, 79.2, 75.3, 68.3, 62.0, 55.7, 46.5, 26.8, 26.1; CIMS *m*/*z* 501 (50, $[M + H]^+$). Anal. Calcd for $C_{25}H_{28}N_2O_7S$: C, 59.99; H, 5.64; N, 5.59. Found: C, 59.80; H, 5.56; N, 5.53.

5-Deoxy-1,2-*O*-isopropylidene-5-(3-methylthioureido)-*β*-L-idofuranose (11): yield 0.58 g (87%); R_f (20:1 CH_2Cl_2−MeOH) 0.27; $[\alpha]_D$ −19.5 (*c* 1.1, MeOH); UV (MeOH) 240 nm (ϵ_{mM} 9.1); IR (KBr) ν_{max} 3376, 2926, 1572 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 313 K) (see also Table 2, Supporting Information) δ 2.97 (s, 3 H, *Me*NH), 1.45, 1.30 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, CD_3OD, 313 K) δ 182.5, 112.6, 105.8, 86.8, 81.0, 75.6, 62.5, 56.5, 33.0, 26.9, 26.3; FABMS *m*/*z* 315 (100, $[M + Na]^+$). Anal. Calcd for $C_{11}H_{20}N_2O_5S$: C, 45.19; H, 6.90; N, 9.58; S, 10.79. Found: C, 45.20; H, 6.72; N, 9.53; S, 11.07.

5-(3-Benzylthioureido)-5-deoxy-1,2-*O*-isopropylidene-*β*-L-idofuranose (12): yield 0.51 g (60%); R_f (20:1 CH_2Cl_2−MeOH) 0.26; $[\alpha]_D$ −27.7 (*c* 1.0, MeOH); UV (MeOH) 242 nm (ϵ_{mM} 19.6); IR (KBr) ν_{max} 3395, 2980, 1562, 1537 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 318 K) (see also Table 2, Supporting Information) δ 7.32−7.19 (m, 5 H, Ph), 4.49 (s, 2 H, CH_2), 1.44, 1.28 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, CD_3OD, 318 K) δ 184.2, 139.8, 129.5, 128.6, 128.2, 112.8, 105.9, 86.9, 81.1, 75.8, 62.6, 56.3, 49.0, 27.0, 26.4; FABMS *m*/*z* 391 (100, $[M + Na]^+$). Anal. Calcd for $C_{17}H_{24}N_2O_5S$: C, 55.42; H, 6.56; N, 7.60. Found: C, 55.08; H, 6.74; N, 7.54.

5-Deoxy-1,2-*O*-isopropylidene-5-(3-phenylthioureido)-*β*-L-idofuranose (13): yield 0.73 g (90%); R_f (20:1 CH_2Cl_2−MeOH) 0.24; $[\alpha]_D$ +14.6 (*c* 0.69, MeOH); UV (MeOH) 250 nm (ϵ_{mM} 14.4); IR (KBr) ν_{max} 3428, 2959, 1657 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 313 K) (see also Table 2, Supporting Information) δ 7.45−7.15 (m, 5 H, Ph), 1.44, 1.29 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, CD_3OD, 313 K) δ 182.0, 139.6, 130.2, 126.7, 125.3, 112.8, 105.9, 86.9, 80.6, 75.8, 62.4, 56.6, 27.0, 26.4; FABMS *m*/*z* 377 (100, $[M + Na]^+$). Anal. Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.22; H, 6.26; N, 7.90; S, 9.05. Found: C, 54.24; H, 6.40; N, 7.89; S, 9.05.

5-Deoxy-1,2-*O*-isopropylidene-5-thioureido-*β*-L-idofuranose (14): yield 65 mg (60%); R_f (45:5:3 AcOEt−EtOH−H_2O) 0.54; $[\alpha]_D$ −27.9 (*c* 0.88, MeOH); UV (MeOH) 242 nm (ϵ_{mM} 16.2); IR (KBr) ν_{max} 3434, 3324, 2980, 1603 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 313 K) (see also Table 2, Supporting Information) δ 1.50, 1.29 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, CD_3OD, 313 K) δ 180.0, 113.6, 106.7, 87.8, 81.9, 76.5, 63.3, 57.8, 27.9, 27.3; CIMS *m*/*z* 279 (100, $[M + H]^+$). Anal. Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.22; H, 6.26; N, 7.90; S, 9.05. Found: C, 54.24; H, 6.40; N, 7.89; S, 9.05.

5-Deoxy-1,2-*O*-isopropylidene-5-[3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)thioureido]-*β*-L-idofuranose (15): yield 1.29 g (93%); R_f (20:1 CH_2Cl_2−MeOH) 0.22; $[\alpha]_D$ −2.6 (*c* 0.76, CH_2Cl_2); UV (MeOH) 248 nm (ϵ_{mM} 14.5); IR (KBr) ν_{max} 3428, 2951, 1760, 1553 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 313 K) (see also Table 2, Supporting Information) δ 2.02, 2.00 (6 H), 1.97 (4 Ac), 1.44, 1.28 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, CD_3OD) δ 185.3, 172.3, 171.6, 171.5, 171.3, 112.6, 105.9, 86.9, 83.5, 80.4, 75.6, 74.8, 74.4, 71.9, 69.7, 63.1, 61.8, 56.5, 27.0, 26.3, 20.8−20.4; FABMS *m*/*z* 631 (100, $[M + Na]^+$). Anal. Calcd for $C_{24}H_{36}N_2O_{14}S$: C, 47.36; H, 5.97; N, 4.60; S, 5.27. Found: C, 47.01; H, 5.90; N, 4.33; S, 5.00.

5-Deoxy-1,2-*O*-isopropylidene-5-[3-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosyd-6-yl)thioureido]-*β*-L-idofuranose (16): yield 1.0 g (76%); R_f (20:1 CH_2Cl_2−MeOH) 0.26; $[\alpha]_D$ +62.0 (*c* 1.0, CH_2Cl_2); UV (CH_2Cl_2) 248 nm (ϵ_{mM} 11.7); IR (KBr) ν_{max} 3497, 2961, 1750, 1562 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 323 K) (see also Table 2, Supporting Information) δ 6.82 (bd, 1 H, NH′), 6.50 (bs, 1 H, NH), 3.38 (s, 3 H, OMe), 2.05, 2.00, 1.96 (3 s, each 3 H, 3 Ac), 1.46, 1.29 (2 s, each 3 H, Me_2C); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 183.4, 170.6−169.9, 111.7, 104.4, 96.5, 84.7, 80.0, 75.1, 70.7, 69.5, 68.8, 68.0, 63.3, 55.4, 54.9, 44.4, 26.6, 25.9, 20.9−20.5; FABMS *m*/*z* 603 (100, $[M + Na]^+$). Anal. Calcd for $C_{23}H_{36}N_2O_{13}S$: C, 47.58; H, 6.25; N, 4.83. Found: C, 47.41; H, 6.23; N, 4.66.

General Procedure for the Preparation of 5-Carbodiimido-5-deoxy-L-idofuranoses (18−20). A solution of azide **17** (1.0 g, 3.04 mmol) in toluene (45 mL) was stirred under nitrogen for 30 min. Then, the corresponding phenyl or sugar-derived isothiocyanate **8** or **9** (3.04 mmol) and a solution of TPP (0.88 g, 3.34 mmol) in toluene (20 mL) were added dropwise at room temperature. The reaction mixture was stirred for 24 h and concentrated, and the residue was purified by column chromatography (1:3 → 1:1 EtOAc−petroleum ether). The resulting carbodiimides were isolated as amorphous solids.

3,6-Di-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-5-(3-phenylcarbodiimido)-*β*-L-idofuranose (18): yield 0.98 g (80%); R_f (2:1 EtOAc−petroleum ether) 0.83; $[\alpha]_D$ −91.4 (*c* 0.5, CH_2Cl_2); IR (KBr) ν_{max} 2991, 2139, 1750, 1593, 1501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (see also Table 2, Supporting Information) δ 7.25−7.03 (m, 5 H, Ph), 2.08, 1.94 (2 s, each 3 H, 2 Ac), 1.46, 1.25 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.2, 169.7, 139.3, 137.8, 129.3, 125.2, 125.1, 123.9, 112.3, 104.3, 83.5, 78.2, 75.9, 64.3, 55.6, 26.6, 26.1, 20.7, 20.5; FABMS *m*/*z* 427 (35, $[M + Na]^+$). Anal. Calcd for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.94; N, 6.93. Found: C, 59.35; H, 6.11; N, 6.91.

3,6-Di-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-5-[3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)carbodiimido]-*β*-L-idofuranose (19): yield 1.81 g (90%); R_f (1:1 EtOAc−petroleum ether) 0.34; $[\alpha]_D$ −15.4 (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 2963, 2143, 1750, 1554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (see also Table 2, Supporting Information) δ 2.15−1.98 (6 s, each 3 H, 6 Ac), 1.52, 1.31 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5−169.2, 138.3, 112.3, 104.1, 84.5, 83.6, 78.2, 75.7, 73.6, 72.9, 72.4, 68.1, 63.9, 61.9, 54.9, 26.6, 26.1, 20.7−20.5; FABMS *m*/*z* 681 (100, $[M + Na]^+$). Anal. Calcd for $C_{28}H_{38}N_2O_{16}$: C, 51.06; H, 5.82; N, 4.25. Found: C, 50.91; H, 5.74; N, 4.10.

3,6-Di-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-5-[3-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-*β*-D-glucopyranosyd-6-yl)-carbodiimido]-*β*-L-idofuranose (20): yield 0.59 g (31%); R_f (1:1 EtOAc−petroleum ether) 0.38; $[\alpha]_D$ +51.5 (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 2961, 2137, 1742, 1574, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (see also Table 3, Supporting Information) δ 3.36 (s, 3 H, OMe), 2.04−192 (5 s, each 3 H, 5 Ac), 1.44, 1.23 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.2−169.4 (5 CO), 140.2, 112.1, 103.4, 96.5, 83.4, 78.4, 75.6, 70.5, 69.8, 69.5, 67.9, 64.1, 55.3, 54.6, 46.5, 26.4, 26.0, 20.5−20.4; FABMS *m*/*z* 653 (100, $[M + Na]^+$). Anal. Calcd for $C_{27}H_{38}N_2O_{15}$: C, 51.42; H, 6.07; N, 4.44. Found: C, 51.21; H, 5.77; N, 4.33.

General Procedure for the Preparation of 5-Deoxy-5-ureido-L-idofuranoses (21−23). To a solution of the corresponding carbodiimide **18**−**20** (1.52 mmol) in 2:1 acetone−water (45 mL) was added TFA (0.5 mL). The reaction mixture

was stirred at room temperature for 2−12 h until the starting material disappeared (TLC), and the solution was then concentrated. Column chromatography of the residue (1:1 → 2:1 EtOAc−petroleum ether) afforded the urea as an amorphous solid.

3,6-Di-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-5-(3-phenylureido)-β-L-idofuranose (21): yield 0.64 g (100%); R_f (2:1 EtOAc−petroleum ether) 0.60; $[\alpha]_D$ −2.3 (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 3384, 2996, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (see also Table 2, Supporting Information) δ 7.32−7.26 (m, Ph), 6.58 (bs, 1 H, NH′), 5.19 (d, 1 H, $J_{NH,5}$ = 8.0 Hz, NH), 2.06 (2 s, each 3 H, 2 Ac), 1.51, 1.31 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8, 169.8, 154.7, 138.3, 129.1, 123.7, 120.3, 112.7, 104.3, 83.5, 77.1, 64.5, 47.6, 26.6, 20.7; FABMS *m*/*z* 445 (100, $[M + Na]^+$). Anal. Calcd for $C_{20}H_{26}N_2O_8$: C, 56.87; H, 6.16; N, 6.63. Found: C, 56.68; H, 6.43; N, 6.60.

3,6-Di-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-5-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)ureido]-β-L-idofuranose (22): yield 0.67 g (65%); R_f (3:1 EtOAc−petroleum ether) 0.34; $[\alpha]_D$ −2.8 (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 3393, 2986, 1750, 1696, 1547 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 313 K) (see also Table 2, Supporting Information) δ 5.43 (d, 1 H, $J_{N'H,1'}$ = 9.3 Hz, NH), 5.11 (d, 1 H, $J_{NH,5}$ = 7.1 Hz, NH), 2.05−1.95 (6 s, each 3 H, 6 Ac), 1.48, 1.27 (2 s, each 3 H, Me_2C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8−169.5, 155.7, 112.1, 104.2, 83.4, 80.1, 77.1, 76.2, 72.9 (2 C), 68.1 (2 C), 63.9, 61.6, 26.4, 26.0, 20.6−20.4; FABMS *m*/*z* 699 (100, $[M + Na]^+$). Anal. Calcd for $C_{28}H_{40}N_2O_{17}$: C, 49.70; H, 5.96; N, 4.14. Found: C, 49.41; H, 5.87; N, 4.14.

3,6-Di-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-5-[3-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-β-D-glucopyranosyd-6-yl)-ureido]-β-L-idofuranose (23): yield 0.95 g (96%); R_f (3:1 EtOAc−petroleum ether) 0.25; $[\alpha]_D$ +57.8 (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 3387, 2988, 1750, 1651, 1559 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (see also Table 2, Supporting Information) δ 4.90 (m, 2 H, 2 NH), 3.38 (s, 3 H, OMe), 2.07−1.98 (5 s, each 3 H, 5 Ac), 1.49, 1.29 (2 s, each 3 H, Me_2C); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 170.6−169.8, 157.1, 112.2, 104.2, 96.8, 83.6, 77.6, 76.4, 71.0, 70.0, 69.4, 68.2, 64.4, 55.3, 47.9, 40.3, 26.5, 26.1, 20.6−20.5; FABMS *m*/*z* 671 (100 $[M + Na]^+$). Anal. Calcd for $C_{27}H_{40}N_2O_{16}$: C, 49.99; H, 6.22; N, 4.32. Found: C, 50.07; H, 6.30; N, 4.34.

General Procedure for the Preparation of *N*-(Thio)-carbamoyl-6-oxacalystegines (24−32). A solution of **11**−**14** or of the product of deacetylation (NaOMe/MeOH) of **15**, **16**, or **21**−**23** (0.5 mmol) in 90% TFA−H_2O (5 mL) was stirred at room temperature for 20−75 min until the starting material disappeared (TLC, 45:5:3 EtOAc−EtOH−H_2O). The reaction mixture was concentrated and the residue coevaporated several times with water. An aqueous solution was further neutralized with Amberlite IRA-68 (OH^-) ion-exchange resin, filtered, and freeze-dried. Where stated, the residue was purified by column chromatography using the eluent indicated in each case. In all cases, the fully unprotected compounds were subjected to GPC (Sephadex G-10, 1:1 MeOH−H_2O) to afford the target 6-oxacalystegine derivatives as white foams after lyophilization of an aqueous solution.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-*N*-(*N*′-methylthiocarbamoyl)-6-oxa-*nor*-tropane (24): column chromatography, eluent 45:5:3 AcOEt−EtOH−H_2O; yield 76 mg (65%); $[\alpha]_D$ +47.7 (*c* 0.6, H_2O); R_f (45:5:3 EtOAc−EtOH−H_2O) 0.39; UV (MeOH) 246 nm (ϵ_{mM} 9.4); IR (KBr) ν_{max} 3364, 2912, 1553 cm^{-1}; ^1H NMR (500 MHz, D_2O, 323 K) (see also Table 3, Supporting Information) δ 3.52 (s, 3 H, *Me*NH); ^{13}C NMR (75.5 MHz, D_2O, 323 K) δ 177.9, 88.4, 75.0, 73.8, 70.5, 67.4, 58.2, 31.9; FABMS *m*/*z* 257 (80, $[M + Na]^+$). Anal. Calcd for $C_8H_{14}N_2O_4S$: C, 41.02; H, 5.98; N, 11.96; S, 13.68. Found: C, 40.82; H, 5.94; N, 11.93; S, 13.79.

(1*S*,2*R*,3*S*,4*R*,5*R*)-*N*-(*N*′-Benzylthiocarbamoyl)-2,3,4-trihydroxy-6-oxa-*nor*-tropane (25): column chromatography, eluent 3:1 EtOAc−petroleum ether; yield 93 mg (60%): R_f (45:5:3 EtOAc−EtOH−H_2O) 0.46; $[\alpha]_D$ +63.1 (*c* 1.0, MeOH); UV (MeOH) 250 nm (ϵ_{mM} 14.7); IR (KBr) ν_{max} 3344, 2948, 1605, 1535 cm^{-1}; ^1H NMR (300 MHz, D_2O) (see also Table 3, Supporting Information) δ 7.40−7.30 (m, 5 H, PhN), 4.70 (bs, 2 H, CH_2); ^{13}C NMR (75.5 MHz, D_2O) δ 178.4, 138.0, 128.9, 127.5, 127.1, 88.5, 74.9, 73.8, 70.6, 66.3, 58.4, 47.4; FABMS *m*/*z* 311 (80, $[M + H]^+$). Anal. Calcd for $C_{14}H_{18}N_2O_4S$: C, 50.89; H, 5.49; N, 8.48. Found: C, 50.78; H, 5.40; N, 8.29.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-6-oxa-*N*-(*N*′-phenylthiocarbamoyl)-*nor*-tropane (26): yield 102 mg (69%); $[\alpha]_D$ +66.1 (*c* 0.6, MeOH); R_f (45:5:3 EtOAc−EtOH−H_2O) 0.55; UV (MeOH) 245 nm (ϵ_{mM} 13.2); IR (KBr) ν_{max} 3341, 2928, 1537 cm^{-1}; ^1H NMR (500 MHz, D_2O, 323 K) (see also Table 3, Supporting Information) δ 7.85−7.65 (m, 5 H, PhN); ^{13}C NMR (125.5 MHz, D_2O, 313 K) δ 179.3, 139.7, 130.4, 128.6, 128.3, 89.7, 76.1, 74.8, 71.7, 67.4, 59.9; FABMS *m*/*z* 319 (40, $[M + Na]^+$). Anal. Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45. Found: C, 52.58; H, 5.33; N, 9.46.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-6-oxa-*N*-thiocarbamoyl-*nor*-tropane (27): column chromatography, eluent 6:1 CH_2Cl_2−MeOH; yield 106 mg (96%); R_f (4:1 CH_2Cl_2−MeOH) 0.35; $[\alpha]_D$ +58.0 (*c* 1.0, H_2O); UV (MeOH) 250 nm (ϵ_{mM} 13.0); IR (KBr) ν_{max} 3407, 3380, 1656, 1553 cm^{-1}; ^1H NMR (300 MHz, D_2O, 313 K) (see also Table 3, Supporting Information); ^{13}C NMR (75.5 MHz, D_2O, 313 K) δ 177.5, 88.5, 75.2, 73.9, 70.7, 66.9, 58.8; FABMS *m*/*z* 221 (30, $[M + H]^+$). Anal. Calcd for $C_7H_{12}N_2O_4S$: C, 38.17; H, 5.49; N, 12.72. Found: C, 38.39; H, 5.39; N, 12.69.

(1*S*,2*R*,3*S*,4*R*,5*R*)-*N*-[*N*′-(β-D-Glucopyranosyl)thiocarbamoyl]-2,3,4-trihydroxy-6-oxa-*nor*-tropane (28): yield 124 mg (65%); $[\alpha]_D$ +21.7 (*c* 0.65, MeOH); R_f (6:3:1 MeCN−H_2O−NH_4OH) 0.33; UV (MeOH) 253 nm (ϵ_{mM} 7.0); IR (KBr) ν_{max} 3404, 1657, 1553 cm^{-1}; ^1H NMR (500 MHz, D_2O) (see also Table 3, Supporting Information); ^{13}C NMR (125.7 MHz, D_2O) δ 179.2, 88.0, 84.1, 77.0, 76.1, 74.3, 72.9, 71.2, 69.8, 68.7, 65.9, 60.0, 57.7; FABMS *m*/*z* 405 (40, $[M + Na]^+$). Anal. Calcd for $C_{13}H_{22}N_2O_9S$: C, 40.83; H, 5.80; N, 7.32. Found: C, 40.81; H, 5.52; N, 7.15.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-*N*-[*N*′-(methyl6-deoxy-α-D-glucopyranosyd-6-yl)thiocarbamoyl]-6-oxa-*nor*-tropane (29): column chromatography, eluent 20:1 → 5:1 EtOAc−EtOH; yield 176 mg (89%); $[\alpha]_D$ +85.0 (*c* 1.1, MeOH); R_f (1:1 EtOAc−EtOH) 0.36; UV (MeOH) 249 nm (ϵ_{mM} 13.8); IR (KBr) ν_{max} 3362, 1651, 1539 cm^{-1}; ^1H NMR (500 MHz, D_2O) (see also Table 3, Supporting Information) δ 3.27 (s, 3 H, OMe); ^{13}C NMR (125.7 MHz, D_2O) δ 178.4, 99.3, 88.6, 75.1, 73.9, 73.1, 71.8, 71.5, 70.7, 69.7, 66.3, 58.4, 55.9, 46.2; FABMS *m*/*z* 603 (40, $[M + Na]^+$). Anal. Calcd for $C_{14}H_{24}N_2O_9S$: C, 42.42; H, 6.10; N, 7.07. Found: C, 42.31; H, 5.99; N, 6.93.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-6-oxa-*N*-(*N*′-phenylcarbamoyl)-*nor*-tropane (30): column chromatography, eluent 15:1 MeCN−H_2O; yield 112 mg (80%); $[\alpha]_D$ +97.4 (*c* 1.0, H_2O); R_f (15:1 MeCN−H_2O) 0.60; IR (KBr) ν_{max} 3333, 1672, 1529 cm^{-1}; ^1H NMR (500 MHz, D_2O) (see also Table 3, Supporting Information) δ 7.34−7.10 (m, 5 H, Ph); ^{13}C NMR (75.5 MHz, D_2O) δ 157.9, 139.5, 131.2, 127.0, 124.2, 87.3, 75.4, 74.9, 71.9, 65.4, 57.3; FABMS *m*/*z* 303 (100, $[M + Na]^+$). Anal. Calcd for $C_{13}H_{14}O_5N_2$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.48; H, 5.60; N, 9.79.

(1*S*,2*R*,3*S*,4*R*,5*R*)-*N*-[*N*′-(β-D-Glucopyranosyl)carbamoyl]-2,3,4-trihydroxy-6-oxa-*nor*-tropane (31): column chromatography, eluent 15:1 MeCN−H_2O; yield 174 mg (95%); $[\alpha]_D$ +25.0 (*c* 1.0, H_2O); R_f (6:3:1 MeCN−H_2O−NH_4OH) 0.30; IR (KBr) ν_{max} 3385, 2907, 1651, 1541 cm^{-1}; ^1H NMR (500 MHz, D_2O) (see also Table 3, Supporting Information); ^{13}C NMR (125.7 MHz, D_2O) δ 156.1, 85.7, 80.8, 76.8, 76.1, 74.7, 74.0, 71.1, 70.8, 68.9, 64.9, 60.2, 56.3; FABMS *m*/*z* 389 (100, $[M + Na]^+$). Anal. Calcd for $C_{13}H_{22}N_2O_{10}$: C, 42.68; H, 6.05; N, 7.65. Found: C, 42.42; H, 5.97; N, 7.41.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-*N*-[*N*′-(methyl6-deoxy-α-D-glucopyranosyd-6-yl)carbamoyl]-6-oxa-*nor*-tropane (32): column chromatography, eluent 7:1 → 5:1 MeCN−H_2O; yield 162 mg (85%); $[\alpha]_D$ +61.2 (*c* 1.0, H_2O); R_f (3:1 MeCN−H_2O) 0.55; IR (KBr) ν_{max} 3380, 2910, 1650, 1543 cm^{-1}; ^1H NMR (500 MHz, D_2O) (see also Table 3, Supporting Information) δ 3.26 (s, 3 H, OMe); ^{13}C NMR (125.7 MHz, D_2O) δ 157.9, 99.1, 87.1, 75.2, 74.7, 73.0, 71.6, 71.4, 71.3, 70.3, 65.1, 57.0, 54.8, 41.4; FABMS *m*/*z* 381 (40, $[M + Na]^+$). Anal. Calcd

for $C_{14}H_{24}N_2O_{10}$: C, 42.21; H, 6.36; N, 7.36. Found: C, 42.20; H, 6.16; N, 7.37.

5-Benzyloxycarbonylamino-5-deoxy-1,2-*O*-isopropylidene-*β*-L-idofuranose (33). A solution of 5-amino-5-deoxy-1,2-*O*-isopropylidene-*β*-L-idofuranose **7** (222 mg, 1.02 mmol) in H_2O (3.46 mL) was adjusted to pH 8 by addition of solid Na_2CO_3 at 0 °C, and benzyl chloroformate (0.22 mL, 1.53 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. The mixture was extracted with EtOAc, and the organic phase was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography (20:1 CH_2Cl_2−MeOH) to give **33** (306 mg 85%) as an amorphous solid: $[\alpha]_D$ −25.5 (*c* 1.0, CH_2Cl_2) [lit.[31] −24 (*c* 0.45, MeOH); lit.[45] −24.5 (*c* 0.5, $CHCl_3$)]; R_f (20:1 CH_2Cl_2−MeOH) 0.20; IR (KBr) ν_{max} 3418, 1699, 1645, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (see also Table 3, Supporting Information) δ 7.47−7.26 (m, 5 H, Ph), 5.35 (sa, 1 H, NH), 5.13 (d, 2 H, $^2J_{H,H}$ = 12.3 Hz, CH_2), 2.17 (sa, 1 H, CH), 1.49, 1.31 (2 s, each 3 H, Me_2C); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 154.0, 135.9−128.0, 111.7, 104.5, 85.1, 80.1, 75.1, 63.3, 51.8, 26.7, 26.0; FABMS *m*/*z* 376 (100, $[M + Na]^+$). Anal. Calcd for $C_{17}H_{23}O_7N$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.91; H, 6.37; N, 3.76.

(1*S*,2*R*,3*S*,4*R*,5*R*)-*N*-(Benzyloxycarbonyl)-2,3,4-trihydroxy-6-oxa-*nor*-tropane (34). A solution of **33** (300 mg, 1 mmol) was treated with 90% TFA−H_2O and worked up as described above for the preparation of **24**−**32**. The residue was purified by column chromatography using 20:1 → 9:1 CH_2Cl_2−MeOH as the eluent to give **34** (180 mg, 80%) as a white foam after the freeze-drying of an aqueous solution: $[\alpha]_D$ +41.3 (*c* 1.0, H_2O); R_f (9:1 CH_2Cl_2−MeOH) 0.39; IR (KBr) ν_{max} 3389, 2963, 1699, 1514 cm^{-1}; ^1H NMR (300 MHz, D_2O, 313 K) (see also Table 3, Supporting Information) δ 7.47−7.26 (m, 5 H, Ph), 5.47 (s, 2 H, CH_2); ^{13}C NMR (125.7 MHz, D_2O, 313 K) δ 152.9, 134.2, 127.3, 127.2, 126.4, 84.7, 73.6, 73.0, 69.8, 64.4, 54.8; FABMS *m*/*z* 296 (100, $[M + H]^+$). Anal. Calcd for $C_{14}H_{17}O_6N$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.79; H, 5.80; N, 4.64.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-6-oxa-*nor*-tropane (35). A solution of **34** (150 mg, 0.5 mmol) in 2:1 EtOAc−MeOH (30 mL) was hydrogenated at atmospheric pressure for 10 min using 10% Pd/C (90 mg) as a catalyst.[46] The suspension was filtered through Celite and concentrated, and the residue was purified by GPC (Sephadex G-10, 1:1 MeOH−H_2O) to afford **35** (48 mg, 60%) as a white foam after the freeze-drying of an aqueous solution: $[\alpha]_D$ +103.8 (*c* 1.0, H_2O) [lit.[30a] $[\alpha]_D$ +114.5 (*c* 1.0, H_2O)]; R_f (6:3:1 MeCN−H_2O−NH_4OH) 0.48; IR (KBr) ν_{max} 3434, 3324, 2980, 1603 cm^{-1}; ^1H NMR (500 MHz, D_2O, 313 K) (see also Table 3, Supporting Information); ^{13}C NMR (75.5 MHz, D_2O) δ 87.9, 73.6, 73.1, 70.1, 63.3, 56.0; FABMS *m*/*z* 162 (100, $[M + H]^+$). Anal. Calcd for $C_6H_{11}O_4N$: C, 44.72; H, 6.88; N, 8.69. Found: C, 44.60; H, 6.73; N, 8.48.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-isothiocyanato-α- and -*β*-D-Xylofuranose (38). To a solution of 1,2,3 tri-*O*-acetyl-5-azido-5-deoxy-α- and *β*-D-xylofuranose **37** (400 mg, 1.33 mmol) in dry dioxane (15 mL) were added CS_2 (1.48 mL, 15 equiv) and TPP (383 mg, 1.46 mmol) under Ar. The mixture was stirred for 48 h at room temperature, concentrated, and chromatographed (1:3 → 1:1 EtOAc−petroleum ether) to give **38** (400 mg, 95%) as an amorphous solid: R_f (1:1 EtOAc−petroleum ether) 0.60; IR (KBr) ν_{max} 2960, 2104, 1755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (see also Table 4, Supporting Information) δ 2.14−2.05 (6 s, Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.1−169.1, 98.8, 92.8, 79.8, 79.4, 75.4, 75.3, 73.9, 49.5, 44.5, 44.4, 21.2−20.4; FABMS *m*/*z* 340 (100, $[M + H]^+$). Anal. Calcd for $C_{12}H_{15}O_7NS$: C, 45.42; H, 4.76; N, 4.41. Found: C, 45.21; H, 4.62; N, 4.34.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-(3-methylthioureido)-α- and -*β*-D-Xylofuranose (39). A solution of methylamine hydrochloride (119 mg, 1.76 mmol) in water (3 mL) was adjusted to pH 8 by addition of saturated aqueous $NaHCO_3$. Isothiocyanate **38** (140 mg, 0.44 mmol) in acetone (6 mL) was then added, and the reaction mixture was stirred for 3 h. Acetone was removed under reduced pressure, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phase was dried ($MgSO_4$) and concentrated, and the resulting residue was chromatographed (1:2 → 1:1 EtOAc−petroleum ether) to give **39** (114 mg, 75%) as an amorphous solid: R_f (1:1 EtOAc−petroleum ether) 0.31; UV (CH_2Cl_2) 250 nm (ϵ_{mM} 19.1); IR (KBr) ν_{max} 3383, 2928, 1750, 1651, 1543 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 313 K) (see also Table 4, Supporting Information) δ 6.25 (bs, $J_{N'H,Me}$ = 4.6 Hz, $N'H_{\alpha-anomer}$), 6.11 (d, $J_{N'H,Me}$ = 4.5 Hz, $N'H_{\beta-anomer}$), 6.03 (bt, $NH_{\alpha-anomer}$), 5.98 (bt, $NH_{\beta-anomer}$), 2.98 (d, *Me*NH), 2.17−2.07 (Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 183.5, 170.3−169.3, 98.9, 92.9, 80.9, 80.1, 77.0, 76.2, 74.8, 44.6, 44.0, 30.5, 20.7−20.2; FABMS *m*/*z* 371 (100, $[M + Na]^+$). Anal. Calcd for $C_{13}H_{19}O_7N_2S$: C, 44.95; H, 5.51; N, 8.06. Found: C, 44.91; H, 5.43; N, 7.91.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-(3-phenylthioureido)-α- and -*β*-D-Xylofuranose (40). A solution of aniline (51 μL, 0.5 mmol) and isothiocyanate **38** (180 mg, 0.5 mmol) in pyridine (4 mL) was stirred for 24 h at room temperature. The solvent was removed and the residue purified by column chromatography (1:3 → 1:1 EtOAc−petroleum ether) to afford **40** (220 mg, 95%) as an amorphous solid: R_f (1:1 EtOAc−petroleum ether) 0.54; UV (CH_2Cl_2) 264 nm (ϵ_{mM} 15.6); IR (KBr) ν_{max} 3335, 3109, 2963, 1748, 1667, 1530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 313 K) (see also Table 4, Supporting Information) δ 7.90 (s, N'H), 7.30−7.18 (Ph), 6.35 (bt, 1 H, $J_{NH,H5\alpha}$ = 6.0 Hz, $NH_{\alpha-anomer}$), 6.26 (bt, 1 H, $J_{NH,H5\beta}$ = 9.0 Hz, $NH_{\beta-anomer}$), 2.08−1.99 (Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.8, 170.2−169.1, 135.4, 130.2, 127.4, 125.0, 98.7, 92.6, 79.9, 79.7, 76.1, 75.9, 74.5, 74.4, 45.0, 44.2, 20.9−20.2; FABMS *m*/*z* 433 (100, $[M + Na]^+$). Anal. Calcd for $C_{18}H_{22}O_7N_2S$: C, 52.67; H, 5.40; N, 6.83. Found: C, 52.93; H, 5.35; N, 6.69.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-[3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)thioureido]-α- and -*β*-D-Xylofuranose (41). A solution of 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylamine (314 mg, 0.9 mmol) and isothiocyanate **38** (285 mg, 0.9 mmol) in pyridine (6 mL) was stirred for 48 h at room temperature. The solvent was removed and the residue purified by column chromatography (1:1 EtOAc−petroleum ether) to yield **41** (418 mg, 70%) as an amorphous solid: R_f (2:1 EtOAc−petroleum ether) 0.54; UV (CH_2Cl_2) 254 nm (ϵ_{mM} 10.3); IR (KBr) ν_{max} 3362, 2958, 1750, 1651, 1541 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 318 K) (see also Table 4, Supporting Information) δ 6.76 (d, $J_{N'H,1'}$ = 9.0 Hz, $N'H_{\alpha-anomer}$), 6.70 (d, $J_{N'H,1'}$ = 9.0 Hz, $N'H_{\beta-anomer}$), 6.64 (m, $NH_{\alpha-anomer}$), 6.60 (dd, $J_{NH,5a}$ = 6.0 Hz, $J_{NH,5b}$ = 4.6 Hz, $NH_{\beta-anomer}$), 2.11−1.99 (Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 183.8, 171.0−169.1, 98.9, 92.9, 82.6, 80.3, 79.9, 77.0, 76.6, 74.6, 73.3, 72.9, 70.8, 68.2, 61.7, 43.9, 20.9−20.2; FABMS *m*/*z* 687 (100, $[M + Na]^+$). Anal. Calcd for $C_{26}H_{36}O_{16}N_2S$: C, 46.98; H, 5.46; N, 4.22. Found: C, 47.03; H, 5.49; N, 4.02.

General Procedure for the Preparation of 5-Carbodiimido-5-deoxy-D-xylofuranoses (42−44). Aza-Wittig-type coupling between azide **37** and the corresponding methyl, phenyl, or glucopyranosyl isothiocyanate **8**, following the procedure described above for the synthesis of **18**−**20**, and purification as indicated in each case afforded the D-xylofuranose thioureas **42**−**44**, respectively, as inseparable mixtures of the α- and *β*-anomers.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-(3-methylcarbodiimido)-α- and -*β*-D-Xylofuranose (42): column chromatography, eluent 1:2 → 3:1 EtOAc−petroleum ether; yield 103 mg (45%); R_f (1:1 EtOAc−petroleum ether) 0.53; IR (KBr) ν_{max} 2980, 2930, 2139, 1748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (see also Table 4, Supporting Information) δ 2.96, 2.94 (2 s, MeN), 2.14, 2.13, 2.12, 2.11, 2.09, 2.08 (6 s, Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.1−168.8, 140.1, 98.7, 92.7, 80.9, 80.0, 76.8, 75.5, 74.2, 73.9, 46.0, 45.5, 32.4, 21.0−20.3; CIMS *m*/*z* 315 (15, $[M + H]^+$). Anal. Calcd for $C_{13}H_{18}O_7N_2$: C, 49.72; H, 5.78; N, 8.92. Found: C, 49.47; H, 5.97; N, 8.66.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-(3-phenylcarbodiimido)-α- and -*β*-D-Xylofuranose (43): column chromatography,

(45) Kayakiri, H.; Oku, T.; Hashimoto, M. *Chem. Pharm. Bull.* **1991**, *39*, 1397.

(46) Longer hydrogenation reaction times resulted in the formation of 1-deoxy-L-idonojirimycin (cf. ref 31) as a side product.

eluent toluene → 1:5 EtOAc−toluene; yield 245 mg (87%); R_f (1:5 EtOAc−toluene) 0.39; IR (KBr) ν_{max} 3055, 2930, 2135, 1751, 1589 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (see also Table 4, Supporting Information) δ 7.28−7.07 (Ph), 2.10−2.01 (Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.1−169.1, 139.3, 137.1, 129.3, 125.0, 123.8, 98.8, 92.8, 80.6, 80.1, 76.7, 75.6, 74.6, 74.3, 46.4, 45.9, 21.0−20.4; FABMS *m/z* 399 (100, [M + Na]$^+$). Anal. Calcd for $C_{18}H_{20}O_7N_2$: C, 57.44; H, 5.36; N, 7.44. Found: C, 57.02; H, 5.14; N, 7.61.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-[3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)carbodiimido]-α- and -*β*-D-Xylofuranose (44): column chromatography, eluents toluene and then 1:3 → 1:1 EtOAc−petroleum ether; yield 387 mg (82%); R_f (1:1 EtOAc−petroleum ether) 0.57; IR (KBr) ν_{max} 2945, 2145, 1748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (see also Table 4, Supporting Information) δ 2.15−2.00 (Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.6−169.1, 138.3, 138.0, 98.7, 92.8, 84.6, 84.5, 80.4, 80.1, 76.3, 75.7, 74.3, 74.1, 73.7, 72.9, 72.7, 68.1, 61.8, 45.9, 45.3, 21.0−20.3; FABMS *m/z* 653 (100, [M + Na]$^+$). Anal. Calcd for $C_{26}H_{34}O_{16}N_2$: C, 49.52; H, 5.43; N, 4.44. Found: C, 49.31; H, 5.36; N, 4.35.

General Procedure for the Preparation of 5-Deoxy-5-ureido-D-xylofuranoses (45−47). To a solution of the corresponding carbodiimide **42**−**44** (0.79 mmol) in 2:1 acetone−water (15 mL) was added TFA (0.05 mL), and the reaction mixture was stirred at room temperature for 2.5−5 h (TLC). After evaporation of the solvents, the residue was purified by column chromatography eluting first with toluene and then with the eluent indicated in each case to give the respective urea **45**−**47** as an amorphous solid.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-(3-methylureido)-α- and -*β*-D-Xylofuranose (45): column chromatography, eluent 3:1 → 4:1 EtOAc−petroleum ether; yield 158 mg (60%); R_f (9:1 CH_2Cl_2−MeOH) 0.39; IR (KBr) ν_{max} 2938, 1748, 1645, 1566 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (see also Table 4, Supporting Information) δ 5.07−4.95 (NH), 2.70 (d, $J_{Me,N'H}$ = 5.3 Hz, MeN), 2.09−2.03 (Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.0−168.9, 158.8, 98.9, 92.8, 81.4, 80.3, 77.6, 76.1, 74.6, 74.4, 40.2, 39.4, 26.8, 20.7−20.0; CIMS *m/z* 333 (55, [M + H]$^+$). Anal. Calcd for $C_{13}H_{20}O_8N_2$: C, 46.948; H, 6.07; N, 8.43. Found: C, 47.13; H, 6.19; N, 8.51.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-(3-phenylureido)-α- and -*β*-D-Xylofuranose (46): column chromatography, eluent 1:1 EtOAc−petroleum ether; yield 289 mg (93%); R_f (1:1 EtOAc−petroleum ether) 0.29; IR (KBr) ν_{max} 3339, 3054, 2992, 1750, 1657, 1553 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (see also Table 4, Supporting Information) δ 7.29−7.06 (m, Ph, N′H), 5.33 (m, NH), 2.08−2.04 (Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.2−169.1, 154.6, 139.1, 129.4, 128.9, 128.8, 98.8, 92.9, 80.0, 79.9, 76.8, 75.8, 74.5, 74.3, 40.0, 39.3, 21.0−20.3; FABMS *m/z* 417 (100 [M + Na]$^+$). Anal. Calcd for $C_{18}H_{22}O_8N_2$: C, 54.82; H, 5.63; N, 7.10. Found: C, 54.50; H, 5.28; N, 6.89. Samples of the pure anomers could be obtained in this case by preparative TLC with the above eluent: α-anomer $[\alpha]_D$ +78.0 (*c* 1.0, CH_2Cl_2); *β*-anomer $[\alpha]_D$ +6.0 (*c* 1.0, CH_2Cl_2).

1,2,3-Tri-*O*-acetyl-5-deoxy-5-[3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)ureido]-α and -*β*-D-Xylofuranose (47): column chromatography, eluent 4:1 CCl_4−acetone; yield 480 mg (95%); R_f (2:1 CCl_4−acetone) 0.42; IR (KBr) ν_{max} 3370, 2944, 1750, 1666, 1555 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (see also Table 4, Supporting Information) δ 5.51 (d, $J_{N'H,1'}$ = 9.5 Hz, $N'H_{\alpha-anomer}$), 5.45 (d, $J_{N'H,1'}$ = 9.5 Hz, $N'H_{\beta-anomer}$), 5.13 (dd, $J_{NH,5b}$ = 6.7 Hz, $J_{NH,5a}$ = 6.3 Hz, $NH_{\alpha-anomer}$), 5.12 (dd, $J_{NH,5a}$ = 7.2 Hz, $J_{NH,5b}$ = 4.6 Hz, $NH_{\beta-anomer}$), 2.13−1.99 (Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.1−169.3, 156.1, 98.9, 92.8, 81.1, 80.2, 77.0, 76.6, 74.6, 74.5, 73.2, 73.1, 72.9, 70.6, 68.9, 68.2, 61.7, 61.5, 40.1, 39.4, 21.1−20.4; FABMS *m/z* 671 (100, [M + Na]$^+$). Anal. Calcd for $C_{26}H_{36}O_{17}N_2$: C, 48.15; H, 5.59; N, 4.32. Found: C, 48.15; H, 5.41; N, 4.25.

General Procedure for the Preparation of Xylonojirimycin-Type Piperidines (48−53). Conventional NaOMe-catalyzed deacetylation of (thio)ureas **39**−**41** and **45**−**47** (0.5 mmol) in MeOH and purification of the reaction product as indicated in each case afforded the corresponding *N*-thiocarbamoyl-2-methoxy (**48**−**50**) and 2-hydroxypiperidines **51**−**53**, respectively, as white foams after the freeze-drying of aqueous solutions.

(2*R*,3*R*,4*S*,5*R*)-3,4,5-Trihydroxy-2-methoxy-*N*-(*N*′-methylthiocarbamoyl)piperidine (48): column chromatography, eluents EtOAc and then 20:1 → 15:1 EtOAc−EtOH; yield 86 mg (73%); $[\alpha]_D$ +61.1 (*c* 1.0, H_2O); R_f (45:5:3 EtOAc−EtOH−H_2O) 0.30; UV (MeOH) 246 nm (ϵ_{mM} 16.9); ^{1}H NMR (300 MHz, D_2O, 313 K) (see also Table 5, Supporting Information) δ 3.07 (s, 3 H, NMe), 3.31 (s, 3 H, OMe); ^{13}C NMR (75.5 MHz, D_2O, 313 K) δ 184.6, 90.5, 76.2, 73.4, 71.3, 57.5, 46.8, 34.7; FABMS *m/z* 237 (30 [M + H]$^+$). Anal. Calcd for $C_8H_{16}O_4N_2S$: C, 40.66; H, 6.83; N, 11.86. Found: C, 40.43; H, 6.71; N, 11.53.

(2*R*,3*R*,4*S*,5*R*)-3,4,5-Trihydroxy-2-methoxy-*N*-(*N*′-phenylthiocarbamoyl)piperidine (49): column chromatography, eluent EtOAc → 20:1 EtOAc−EtOH; yield 80 mg (54%); $[\alpha]_D$ +54.0 (*c* 1.0, MeOH); R_f (45:5:3 EtOAc−EtOH−H_2O) 0.47; UV (MeOH) 250 nm (ϵ_{mM} 18.9); ^{1}H NMR (500 MHz, D_2O, 313 K) (see also Table 5, Supporting Information) δ 7.50−7.30 (m, 5 H, Ph), 3.45 (s, 3 H, OMe); ^{13}C NMR (125.7 MHz, D_2O, 313 K) δ 183.7, 139.5, 129.4, 127.3, 126.9, 88.8, 74.0, 70.8, 69.2, 55.7, 47.9; FABMS *m/z* 299 (60, [M + H]$^+$). Anal. Calcd for $C_{13}H_{18}O_4N_3S$: C, 52.33; H, 6.08; N, 9.39. Found: C, 52.32; H, 5.98; N, 9.14.

(2*R*,3*R*,4*S*,5*R*)-*N*-(*N*′-*β*-D-Glucopyranosylthiocarbamoyl)-3,4,5-trihydroxy-2-methoxypiperidine (50): column chromatography, eluent 3:1 MeCN−H_2O; yield 169 mg (88%); $[\alpha]_D$ +27.5 (*c* 1.0, H_2O); R_f (6:3:1 MeCN−H_2O−NH_4OH) 0.41; UV (MeOH) 254 nm (ϵ_{mM} 13.9); ^{1}H NMR (500 MHz, D_2O, 313 K) (see also Table 5, Supporting Information) δ 3.25 (s, 3 H, OMe); ^{13}C NMR (125.7 MHz, D_2O, 313 K) δ 184.5, 88.8, 85.1, 77.6, 76.7, 73.9, 71.8, 70.5, 69.4, 68.7, 60.7, 55.6, 44.9; FABMS *m/z* 407 (40, [M + Na]$^+$). Anal. Calcd for $C_{13}H_{24}O_9N_2S$: C, 40.62; H, 6.29; N, 7.28. Found: C, 40.55; H, 6.41; N, 7.28.

(2*R*,3*R*,4*S*,5*R*)-2,3,4,5-Tetrahydroxy-*N*-(*N*′-methylcarbamoyl)piperidine (51): column chromatography, eluent EtOAc → 20:1 EtOAc−EtOH; yield 72 mg (70%); $[\alpha]_D$ −2.0 (*c* 1.0, H_2O); R_f (4:1 CH_2Cl_2−MeOH) 0.29; ^{1}H NMR (500 MHz, D_2O) (see also Table 5, Supporting Information) δ 3.13 (s, 3 H, MeN); ^{13}C NMR (125.5 MHz, D_2O) δ 159.2, 77.2, 73.8, 72.1, 69.9, 42.9, 26.5; FABMS *m/z* 229 (100, [M + Na]$^+$). Anal. Calcd for $C_7H_{13}O_5N_2$: C, 40.97; H, 6.39; N, 13.65. Found: C, 40.84; H, 6.25; N, 13.41.

(2*R*,3*R*,4*S*,5*R*)-2,3,4,5-Tetrahydroxy-*N*-(*N*′-phenylcarbamoyl)piperidine (52): column chromatography, eluent 45:5:3 EtOAc−EtOH−H_2O; yield 87 mg (65%); $[\alpha]_D$ −6.0 (*c* 0.5, MeOH); R_f (45:5:3 EtOAc−EtOH−H_2O) 0.36; ^{1}H NMR (500 MHz, D_2O) (see also Table 5, Supporting Information) δ 7.47−7.31 (m, 5 H, Ph); ^{13}C NMR (75.5 MHz, D_2O, 313 K) (see also Table 2) δ 157.8, 138.1, 129.5, 125.2, 123.3, 77.2, 73.7, 71.9, 69.8, 43.1; FABMS *m/z* 269 (55, [M + H]$^+$). Anal. Calcd for $C_{12}H_{16}O_5N_2$: C, 57.73; H, 6.01; N, 10.44. Found: C, 57.84; H, 5.78; N, 10.47.

(2*R*,3*R*,4*S*,5*R*)-*N*-(*N*′-*β*-D-Glucopyranosylcarbamoyl)-2,3,4,5-tetrahydroxypiperidine (53): column chromatography, eluent 6:1 → 4:1 MeCN−H_2O; yield 106 mg (60%); $[\alpha]_D$ +6.0 (*c* 1.0, CH_2Cl_2); R_f (6:3:1 MeCN−H_2O−NH_4OH) 0.26; ^{1}H NMR (500 MHz, D_2O) (see also Table 5, Supporting Information); ^{13}C NMR (125.7 MHz, D_2O) δ 158.1, 81.6, 77.3, 76.7, 76.6, 73.3, 71.6, 71.5, 69.4, 69.3, 60.6, 42.4; FABMS *m/z* 377 (25, [M + Na]$^+$). Anal. Calcd for $C_{12}H_{22}O_{10}N_2$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.63; H, 6.43; N, 7.71.

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Supporting Information Available: Tables 2−9 containing ^{1}H and ^{13}C NMR data for all new compounds and the experimental details for the preparation of the per-O-protected sugar azides **16** and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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