Straightforward Synthesis of (1→2)-Linked Pseudo Aza-*C*-disaccharides by the Novel Cycloaddition of Enantiopure Cyclic Nitrones to Glycals

Francesca Cardona,† Silvia Valenza,† Sylviane Picasso,‡ Andrea Goti,*,† and Alberto Brandi*,†

Dipartimento di Chimica Organica "Ugo Schiff", Centro di Studio C.N.R. sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Università di Firenze, via G. Capponi 9, I-50121, Firenze, Italy, and Institut de Chimie Organique de l'Université de Lausanne, BCH, CG-1015 Lausanne-Dorigny, Switzerland

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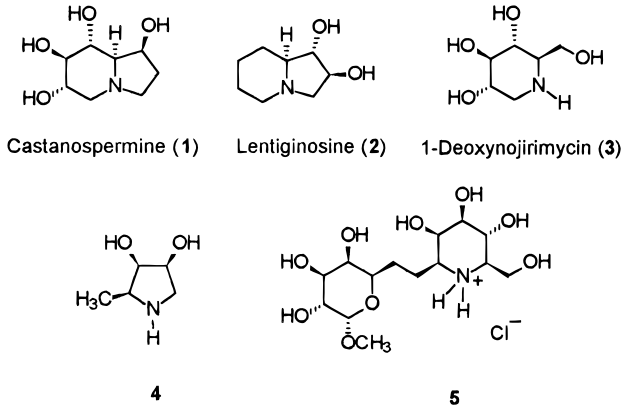
The novel, highly stereoselective, intermolecular cycloaddition reaction of enantiopure cyclic nitrones **8** to 1,2-glycals **9** opens the way to a straightforward synthesis of a broad class of new (1→2)-linked pseudo aza-*C*-disaccharides **6**, suitable substrates for selective inhibition of glycosidase enzymes. The cycloadditions occur with high stereocontrol, displaying preferential interaction between the *bottom* face of the glycal and the face of the nitrone *anti* to the substituent on C-3, with the reagents approaching in an *exo* fashion. The cycloadditions produced tricyclic isoxazolidines **7** that represent nonreducing pseudo aza-*C*-disaccharides stable to hydrolytic conditions. The target pseudo aza-disaccharides **6** were obtained by sequential deprotection of the hydroxyl groups and isoxazolidine ring-opening.

Introduction

The great interest mounted in recent years toward glycosidase inhibitors is related to the key role carried out by some glycosidases in the biosynthesis and processing of glycoproteins, membrane-conjugated proteins responsible for several cell−cell interactions and cellular recognition processes (viral infections, bacteria cell-adhesion, neoplastic cell growth, migration of lymphocytes, etc.).[1] In this connection, glycosidase inhibitors are regarded as potential antiviral, antibacterial, antitumor, and immunostimulatory agents.[2,3]

Several polyhydroxylated indolizidines (e.g. castanospermine **1**, lentiginosine **2**, Chart 1) and monocyclic piperidine and pyrrolidine azasugars (e.g. deoxynojirimycin **3**, 3,4-dihydroxy-2-methylpyrrolidine **4**, Chart 1) have shown a remarkable inhibition activity toward glycosidases,[3b,4,5] likely related to their structural resemblance with the natural enzymes' substrates. It is thought indeed that the heterocyclic nitrogen, which is protonated at physiological pH, can mimic the positive charge developed in the high-energy intermediate occurring in the glycosidic hydrolysis process.[5b,c]

Chart 1



Many glycosidases display an aglycon specificity, in that they selectively recognize substrates having the same terminal glycosyl moiety and differing only in the aglycon (or oligosaccharide) portion and glycosidic linkage. It has been suggested therefore that the design and synthesis of inhibitors embodying both the information of the glycosyl moiety, which is released in the hydrolysis process, and of the aglycon (or saccharide moiety) attached to it, might sensibly improve the selectivity of inhibitors toward glycosidases.[5b,c,6−10] In this context, azasugars linked to common monosaccharides by a nonhydrolyzable C−C link (aza-*C*-disaccharides) are promising substrates as new selective glycosidase inhibitors and have become attractive synthetic targets.

The first synthesis of an aza-*C*-disaccharide, 1,5-dideoxy-1,5-imino-D-mannitol linked to C(6) of D-galactose through a CH_2 unit (D-azaMan-*C*-β-(1→6)-D-Gal (**5**)), has

† Dipartimento di Chimica Organica "Ugo Schiff", Centro dei Composti Eterociclici-C. N. R., Università di Firenze.

‡ Institut de Chimie Organique de l'Université de Lausanne.

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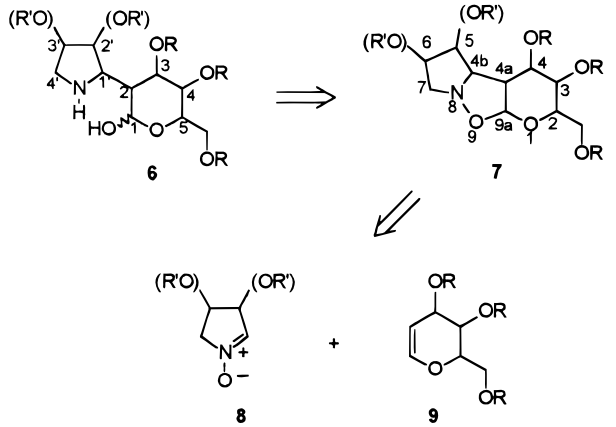
Scheme 1



been recently performed by Johnson and co-workers.[6] Shortly after, other examples have been reported: a (1→6)-*C*-linked azadisaccharide precursor was synthesized by Martin et al.;[7] some (1→3)-*C*-linked azadisaccharides in which the azasugar is linked to the sugar through a methylene or a hydroxymethylene bridge were reported by Vogel.[8] Syntheses of pseudo azadisaccharides containing heteroatoms in the linkage between the two units have been previously performed.[5b,c,9] Finally, Johnson and co-workers have reported the syntheses and enzymatic evaluations of (1→1)-, (1→4)- and (1→6)-*C*-linked azadisaccharides where a six-membered azasugar (aza-mannose) is linked to a pyranose sugar (glucose, talose, or mannose) through a methylene or ethylene unit.[10] Among these, D-azaMan-*C*-*β*-(1→6)-D-Glc **5** has shown to be a good selective glucoamylase inhibitor (IC_{50} = 12 μM).

We report in this paper a novel approach to the synthesis of new (1→2)-linked pseudo azadisaccharides **6** by 1,3-dipolar cycloaddition of enantiopure polyhydroxylated pyrroline *N*-oxides **8** to 1,2-glycals **9** (Scheme 1).[11] The pseudo aza-*C*-disaccharide **6** can be obtained by simple reductive ring-opening of the tricyclic isoxazolidine **7** with an N−O bond cleavage.

The simple and straightforward approach to the synthesis of pseudo azadisaccharides reported here is based on the unprecedented intermolecular 1,3-dipolar cycloaddition reactions of nitrones to glycals. Glycals are indeed widely and increasingly used in organic synthesis as building blocks for oligosaccharides and glycoconjugates assembly,[12] but their use in cycloaddition reactions is limited to a few enophile systems in [2 + 2] or hetero-Diels−Alder cycloadditions.[13] Cycloadditions of glycals with sulfonyl and acetyl isocyanates afford *β*-lactams and [4 + 2] adducts, the mixture composition and reaction rate depending on the glycal and the isocyanate structures and the reaction conditions employed.[14] An inverse electron demand Bradsher cycloaddition[15] of an isoquinolinium salt to L-fucal has been used by Franck and Gupta for the total synthesis of (−)-cryptosporin.[16] The UV light promoted [4 + 2] cycloaddition of dibenzyl azodicarboxylate to glycals to form oxadiazenes was reported.[17] More recently, acetamidodeoxy disaccharides were prepared via a thermal hetero-Diels−Alder reaction of *O*-silyl protected lactal and bis(2,2,2-trichloroethyl)azodicarboxylate.[18] Finally, several examples of hetero-Diels−Alder cycloadditions of glycals to α-oxothiones were also reported recently.[19]

1,3-Dipolar cycloaddition chemistry employing glycals is almost completely unexplored, as only a single example of high-pressure cycloaddition to mesitonitrile oxide[20] and an intramolecular cycloaddition of a single nitrone and a nitrile oxide en route to the synthesis of chiral tetrahydrofurans have been reported.[21] Examples of intermolecular 1,3-dipolar cycloadditions of pyrroline *N*-oxide to dihydropyran and dihydrofuran and of tetrahydropyridine *N*-oxide to dihydropyran, affording poor yields of adducts, were also reported.[22]

The process described in this paper allows the synthesis of a wide series of new (1→2)-linked pseudo aza-*C*-disaccharides containing "azasugars" of the pyrrolidine type: the desired configuration at the stereogenic centers is ensured by the choice of the appropriate partners in the cycloaddition step.

Results and Discussion

A systematic study of the cycloaddition reaction of acetyl and benzyl protected glucals **10** and **11** and galactals **12** and **13** (Chart 2) to six different nitrones **14**−**19** has been performed. The results are reported in Table 1. High temperature (100 °C), toluene as solvent, and an excess of glycal were necessary to accomplish complete conversions of nitrones; the unreacted glycal can be recovered on purification of the crude reaction mixtures on silica gel. Nitrone **14** (entry 1, Table 1),

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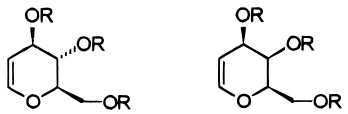
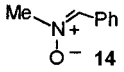
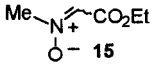
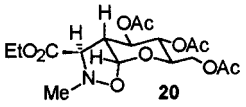
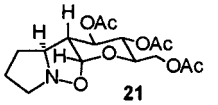
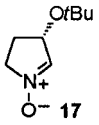
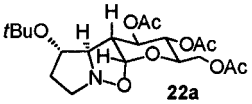
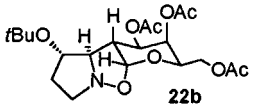
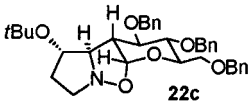
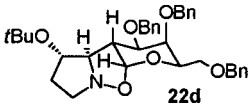
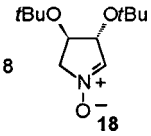
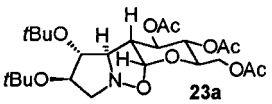
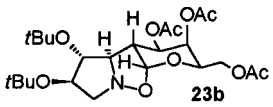
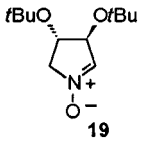
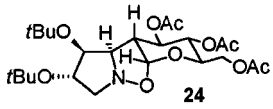
Chart 2



Glucals
10 R=Ac
11 R=Bn

Galactals
12 R=Ac
13 R=Bn

Table 1. Cycloadditions of Nitrones 14−19 to Glycals 10−13[a]

Entry	Nitrone	Glycal	Adduct	Reaction time	Yield (%)
1	 **14**	**10**	n.r.[b]	13 d	n.r.
2	 **15**	**10**	 **20**	2 d	36
3	 **16**	**10**	 **21**	40 min[c]	12
4	 **17**	**10**	 **22a**	4 d	68
5	**17**	**12**	 **22b**	7 d	42
6	**17**	**11**	 **22c**	9 d	35
7	**17**	**13**	 **22d**	7 d	27
8	 **18**	**10**	 **23a**	3 d	61
9	**18**	**12**	 **23b**	3 d	28
10	 **19**	**10**	 **24**	11 d	33

[a] Reactions conditions: 3 equiv of glycals, toluene, 100 °C. [b] n. r. = no reaction. [c] 1.5 equiv of nitrone **16**, mesitylene, 152 °C.

commonly used as a model nitrone in 1,3-dipolar cycloaddition reactions, was absolutely unreactive under these conditions. The more reactive glyoxylate nitrone **15** and pyrroline *N*-oxide (**16**) gave the corresponding cycloadducts **20** and **21** in modest yield (entries 2 and 3, Table 1), revealing the low reactivity of the glucal. The high temperature required for the reaction to occur is incompatible with nitrone stability, causing its partial decomposition. With nitrone **16**, due to its especially high lability, the best results were obtained by using an excess of nitrone, slowly added to a refluxing solution of glycal **10** in mesitylene (entry 3, Table 1). Polyhydroxylated nitrones **17**[23] and **18**[24,4b] were reactive and stable enough under the reaction conditions to afford good yields of cycloadducts **22a** and **23a** (entries 4 and 8, Table 1) with triacetyl glucal **10**. The galactal **12** afforded with the same nitrones the analogous adducts **22b** and **23b** (entries 5 and 9, Table 1), but in considerably lower yields. These results cannot be rationalized, but benzyl glycals **11** and **13** gave also lower yields of cycloadducts **22c** and **22d** (entries 6 and 7, Table 1), compared to their acetyl counterparts, probably because of the increased steric hindrance, which renders these glycals less reactive. Yield lowering as a result of a cycloreversion process could be ruled out since neither trace of the nitrone, nor of the glycal, or of the cycloadducts to butenol was detected on heating the cycloadducts to 100 °C in the presence of 3-butenol.[4c,23] A similarly moderate yield of adduct **24** was obtained in the cycloaddition of glucal **10** with the dihydroxylated nitrone **19** having the opposite absolute stereochemistry as compared with **18**.

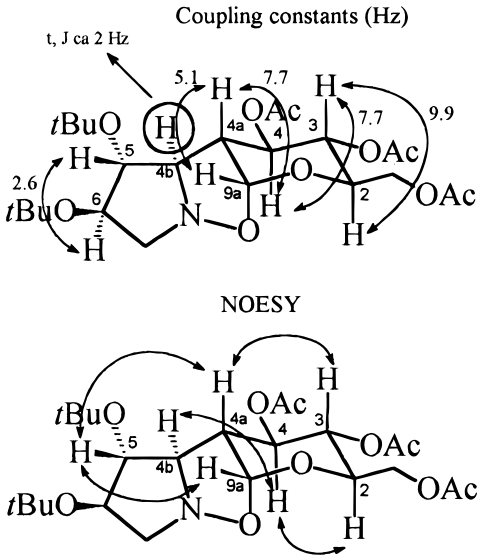


Figure 1. Coupling constants and 2D NOESY correlation peaks for cycloadduct **23a**.

The cycloadditions are completely regio- and stereoselective in most cases. Only a single product was isolated in each case. Traces of minor products (less than 5%) were detected, however, in the crude reaction mixture of the cycloaddition of nitrone **16** to glucal **10** (entry 3, Table 1). Unfortunately, they could not be identified. The low field doublets (δ ~5.5−6.0 ppm) observed for the acetal protons H-9a in the NMR spectra, are consistent with the regiochemistry reported in Scheme 1 for compounds **7**. The assignment of the relative configuration (Table 1) relies on the spectral data, including 2D COSY and NOESY NMR spectra, as exemplified in Figure 1 for compound **23a**. A pseudo triplet with a small coupling constant (J ~2 Hz) was observed for H-4b, indicating

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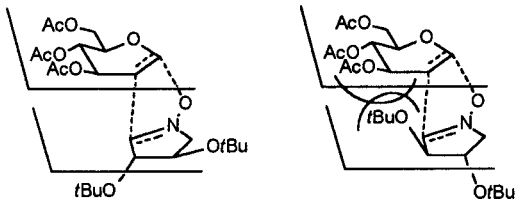


Figure 2. *Bottom-exo* transition states for cycloadditions of nitrones derived from D and L tartaric acids to glucal **10**. **A** = *Anti* approach of nitrone **18** (3*R*,4*R*). **B** = *Syn* approach of nitrone **19** (3*S*,4*S*).

trans relationships with both H-4a and H-5.[25] Three NOESY correlation peaks (between H-4b and H-4, between H-5 and H-4a, and between H-5 and H-9a) confirm this *exo-anti* structure. Accordingly, relatively small ^3J(H-4a, H-4b) and ^3J(H-4b, H-5) coupling constants were observed in all the *exo-anti* isoxazolidines cycloadducts **20**−**23** (J < 3.0 Hz), while the *exo-syn* adduct **24** displayed a higher value (J = 7.5 Hz) for ^3J(H-4b, H-5). These values are consistent with those reported for diastereoisomeric cycloadducts (obtained from similar nitrones with other dipolarophiles), the stereochemistry of which has been confirmed also by X-ray analysis.[26] The structure of the *exo-syn* adduct **24** relies upon the NOESY correlation peaks found between H-4b and H-4, between H-5 and H-4, and between H-6 and H-9a. The large coupling constants (J ∼ 7.5−10 Hz) observed between the axial protons and the presence of correlation peaks from 2D NOESY experiments confirmed the preference for the "chair" conformation of the sugar moiety in all cycloadducts **20**−**24** (entries 2−10, Figure 1).

As reported for other cycloadditions examples on 1,2-glycals,[14a,19b] the pseudoequatorial group on C(3) of the glycal controls the stereoselectivity of the cycloaddition, favoring an approach of the nitrones to the *bottom* face of D-series glycals (Figure 2-A). In turn, nitrones approach *exo* in order to minimize repulsive steric hindrance effects. L-Malic acid derived nitrone **17** and D-tartaric acid derived nitrone **18** therefore give a "matched" interaction with glycals **10**−**13**, because they can approach the glycals' *bottom* face presenting the vicinal *O-tert*-butyl group *anti* in the *exo* orientation.[4b−c,23] Neither *top* nor *endo* cycloadducts were, in fact, observed in any case. Even nitrone **19** (entry 10), enantiomer of **18**, afforded the *bottom-exo* cycloadduct **24**, which derives from a "mismatched" interaction of the nitrone approaching *syn* with respect to the vicinal *O-tert*-butyl group. This disfavored approach probably accounts for the lower reactivity and reaction yield (Figure 2-B).

Triacetyl cycloadducts can readily afford nonreducing pseudo aza-*C*-disaccharides by simple deprotection protocols. Deprotection of the hydroxy groups on the sugar moiety and on the pyrrolidine ring is carried out sequentially and selectively. The reactions sequences and the procedures are the same for the "gluco" and "galacto" series. Treatment of the cycloadducts **21**, **22a**,**b**, **23a**,**b**, and **24** with catalytic amounts of MeONa in anhydrous MeOH for 12 h at rt afforded the trihydroxy tricyclic

Table 2. Deprotection Sequence for Acetylated Adducts 21, 22a,b, 23a,b, 24

Adduct	Deprotection of acetoxy groups[a,b]	Yield (%)	Deprotection of *tert*-butoxy groups[a,c]	Yield (%)
21	**25**	90		
22a	**26a**	95	**29a**	88
22b	**26b**	92	**29b**	74
23a	**27a**	84	**30a**	96
23b	**27b**	78	**30b**	70
24	**28**	70	**31** R=*t*Bu	93
			32 R=H[d]	40

[a] Products **a**: R_1 = H, R_2 = OH; products **b**: R_1 = OH, R_2 = H. [b] Reaction conditions: MeONa (cat.), MeOH, 12 h, rt. [c] Reaction conditions: (1) CF_3COOH, 1.5 h, rt; (2) Amberlyst A26, MeOH, 2 h, rt. [d] Reaction conditions: (1) CF_3COOH, 24 h, rt; (2) Amberlyst A26, MeOH, 2 h, rt.

derivatives **25**−**28** (Table 2) in very good yields (70−95%). Further reaction of partially deprotected products **26**−**28** with TFA, followed by treatment with Amberlyst A26 (OH^- form), afforded the fully deprotected adducts **29** and **30** (70−96%) and **32** (40%). The lower yield observed for compound **32** is attributed to the inertness of 5-*tert*-butoxy group, which, being placed into the highly hindered concave region of the pyrido-isoxazolidine portion of the molecule, is more difficult to be removed and requires a longer reaction time. The selective deprotection of 6-*tert*-butoxy group can be achieved in high yield (compound **31**, 93%) applying the standard procedure. It is interesting to note that the α values increase from fully protected to unprotected systems. For instance, **23b** and **30b** show divergent optical rotation ($[\alpha]_D$ = −24.6 and +29.7, respectively).

The polyhydroxylated tricyclic isoxazolidines **25** and **29**−**32** are stable to acid-catalyzed glycosidic bond hydrolysis, and can be considered nonreducing constrained disaccharides, as they contain all the features of a disaccharide frozen in a stable isoxazolidine ring. Their structures hold promise for glycosidase inhibitor activity; preliminary enzymatic tests against a series of glycosidases have shown that two of them (**25** and **29a**) behave as selective inhibitors of amyloglucosidases.[27]

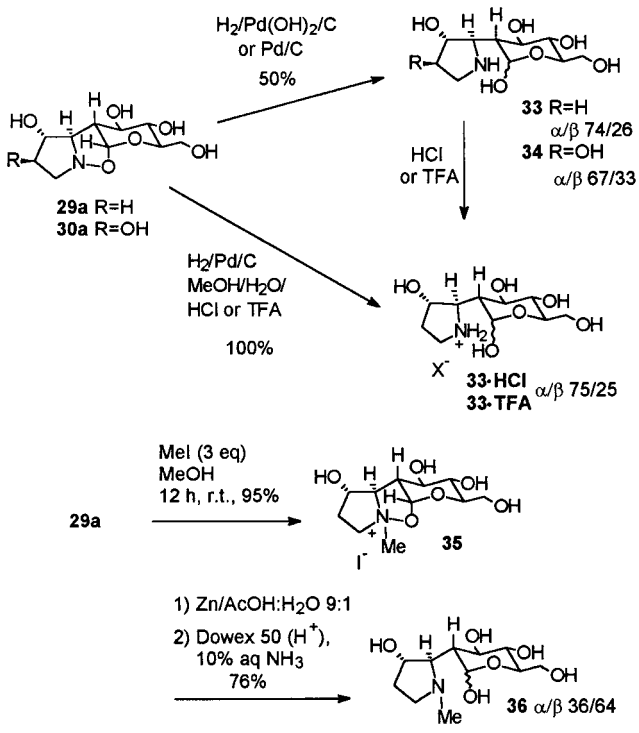
The final reductive ring-opening by cleavage of the N−O bond was achieved by hydrogenation over Pd or $Pd(OH)_2$ and afforded quantitatively the new (1→2)-linked pseudo azadisaccharides **33** and **34** as anomeric

(25) A small coupling constant is always observed in isoxazolidine adducts for bridgehead protons presenting trans relationship with vicinal protons.[4b,c,23]

(26) Pietrusiewicz, K. M.; Wieczorek, W.; Cicchi, S.; Brandi, A. *Phosphorus, Sulfur, Silicon* **1994**, *97*, 233−238.

(27) Activity toward amyloglucosidase from *Aspergillus niger*: 72% inhibition rate, IC_{50} = 250 μM, K_i = 95 μM for **25**; 45% inhibition rate for **29a**. Activity toward amyloglucosidase from *Rhizopus* mold: 53% inhibition rate, IC_{50} = 500 μM, K_i = 435 μM for **25**; 25% inhibition rate for **29a**.

Scheme 2



mixtures (α/β = 74/26 and 67/33 respectively, Scheme 2). These compounds were isolated in yields decreasing down to 50% on purification by silica gel column chromatography.

Unfortunately, these compounds showed limited stability, as indicated by their transformation into complex mixtures when left in water solution at rt for one week. To increase their stability, it was necessary to protect the basic nitrogen atom and to use a different reduction protocol. Ring-opening in the presence of HCl or CF_3-COOH produced the corresponding ammonium salts **33**·HCl and **33**·TFA (α/β = 75/25, Scheme 2), which were more stable. However, their purification could not be achieved and the hydrochloride **33**·HCl turned out to be highly hygroscopic and particularly difficult to handle. We postulated that the high nucleophilicity of the pyrrolidine nitrogen atom might be responsible for the low stability of compounds **33** and **34** which are susceptible to reaction with the secondary amine at the hemiacetal center. To rule out this possibility, the formation of a tertiary amine has been considered. Alkylation of nitrogen was easily carried out before the reduction step. Treatment of the fully deprotected cycloadduct **29a** with MeI gave the *N*-methyl isoxazolidinium iodide **35**, which was transformed quantitatively into the ammonium salt of **36** by reductive cleavage of the N−O bond with Zn in AcOH/H_2O (Scheme 2). The free base **36** (α/β 36/64), obtained by passing a solution of the salt on an acidic ionic exchange resin (Dowex 50) and eluting with a dilute ammonia solution, was found to be much more stable than **33**, and only after long standing in water solution did it undergo some decomposition.

Conclusions

A study of the intermolecular cycloaddition of nitrones to glycals has been reported. The low reactivity of glycals toward nitrones does not seem to be related to unfavorable orbital interactions,[28] rather by a steric hindrance of glycal dipolarophiles. Moreover the low reactivity requires forcing reaction conditions, and the stability of the nitrones becomes crucial. The results obtained with pyrroline *N*-oxide **16** and its hydroxylated derivatives **17** and **18** suggest that also electronic effects are involved. The reactions disclosed here allow access to a new class of (1→2)-linked pseudo aza-*C*-disaccharides, which are potential selective glycosidase inhibitors. These compounds have a sugar portion directly linked to C(2) of a polyhydroxylated pyrrolidine. The intermediate polyhydroxylated isoxazolidines, due to their stability under hydrolytic conditions, can be seen as mimics of nonreducing pseudo aza-*C*-disaccharides, as enzymatic tests on two of them have shown a selective inhibition of amyloglucosidases.

Experimental Section

Triacetyl glucal (**10**) is commercially available, whereas triacetyl galactal (**12**) has been synthesized by the standard methodology employing a zinc-mediated reduction[29] of the acetobromo sugar intermediate.[30] Benzyl glycals **11** and **13** were obtained from the corresponding triacetyl derivatives as reported in the literature.[31]

Cycloaddition Reactions: Syntheses of Compounds 20−24. General Procedure. A 1 M toluene solution of nitrone (**15−19**, 0.5 mmol, 1 equiv) and a 3-fold excess of glycal (**10−13**, 1.5 mmol, 3 equiv) was heated at 100 °C for 2−11 days until the nitrone was completely consumed (TLC control). Purification of the crude reaction mixtures by flash chromatography afforded light yellow oils or white crystalline solids (**20−24**, 28−65% yields).

(3*S*,3a*R*,4*R*,5*R*,6*R*,7a*R*)-4,5-Diacetoxy-6-(acetoxymethyl)-3-(ethoxycarbonyl)-2-methyl-hexahydro-4*H*-pyrano[3,2-*d*]isoxazole (20): Reaction time: 2 days; 36% yield; R_f = 0.30 (petroleum ether−AcOEt 3:1); $[\alpha]^{22}_D$ = +5.7 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.69 (d, *J* = 5.8 Hz, 1H), 5.26 (t, *J* = 7.3 Hz, 1H), 5.03 (t, *J* = 8.5 Hz, 1H), 4.36 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.22 (q, *J* = 7.4 Hz, 2H), 4.17−4.06 (m, 2H), 3.70 (d, *J* = 3.3 Hz, 1H), 2.93 (td, *J* = 6.2, 4.0 Hz, 1H), 2.85 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.28 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6 (s), 170.2 (s), 169.5 (s), 168.7 (s), 98.2 (d), 72.3 (d), 71.4 (d), 69.4 (d), 67.6 (d), 62.0 (t), 61.6 (t), 49.1 (d), 44.2 (q), 20.8 (q), 20.6 (q), 20.7 (q), 14.1 (q); IR ($CDCl_3$): 2987, 2943, 2909, 1753, 1429, 1366 cm^{-1}; MS (70 eV): *m*/*z* (%): 403 ($M^{+\bullet}$, 2), 330 (30), 270 (68), 168 (49), 112 (100). Anal. Calcd for $C_{17}H_{25}NO_{10}$: C, 50.62; H, 6.25; N, 3.47. Found: C, 50.56; H, 6.27; N, 3.66.

(2*R*,3*R*,4*R*,4a*R*,4b*S*,9a*R*)-3,4-Diacetoxy-2-(acetoxymethyl)-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (21): Reaction time: 40 min, 1.5 equiv of nitrone **16**; 12% yield; R_f = 0.19 (CH_2Cl_2-MeOH 50:1); mp 102−104 °C; $[\alpha]^{23}_D$ = +7.1 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (d, *J* = 5.4 Hz, 1H), 5.33 (t, *J* = 7.6 Hz, 1H), 4.97 (dd, *J* = 9.7, 8.1 Hz, 1H), 4.32 (dd, *J* = 12.3, 4.5 Hz, 1H), 4.23 (ddd, *J* = 9.7, 4.4, 2.2 Hz, 1H), 4.07 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.71 (t, *J* = 6.5 Hz, 1H), 3.45 (ddd, *J* = 14.0, 6.5, 2.5 Hz, 1H), 2.93 (ddd, *J* = 13.9, 9.6, 7.2 Hz, 1H), 2.58 (t, *J* = 5.7 Hz, 1H), 2.10−1.93 (m, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.80−1.75 (m, 1H), 1.53−1.47 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6 (s), 170.1 (s), 169.6 (s), 98.6 (d), 72.8 (d), 69.4 (d), 68.9 (d), 68.0 (d), 62.1 (t), 58.1 (t), 52.4 (d), 30.1 (t), 24.7 (t), 20.8 (q), 20.6 (q, 2C); IR

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($CDCl_3$): 2963, 2880, 1741, 1365, 1230 cm^{-1}; MS (70 eV): *m*/*z* (%): 297 (3, M^+-CH_3COOH), 195 (42), 152 (22), 86 (100). Anal. Calcd for $C_{16}H_{23}NO_8$: C, 53.78; H, 6.49; N, 3.92. Found: C, 54.10; H, 6.85; N, 3.56.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,9a*R*)-3,4-Diacetoxy-2-(acetoxymethyl)-5-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (22a): Reaction time: 4 days; 68% yield; R_f = 0.22 (AcOEt−petroleum ether 1:1); mp 98−99 °C; $[\alpha]^{21}_D$ = +2.8 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.48 (d, *J* = 5.4 Hz, 1H), 5.29 (dd, *J* = 7.0, 6.6 Hz, 1H), 4.98 (ddt, *J* = 9.4, 7.0, 2.2 Hz, 1H), 4.36−4.24 (m, 2H), 4.14−4.07 (m, 1H), 3.83 (ddd, *J* = 6.8, 3.4, 2.6 Hz, 1H), 3.51 (dd, *J* = 2.6, 2.4 Hz, 1H), 3.39 (ddd, *J* = 13.7, 7.3, 2.4 Hz, 1H), 3.24 (ddd, *J* = 13.7, 10.8, 6.2 Hz, 1H), 2.73 (ddd, *J* = 6.6, 5.4, 2.6 Hz, 1H), 2.07−2.04 (m, 1H), 1.75−1.64 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9 (s), 170.2 (s), 170.0 (s), 98.8 (d), 77.8 (d), 77.3 (d), 74.1 (s), 72.8 (d), 69.8 (d), 68.5 (d), 62.7 (t), 57.1 (t), 50.9 (d), 34.4 (t), 28.7 (q, 3C), 21.1 (q), 21.0 (q, 2C); IR ($CDCl_3$): 2977, 1749, 1434, 1365 cm^{-1}; MS (70 eV): *m*/*z* (%): 430 ($M^{+\bullet}$, 7), 312 (41), 154 (51), 128 (96), 84 (90), 57 (100). Anal. Calcd for $C_{20}H_{31}NO_9$: C, 55.93; H, 7.28; N, 3.26. Found: C, 56.36; H, 7.35; N, 3.24.

(2*R*,3*S*,4*R*,4a*R*,4b*R*,5*S*,9a*R*)-Octahydro-3,4-diacetoxy-2-(acetoxymethyl)-5-*tert*-butoxy-2*H*-pyrano[3,2-*d*]pyrrolo-[1,2-*b*]isoxazole (22b): Reaction time: 7 days; 35% yield; R_f = 0.20 (AcOEt−petroleum ether 1:1); mp 138−140 °C; $[\alpha]^{20}_D$ = +17.6 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.48 (d, *J* = 4.8 Hz, 1H), 5.31 (dd, *J* = 2.9, 1.5 Hz, 1H), 5.11 (dd, *J* = 9.9, 2.9 Hz, 1H), 4.34−4.23 (m, 1H), 4.05−4.02 (m, 2H), 3.77 (ddd, *J* = 7.0, 3.5, 2.6 Hz, 1H), 3.34 (d, *J* = 2.8 Hz, 1H), 3.36 (ddd, *J* = 13.4, 7.4, 2.3 Hz, 1H), 3.16 (ddd, *J* = 13.7, 11.0, 6.3 Hz, 1H), 2.57 (dd, *J* = 9.9, 4.8 Hz, 1H), 2.15−1.96 (m, 1H), 1.73−1.63 (m, 1H), 2.08 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9 (s), 170.5 (s), 170.4 (s), 99.5 (d), 78.2 (d), 77.6 (d), 74.2 (s), 70.8 (d), 68.9 (d), 65.7 (d), 62.4 (t), 57.6 (t), 45.9 (d), 35.5 (t), 28.9 (q, 3C), 21.1 (q, 2C), 21.0 (q); IR ($CDCl_3$): 2979, 2947, 1746, 1365, 1234 cm^{-1}; MS (70 eV): *m*/*z* (%): 430 ($M^{+\bullet}$, 6), 372 (3), 128 (60), 84 (60), 57 (100). Anal. Calcd for $C_{20}H_{31}NO_9$: C, 55.93; H, 7.28; N, 3.26. Found: C, 56.01; H, 7.24; N, 2.91.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,9a*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]-pyrrolo[1,2-*b*]isoxazole (22c): Reaction time: 9 days; 42% yield; R_f = 0.32 (AcOEt−petroleum ether 1:1); $[\alpha]^{24}_D$ = +23.7 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.20 (m, 15H), 5.52 (d, *J* = 5.0 Hz, 1H), 4.89−4.46 (m, 6H), 4.04 (ddd, *J* = 9.2, 3.0, 2.6 Hz, 1H), 3.90 (t, *J* = 7.6 Hz, 1H), 3.84−3.64 (m, 4H), 3.57 (br s, 1H), 3.43−3.25 (m, 2H), 2.64 (ddd, *J* = 7.0, 5.0, 1.6 Hz, 1H), 2.23−2.05 (m, 1H), 1.73−1.64 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4 (s), 138.3 (s), 138.2 (s), 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6 (d, 15C), 99.3 (d), 80.6 (d), 77.7 (d), 77.3 (d), 77.1 (d), 74.2 (t), 73.8 (t), 73.7 (t), 73.4 (t), 72.8 (d), 68.9 (s), 56.7 (t), 52.3 (d), 34.2 (t), 28.5 (q, 3C).; IR ($CDCl_3$): 3068, 3033, 2980, 2937, 2868, 1451, 1360, cm^{-1}; MS (70 eV): *m*/*z* (%): 409 (3), 154 (14), 107 (23), 91 (100), 57 (42). Anal. Calcd for $C_{35}H_{43}NO_6$: C, 73.27; H, 7.55; N, 2.44. Found: C, 72.80; H, 7.41; N, 2.69.

(2*R*,3*S*,4*R*,4a*R*,4b*R*,5*S*,9a*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]-pyrrolo[1,2-*b*]isoxazole (22d): Reaction time: 7 days; 27% yield; R_f = 0.30 (AcOEt−petroleum ether 1:1); $[\alpha]^{22}_D$ = +7.9 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.20 (m, 15H), 5.48 (d, *J* = 4.8 Hz, 1H), 4.91−4.74 (m, 2H), 4.63−4.40 (m, 4H), 4.09 (m, 1H), 4.01 (br s, 1H), 3.85 (ddd, *J* = 5.8, 3.0, 2.8 Hz, 1H), 3.76 (dd, *J* = 9.8, 2.2 Hz, 1H), 3.60 (m, 3H), 3.38 (ddd, *J* = 13.6, 7.4, 3.0 Hz, 1H), 3.23 (ddd, *J* = 13.6, 10.2, 6.2 Hz, 1H), 2.79 (dd, *J* = 9.8, 4.8 Hz, 1H), 2.15−2.03 (m, 1H), 1.77−1.65 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5 (s), 138.0 (s), 137.9 (s), 128.3, 128.2, 128.0, 127.8, 127.6, 127.6, 127.4 (d, 15C), 99.5 (d), 79.4 (d), 77.9 (d), 77.1 (d), 74.1 (t), 73.7 (t), 73.3 (t), 71.6 (d), 71.5 (t),69.9 (d), 68.4 (s), 65.9 (t), 47.8 (d), 34.8 (t), 28.6 (q, 3C); IR ($CDCl_3$): 3069, 3035, 2980, 2931, 1452, 1361 cm^{-1}; MS (70 eV): *m*/*z* (%): 574 ($M^{+\bullet}$, 0.2), 408 (8), 91 (100), 57 (34). Anal. Calcd for $C_{35}H_{43}NO_6$: C, 73.27; H, 7.55; N, 2.44. Found: C, 73.17; H, 7.89; N, 2.17.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*R*,6*R*,9a*R*)-3,4-Diacetoxy-2-(acetoxymethyl)-5,6-bis-*tert*-butoxy-octahydro-2*H*-pyrano-[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (23a): Reaction time: 3 days; 61% yield; R_f = 0.21 (CH_2Cl_2−MeOH 30:1); $[\alpha]^{25}_D$ = −20.7 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.84 (d, *J* = 5.1 Hz, 1H), 5.28 (t, *J* = 7.7 Hz, 1H), 5.00 (dd, *J* = 9.9, 7.7 Hz, 1H), 4.35 (dd, *J* = 12.1, 4.4 Hz, 1H), 4.20 (ddd, *J* = 9.9, 4.4, 2.2 Hz, 1H), 4.08 (dd, *J* = 12.1, 2.2 Hz, 1H), 3.84 (dt, *J* = 5.2, 2.6 Hz, 1H), 3.75 (br s, 1H), 3.53 (br s, 1H), 3.42 (dd, *J* = 13.9, 5.1 Hz, 1H), 3.26 (d, *J* = 13.9 Hz, 1H), 2.79 (ddd, *J* = 7.6, 5.1, 2.5 Hz, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.17 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7 (s), 170.0 (s), 169.8 (s), 98.8 (d), 83.1 (d), 78.7 (d), 75.8 (d), 74.2 (s), 74.2 (s), 72.8 (d), 69.1 (d), 68.2 (d), 64.0 (t), 62.2 (t), 49.5 (d), 28.6 (q, 3C), 28.3 (q, 3C), 20.8 (q, 2C), 20.7 (q); IR ($CDCl_3$): 2978, 1741, 1363, 1231 cm^{-1}; MS (70 eV): *m*/*z* (%): 502 ($M^{+\bullet}$, 8), 444 (5), 385 (12), 84 (38), 57 (100). Anal. Calcd for $C_{24}H_{39}NO_{10}$: C, 57.47; H, 7.84; N, 2.79. Found: C, 57.08; H, 7.86; N, 2.76.

(2*R*,3*S*,4*R*,4a*R*,4b*R*,5*R*,6*R*,9a*R*)-3,4-Diacetoxy-2-(acetoxymethyl)-5,6-bis-*tert*-butoxy-octahydro-2*H*-pyrano-[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (23b): Reaction time: 3 days; 26% yield; R_f = 0.20 (AcOEt−petroleum ether 1:1); $[\alpha]^{20}_D$ = −24.6 (*c* = 0.35, Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.97 (d, *J* = 4.4 Hz, 1H), 5.33 (d, *J* = 3.0 Hz, 1H), 5.07 (dd, *J* = 10.2, 3.0 Hz, 1H), 4.35−4.28 (m, 1H), 4.17−4.06 (m, 2H), 3.82 (ddd, *J* = 4.8, 2.6, 2.2 Hz, 1H), 3.74 (br s, 1H), 3.44−3.38 (m, 2H), 3.32−3.25 (m, 1H), 2.60 (dd, *J* = 10.2, 4.4 Hz, 1H), 2.14 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.18 (s, 9H), 1.17 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5 (s), 170.1 (s), 169.9 (s), 99.0 (d), 83.4 (d), 78.3 (d), 76.4 (d), 74.3 (s), 74.1 (s), 71.0 (d), 68.4 (d), 65.2 (d), 64.2 (t), 62.2 (t), 44.0 (d), 28.6 (q, 3C), 28.3 (q, 3C), 20.7 (q, 2C), 20.6 (q); IR ($CDCl_3$): 2979, 1745, 1467, 1368, 1235 cm^{-1}; MS (70 eV): *m*/*z* (%) 501 ($M^{+\bullet}$, 2), 444 (6), 384 (6), 84 (16), 57 (100). Anal. Calcd for $C_{24}H_{39}NO_{10}$: C, 57.47; H, 7.84; N, 2.79. Found: C, 57.22; H, 7.93; N, 2.46.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,6*S*,9a*R*)-3,4-Diacetoxy-2-(acetoxymethyl)-5,6-bis-*tert*-butoxy-octahydro-2*H*-pyrano-[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (24): Reaction time: 11 days; 33% yield; R_f = 0.25 (CH_2Cl_2−MeOH 16:1); $[\alpha]^{21}_D$ = +29.2 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (d, *J* = 5.5 Hz, 1H), 5.29 (t, *J* = 8.0 Hz, 1H), 5.01 (dd, *J* = 9.5, 8.0 Hz, 1H), 4.33 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.18 (ddd, *J* = 9.5, 4.5, 2.0 Hz, 1H), 4.06 (dd, *J* = 12.5, 2.0 Hz, 1H), 4.01 (dt, *J* = 8.5, 6.0 Hz, 1H), 3.83 (dd, *J* = 7.5, 6.0 Hz, 1H), 3.69 (d, *J* = 7.5 Hz, 1H), 3.38 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.91 (t, *J* = 6.0 Hz, 1H), 2.76 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.03 (s, 3H), 1.98 (s, 6H), 1.12 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8 (s), 170.1 (s), 169.9 (s), 99.8 (d), 77.4 (d), 76.9 (d), 74.6 (s), 73.8 (s), 72.5 (d), 69.1 (d), 69.0 (d), 68.3 (d), 62.2 (t), 60.5 (t), 47.3 (d), 28.4 (q, 3C), 28.3 (q, 3C), 20.7 (q, 2C), 20.7 (q); IR ($CDCl_3$): 2979, 2937, 1744, 1366, 1232 cm^{-1}; MS (70 eV): *m*/*z* (%): 501 ($M^{+\bullet}$, 0.5), 385 (4), 118 (92), 57 (100). Anal. Calcd for $C_{24}H_{39}NO_{10}$: C, 57.47; H, 7.84; N, 2.79. Found: C, 57.18; H, 7.83; N, 2.34.

Deprotection of Acetoxy Groups: Syntheses of Compounds 25−28. General Procedure. A catalytic amount of Na (20 mol %) was added to a 0.25 M solution of acetylated cycloadducts (**21, 22a,b, 23a,b, 24**, 0.25 mmol) in anhydrous MeOH, and the mixture was stirred for 12 h at rt under N_2. After solvent removal, the crude reaction mixtures were purified by crystallization from ethyl acetate or by flash chromatography to afford white crystalline solids (**25**−**28**, 70−95% yields).

(2*R*,3*R*,4*R*,4a*R*,4b*S*,9a*R*)-3,4-Dihydroxy-2-(hydroxymethyl)octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (25): 90% yield; R_f = 0.32 (CH_2Cl_2−MeOH−NH_4OH 8:2:0.5); mp 149−151 °C; $[\alpha]^{24}_D$ = +31.4 (*c* = 0.5, MeOH); ^{1}H-NMR (200 MHz, D_2O) δ 5.65 (d, *J* = 4.8 Hz, 1H), 3.84 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.78 (d, *J* = 3.6 Hz, 2H), 3.66 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.62 (t, *J* = 9.2 Hz, 1H), 3.41 (t, *J* = 9.2 Hz, 1H), 3.36−3.23 (m, 1H), 2.94 (ddd, *J* = 14.0, 9.2, 7.2 Hz, 1H), 2.41 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.75−2.15 (m, 3H), 1.64−1.54 (m, 1H); ^{13}C NMR (50 MHz, D_2O) δ 102.7 (d), 76.5 (d), 76.0 (d), 72.2 (d), 71.5 (d), 63.2 (t), 61.0 (t), 56.1 (d), 32.4 (t), 27.2 (t); MS (70 eV): *m*/*z* (%): 231 ($M^{+\bullet}$, 0.2), 111 (34), 86 (74), 85 (100). Anal.

Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.67; H, 7.79; N, 5.63.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,9a*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (26a): 95% yield; R_f = 0.20 (AcOEt−MeOH 10:1); mp 115 °C; $[\alpha]^{21}_D$ = +23.8 (*c* = 0.5, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 5.51 (d, *J* = 4.6 Hz, 1H), 4.02 (ddd, *J* = 5.9, 3.5, 2.4 Hz, 1H), 3.84−3.50 (m, 5H), 3.39−3.11 (m, 3H), 2.43 (dd, *J* = 8.8, 4.6 Hz, 1H), 2.23−2.04 (m, 1H), 1.77−1.66 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (50 MHz, CD_3OD) δ 104.4 (d), 82.7 (d), 80.9 (d), 78.6 (d), 78.2 (s), 77.8 (d), 73.7 (d), 65.4 (t), 61.2 (t), 56.6 (d), 38.7 (t), 31.9 (q, 3C); MS (70 eV): *m*/*z* (%): 304 ($M^{+\bullet}$, 4), 247 (7), 154 (75), 83 (65), 57 (100). Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.43; H, 8.31; N, 4.62. Found: C, 55.31; H, 8.64; N, 4.35.

(2*R*,3*S*,4*R*,4a*R*,4b*R*,5*S*,9a*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (26b): 92% yield; R_f = 0.20 (AcOEt−MeOH 10:1); mp 153 °C; $[\alpha]^{20}_D$ = +43.1 (*c* = 0.2, MeOH); ^{1}H NMR (200 MHz, D_2O) δ 5.60 (d, *J* = 4.8 Hz, 1H), 4.16 (pseudo quint, *J* = 3.5 Hz, 1H), 3.88−3.60 (m, 5H), 3.40−3.10 (m, 3H), 2.58 (dd, *J* = 10.0, 4.8 Hz, 1H), 2.30−2.10 (m, 1H), 1.80−1.70 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (50 MHz, D_2O) δ 102.8 (d), 80.3 (d), 79.2(d), 78.7 (s), 75.7 (d), 72.3 (d), 69.1 (d), 64.2 (t), 59.5 (t), 49.1 (d), 36.6 (t), 30.4 (q, 3C); MS (70 eV): *m*/*z* (%): 303 ($M^{+\bullet}$, 0.1), 246 (5), 154 (18), 84 (48), 57 (100). Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.43; H, 8.31; N, 4.62. Found: C, 55.14; H, 8.46; N, 4.25.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*R*,6*R*,9a*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5,6-bis-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (27a): 84% yield; R_f = 0.22 (CH_2Cl_2−MeOH 15:1); mp 194−196 °C; $[\alpha]^{21}_D$ = −9.2 (*c* = 0.5, MeOH); ^{1}H NMR (200 MHz, D_2O) δ 5.82 (d, *J* = 4.8 Hz, 1H), 4.02−4.00 (m, 2H), 3.77−3.76 (m, 2H), 3.70−3.64 (m, 1H), 3.57−3.39 (m, 4H), 3.17 (br d, *J* = 11.8 Hz, 1H), 2.69−2.62 (m, 1H), 1.22 (s, 9H), 1.18 (s, 9H); ^{13}C NMR (50 MHz, CD_3OD) δ 101.4 (d), 84.9 (d), 79.9 (d), 79.0 (d), 76.1 (d), 75.8 (d), 75.7 (s, 2C), 71.1 (d), 65.6 (t), 62.7 (t), 52.9 (d), 29.4 (q, 3C), 29.0 (q, 3C); MS (70 eV): *m*/*z* (%): 375 ($M^{+\bullet}$, 0.5), 318 (2), 246 (2), 84 (29), 57 (100). Anal. Calcd for $C_{18}H_{33}NO_7$: C, 57.58; H, 8.86; N, 3.73. Found: C, 57.23; H, 8.83; N, 4.00.

(2*R*,3*S*,4*R*,4a*R*,4b*R*,5*R*,6*R*,9a*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5,6-bis-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (27b): 78% yield; R_f = 0.19 (AcOEt−MeOH 10:1); mp 153−154 °C; $[\alpha]^{25}_D$ = 0.0 (*c* = 0.2, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 5.94 (d, *J* = 4.4 Hz, 1H), 3.90−3.68 (m, 6H), 3.56 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.44−3.20 (m, 3H), 2.51 (dd, *J* = 9.6, 4.4 Hz, 1H), 1.23 (s, 9H), 1.22 (s, 9H); ^{13}C NMR (50 MHz, CD_3OD) δ 101.6 (d), 85.1 (d), 79.8 (d), 79.0 (d), 75.8 (s), 75.7 (s), 74.7 (d), 72.5 (d), 68.7 (d), 65.7 (t), 63.0 (t), 47.9 (d), 29.4 (q, 3C), 29.0 (q, 3C); MS (70 eV): *m*/*z* (%): 375 ($M^{+\bullet}$, 0.5), 318 (6), 84 (27), 58 (100), 57 (99). Anal. Calcd for $C_{18}H_{33}NO_7$: C, 57.58; H, 8.86; N, 3.73. Found: C, 57.32; H, 8.72; N, 3.43.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,6*S*,9a*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5,6-bis-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (28): 70% yield; R_f = 0.10 (AcOEt−petroluem ether 1:1); mp 219−221 (dec) °C; $[\alpha]^{25}_D$ = +27.8 (*c* = 0.6, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 5.39 (d, *J* = 4.4 Hz, 1H), 3.94−3.75 (m, 3H), 3.63−3.42 (m, 4H), 3.28−3.08 (m, 2H), 2.90 (dd, *J* = 12.5, 5.2 Hz, 1H), 2.30 (dd, *J* = 9.1, 4.4 Hz, 1H), 1.10 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (50 MHz; CD_3OD) δ 102.3 (d), 78.4 (d), 77.9 (d), 75.7 (s), 75.5 (d), 75.0 (s), 74.5 (d), 71.3 (d), 70.9 (d), 62.7 (t), 62.4 (t), 50.0 (d), 28.8 (q, 3C), 28.8 (q, 3C); MS (70 eV): *m*/*z* (%): 375 ($M^{+\bullet}$,17), 319 (7), 244 (21), 185 (24), 112 (46), 84 (100). Anal. Calcd for $C_{18}H_{33}NO_7$: C, 57.58; H, 8.86; N, 3.73. Found: C, 57.06; H, 8.85; N, 3.82.

Deprotection of *tert*-Butoxy Groups: Syntheses of Compounds 29−31. General Procedure. The deacetylated cycloadduct (**26**−**28**, 0.2 mmol) was dissolved at 0 °C in TFA (0.8 mL) and stirred at rt for 1.5 h. The TFA was distilled off, and the light brown residue was dissolved in MeOH (10 mL) and stirred with Amberlyst A26 for 2 h at rt. The resin was filtered off and the solution concentrated to afford a yellow oil. Purification by crystallization from EtOH or by flash chromatography gave white crystalline solids (**29**−**32**, 40−96% yields).

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,9a*R*)-3,4,5-Trihydroxy-2-(hydroxymethyl)-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (29a): 88% yield; R_f = 0.45 (CH_2Cl_2−MeOH−NH_4OH 10:10:1); mp 211 °C; $[\alpha]^{20}_D$ = +41.8 (*c* = 0.6, H_2O); ^{1}H NMR (200 MHz; D_2O) δ 5.52 (d, *J* = 4.8 Hz, 1H), 4.18 (ddd, *J* = 6.2, 3.1, 3.1 Hz, 1H), 3.76−3.20 (m, 8H), 2.53 (dd, *J* = 8.0, 4.8 Hz, 1H), 2.24−2.05 (m, 1H), 1.83−1.70 (m, 1H); ^{13}C NMR (50 MHz; D_2O) δ 102.8 (d), 80.4 (d), 78.6 (d), 76.8 (d), 75.7 (d), 71.4 (d), 63.2 (t), 59.1 (t), 54.3 (d), 36.3 (t); MS (70 eV): *m*/*z* (%): 248 ($M^{+\bullet}$ − H, 3), 229 (5), 112 (60), 102 (60), 84 (100), 57 (68). Anal. Calcd for $C_{10}H_{17}NO_6$: C, 48.58; H, 6.93; N, 5.67. Found: C, 48.28; H, 7.22; N, 5.61.

(2*R*,3*S*,4*R*,4a*R*,4b*R*,5*S*,9a*R*)-3,4,5-Trihydroxy-2-(hydroxymethyl)-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (29b): 74% yield; R_f = 0.40 (CH_2Cl_2−MeOH−NH_4OH 10:10:1); mp 210−211 °C (dec); $[\alpha]^{24}_D$ = +61.2 (*c* = 0.25, H_2O); ^{1}H NMR (200 MHz; D_2O) δ 5.54 (d, *J* = 4.8 Hz, 1H), 4.20 (ddd, *J* = 6.2, 3.2, 3.0 Hz, 1H), 3.88−3.82 (m, 2H), 3.69−3.61 (m, 4H), 3.33−3.20 (m, 2H), 2.52 (dd, *J* = 9.8, 4.8 Hz, 1H), 2.24−2.05 (m, 1H), 1.84−1.71 (m, 1H); ^{13}C NMR (50 MHz; D_2O) δ 97.8 (d), 75.1 (d), 73.5 (d), 70.6 (d), 67.2 (d), 64.0 (d), 59.0 (t), 54.1 (t), 44.0 (d), 31.3 (t); MS (70 eV): *m*/*z* (%): 249 ($M^{+\bullet}$, 16), 248 (13), 112 (100), 102 (69), 84 (73), 57 (72). Anal. Calcd for $C_{10}H_{17}NO_6$: C, 48.58; H, 6.93; N, 5.67. Found: C, 48.94; H, 7.28; N, 5.15.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*R*,6*R*,9a*R*)-3,4,5,6-Tetrahydroxy-2-(hydroxymethyl)-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (30a): 96% yield; R_f = 0.21 (CH_2Cl_2−MeOH−NH_4OH 7:5:1); mp 199 °C (dec); $[\alpha]^{24}_D$ = +13.3 (*c* = 0.5, MeOH); ^{1}H NMR (200 MHz; D_2O) δ 5.78 (d, *J* = 4.7 Hz, 1H), 4.15 (q, *J* = 4.0 Hz, 1H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.78−3.76 (m, 2H), 3.70−3.61 (m, 2H), 3.56−3.44 (m, 3H), 3.27 (dd, *J* = 14.5, 3.9 Hz, 1H), 2.61 (dd, *J* = 8.8, 4.8 Hz, 1H); ^{13}C NMR (50 MHz; D_2O) δ 102.2 (d), 84.4 (d), 79.9 (d), 78.2 (d), 77.1 (d), 75.8 (d), 71.4 (d), 64.4 (t), 63.2 (t), 53.8 (d); MS (70 eV): *m*/*z* (%): 167 (3), 149 (95), 111 (8), 101 (12), 97 (12), 86 (52), 59 (51), 58 (100). Anal. Calcd for $C_{10}H_{17}NO_7$: C, 45.63; H, 6.51; N, 5.32. Found: C, 45.77; H, 6.50; N, 5.07.

(2*R*,3*S*,4*R*,4a*R*,4b*R*,5*R*,6*R*,9a*R*)-3,4,5,6-Tetrahydroxy-2-(hydroxymethyl)-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazole (30b): 70% yield; R_f = 0.38 (CH_2Cl_2−MeOH−NH_4OH 10:10:1); mp 205−206 °C (dec); $[\alpha]^{23}_D$ = +29.7 (*c* = 0.3, H_2O); ^{1}H NMR (200 MHz; D_2O) δ 5.80 (d, *J* = 4.7 Hz, 1H), 4.14 (q, *J* = 4.6 Hz, 1H), 4.04 (t, *J* = 4.6 Hz, 1H), 3.89−3.82 (m, 2H), 3.71−3.61 (m, 4H), 3.49 (dd, *J* = 14.3, 5.5 Hz, 1H), 3.25 (dd, *J* = 14.3, 4.4 Hz, 1H), 2.55 (dd, *J* = 9.8, 4.7 Hz, 1H); ^{13}C NMR (50 MHz; D_2O) δ 101.9 (d), 84.0 (d), 79.3 (d), 77.6 (d), 75.6 (d), 72.0 (d), 68.8 (d), 64.1 (t), 63.8 (t), 48.1 (d); MS (70 eV): *m*/*z* (%): 214 (7), 169 (8), 112 (97), 97 (25), 84 (43), 57 (100).

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,6*S*,9a*R*)-3,4,6-Trihydroxy-2-(hydroxymethyl)-5-*tert*-butoxy-octahydro-2*H*-pyrano[3,2-*d*]-pyrrolo[1,2-*b*]isoxazole (31): 93% yield; R_f = 0.2 (CH_2Cl_2−MeOH 6:1); ^{1}H NMR (200 MHz; D_2O) δ 5.53 (d, *J* = 4.8 Hz, 1H), 4.22 (q, *J* = 6.0 Hz, 1H), 4.12−4.06 (m, 2H), 3.83−3.75 (m, 2H), 3.69−3.55 (m, 2H), 3.49−3.30 (m, 2H), 3.05 (dd, *J* = 13.9, 6.6 Hz, 1H), 2.61 (dd, *J* = 8.4, 5.1 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (50 MHz; D_2O) δ 103.2 (d), 79.3 (d), 78.8 (s), 78.4 (d), 76.4 (d), 75.3 (d), 72.9 (d), 71.2 (d), 62.8 (t), 62.3 (t), 50.8 (d), 29.8 (q, 3C); MS (70 eV): *m*/*z* (%): 320 ($M^{+\bullet}$ + H, 2), 319 (M^+, 1), 262 (11), 96 (56), 84 (28), 59 (100).

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,6*S*,9a*R*)-3,4,5,6-Tetrahydroxy-2-(hydroxymethyl)-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo-[1,2-*b*]isoxazole (32): 40% yield; R_f = 0.40 (CH_2Cl_2−MeOH−NH_4OH 10:10:1); ^{1}H NMR (200 MHz; D_2O) δ 5.54 (d, *J* = 4.8 Hz, 1H), 4.28−4.21 (m, 1H), 4.10 (dd, *J* = 6.0, 2.6 Hz, 1H), 4.00 (d, *J* = 5.8 Hz, 1H), 3.75 (d, *J* = 3.4 Hz, 2H), 3.69−3.38 (m, 3H), 3.36−3.15 (m, 2H), 2.55 (dd, *J* = 9.2, 4.8 Hz, 1H); ^{13}C NMR (50 MHz; D_2O) δ 103.2 (d), 79.1 (d), 78.1 (d), 76.6 (d), 75.2 (d), 73.3 (d), 71.2 (d), 63.1 (t), 62.8 (t), 50.0 (d). Anal. Calcd for $C_{10}H_{17}NO_7$: C, 45.63; H, 6.51; N, 5.32. Found: C, 45.57; H, 6.55; N, 5.40.

Reductive Cleavage of N−O Bond by Catalytic Hydrogenation: Syntheses of Compounds 33 and 34. General Procedure. The polyhydroxylated isoxazolidine (**29a** or **30a**, 0.15 mmol) was dissolved in 1 mL of MeOH/H_2O 10% and the solution bubbled with H_2 at rt in the presence of 5% Pd/C or 20% $Pd(OH)_2$/C (50 mg). After 2 h the catalyst was filtered off, the solution was concentrated, and the residual oil was purified by flash chromatography, to give pseudo aza-*C*-disaccharides **33** and **34**. The compounds proved unstable and could be only characterized by rapid acquisition of NMR spectra.

(2′*R*,3′*S*)-2-Deoxy-2-[2-(3-hydroxy)pyrrolidinyl]-D-glucose (33): 51% yield; α/β = 74/26; R_f = 0.32 (CH_2Cl_2-MeOH−NH_4OH 10:10:1); ^{1}H NMR (200 MHz; D_2O) δ 5.30 (d, *J* = 3.4 Hz, α1H), 4.81 (d, *J* = 8.8 Hz, β1H), 4.74−4.56 (m, β1H), 4.29−4.20 (m, α1H), 3.84−3.68 (m, α3H, β4H), 3.43−3.29 (m, α2H, β1H), 3.16 (t, *J* = 6.0 Hz, α1H), 3.05−2.96 (m, α1H, β2H), 2.14−1.70 (m, α3H, β3H); ^{13}C NMR (50 MHz; D_2O) δ 97.3 (d, β), 94.7 (d, α), 78.1 (d, β), 75.9 (d, α), 75.4 (d, β), 75.3 (d, β), 73.9 (d, α), 73.3 (d, α), 72.9 (d, α), 72.8 (d, β), 66.9 (d, β), 66.6 (d, α), 63.4 (t, β), 63.2 (t, α), 50.4 (d, β), 48.6 (d, α), 45.9 (t, β), 45.5 (t, α), 36.3 (t, β), 35.5 (t, α).

(2′*R*,3′*R*,4′*R*)-2-Deoxy-2-[2-(3,4-dihydroxy)pyrrolidinyl]-D-glucose (34): 50% yield; α/β = 67/33; R_f = 0.20 (CH_2Cl_2−MeOH−NH_4OH 5:7:1.5); ^{1}H NMR (200 MHz; D_2O) δ 5.32 (d, *J* = 3.3 Hz, α 1H), 4.80 (d, *J* = 9.2 Hz, β 1H), 4.23−4.07 (m, α 1H, β 2H), 3.94 (dd, *J* = 7.2, 3.8 Hz, α 1H), 3.89−3.61 (m, α 3H, β 3H), 3.41−3.28 (m, α 2H, β 2H), 3.19−3.01 (m, α 2H, β 2H), 2.84 (dd, *J* = 12.1, 3.7 Hz, α 1H, β 1H), 1.94 (ddd, *J* = 11.0, 5.5, 3.3 Hz, α 1H), 1.85 (ddd, *J* = 11.0, 9.2, 3.7 Hz, β 1H).

Ammonium Salts of Pseudo Aza-*C*-disaccharide 33. The quaternary ammonium salts of **33** were obtained by adding an excess of HCl or TFA to the solution of hydrogenolysis of **29a**. Distillation of the solvent gave the salts quantitatively as viscous oils. Alternatively, the ammonium salts were obtained carrying out the catalytic hydrogenation procedure in acidic solution of HCl or TFA, respectively.

(33·HCl or 33·TFA): α/β = 75/25; ^{1}H NMR (200 MHz; D_2O) δ 5.38 (d, *J* = 3.0 Hz, α 1H), 4.85 (d, β 1H), 4.75 (br s, 3H), 3.84−3.67 (m, 3H), 3.42−3.33 (m, 3H), 2.31−2.14 (m, 1H), 2.01−1.92 (m, 1H); ^{13}C NMR (50 MHz; D_2O) δ 96.6 (d, β), 93.4 (d, α), 78.3 (d, β), 74.7 (d, β), 74.1 (d, α), 73.5 (d, α), 73.2 (d, β), 73.0 (d, α), 72.7 (d, β), 71.6 (d, α), 67.0 (d, β), 65.4 (d, α), 63.4 (t, β), 63.2 (t, α), 49.1 (d, β), 46.2 (t, α), 45.7 (d, α), 45.7 (t, β), 34.7 (t, β), 34.5 (t, α). **(33·TFA):** $[\alpha]^{20}_D$ = +49.3 (*c* = 0.8, H_2O). Anal. Calcd for $C_{12}H_{20}NO_8F_3$: C, 39.67; H, 5.55; N, 3.86. Found: C, 39.98; H, 5.53; N, 3.52.

Synthesis of the *N*-Methyl Disaccharide 36. MeI (3 equiv) was added to a 0.1 M MeOH solution of deprotected cycloadduct **29a** (0.2 mmol). The solution was left overnight at rt under stirring and then concentrated to give quantitatively the *N*-methyl iodide cycloadduct **35** as a yellow oil, which was used for the next step without purification.

(2*R*,3*R*,4*R*,4a*R*,4b*R*,5*S*,8*S*,9a*R*)-3,4,5-Trihydroxy-2-(hydroxymethyl)-8-methyl-octahydro-2*H*-pyrano[3,2-*d*]pyrrolo[1,2-*b*]isoxazolium iodide (35): ^{1}H NMR (200 MHz; D_2O) δ 6.12 (d, *J* = 4.8 Hz, 1H), 4.71−4.66 (m, 2H), 4.35−4.10 (m, 2H), 3.97−3.77 (m, 4H), 3.82 (s, 3H), 3.63 (t, *J* = 7.8 Hz, 1H), 2.84 (ddd, *J* = 7.8, 4.4, 3.4 Hz, 1H), 2.62−2.44 (m, 1H), 2.30−2.20 (m, 1H); ^{13}C NMR (50 MHz; D_2O) δ 106.2 (d), 91.8 (d), 79.6 (d), 76.7 (d), 73.7 (d), 71.7 (t), 69.8 (d), 62.2 (t), 59.8 (q), 52.5 (d), 34.3 (t); MS (70 eV): *m*/*z* (%): 225 (6), 155 (29), 127 (100), 83 (74), 81 (89), 54 (56), 44 (70), 41 (85).

The *N*-methyl iodide **35** (0.2 mmol) was dissolved in 0.8 mL of AcOH/H_2O 9:1. Zinc powder (0.8 mmol) was added, and the reaction mixture was stirred for 2 h. The excess zinc powder and salts were then filtered off, and the solution was concentrated and passed through a Dowex 50 (H^+) column eluting with ammonia 10% to afford a yellow oil, which solidified under high vacuum in the presence of KOH.

(2′*R*,3′*S*)-2-Deoxy-2-[2-(3-hydroxy-1-methyl)pyrrolidinyl]-D-glucose (36): 76% yield; α/β = 36/64; mp 111−113 °C; $[\alpha]^{23}_D$ = +0.3 (*c* = 0.6, H_2O); ^{1}H NMR (400 MHz; D_2O) δ 5.20 (br s, α 1H), 4.79 (d, *J* = 11.7 Hz, β 1H), 4.48 (br s, α 1H, β 1H), 3.89−3.63 (m, α 4H, β 3H), 3.64−3.27 (m, α 1H, β 2H), 3.20 (t, *J* = 8.0 Hz, α 1H), 3.07 (t, *J* = 8.2 Hz, β 1H), 2.94 (br s, α 1H), 2.80 (br s, β 1H), 2.71−2.69 (m, α 1H), 2.58−2.50 (m, β 1H), 2.53 (s, α 3H), 2.41 (s, β 3H), 2.05−1.76 (m, α3H, β 3H); ^{13}C NMR (100.61 MHz; D_2O) δ 94.9 (d, β), 93.1 (d, α), 76.5 (d, β), 74.6 (d, β), 74.2 (d, α), 73.9 (d, β), 73.8 (d, α), 72.4 (d, β), 72.2 (d, α), 71.8 (d, α), 71.1 (d, β), 70.4 (d, α), 61.5 (t, β), 61.2 (t, α), 54.9 (t, α), 53.9 (t, β), 45.4 (d, β), 44.7 (d, α), 42.3 (q, α), 40.5 (q, β), 34.7 (t, β), 33.7 (t, α). MS (CI, NH_3): *m*/*z* (%): 264 ($M^{+\bullet}$ + 1, 83), 263 ($M^{+\bullet}$, 33), 246 (49), 228 (71), 168 (34), 144 (39), 100 (100). Anal. Calcd for $C_{11}H_{21}NO_6$: C, 50.18; H, 8.04; N, 5.32. Found: C, 50.37; H, 8.02; N, 5.02.

Enzymatic Assays. Twenty-five commercially available (Oxford Glycosystem, Sigma Chemical Co) glycosidases (bovine epididymis and human placenta α-L-fucosidases (EC 3.2.1.51), coffee beans, *Aspergillus niger* and *Escherichia coli* α-galactosidases (EC 3.2.1.22), jack beans, bovine liver, *Aspergillus niger*, *Aspergillus orizae*, and *Escherichia coli* β-galactosidases (EC 3.2.1.23), yeast and rice maltases (EC 3.2.1.20), isomaltase from bakers' yeasts (EC 3.2.1.10), *Aspergillus niger* and *Rhizopus* mold amyloglucosidases (EC 3.2.1.3), almonds and *Caldocellum saccharolyticum* β-glucosidases (EC 3.2.1.21), jack beans and almonds α-mannosidases (EC 3.2.1.24), *Helix pomatia* β-mannosidase (EC 3.2.1.25), *Aspergillus niger* β-xylosidase (EC 3.2.1.37), chicken liver α-*N*-acetylgalactosaminidase (EC 3.2.1.49), and jack beans and bovine epididymis A and B β-*N*-acetylgalactosaminidases (EC 3.2.1.30)) were assayed by incubation at 37 °C with appropriate *p*-nitrophenyl glycoside substrates (Sigma) as reported in ref 4b.

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Supporting Information Available: Figures showing ^{13}C NMR spectra for **30b**, **31**, **32**, **33**·HCl, and **35** are provided (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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