

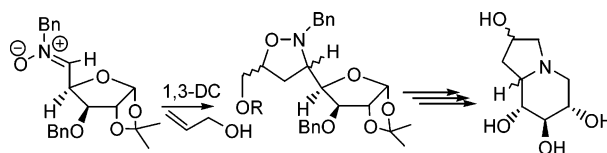
1,3-Dipolar Cycloaddition Reaction of D-Glucose-Derived Nitronone with Allyl Alcohol: Synthesis of 2-Hydroxy-1-deoxycastanospermine Analogues

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The synthesis and evaluation of glycosidase inhibitory activity of polyhydroxylated indolizidine alkaloids namely 2-hydroxy-1-deoxycastanospermine **3a,b** and 2-hydroxy-1-deoxy-8a-*epi*-castanospermine **3c,d** is reported. The key step involves the intermolecular 1,3-dipolar cycloaddition of allyl alcohol to D-glucose-derived nitronone **4**, followed by tosylation, that afforded four diastereomeric sugar-substituted isoxazolidines **5a–d** with the desired regioselectivity. The one-pot conversion of **5a–d** to pyrrolidines **8a–d** by hydrogenolysis, removal of 1,2-acetone functionality, and hydrogenation afforded corresponding target molecules **3a–d**.

Introduction

The 1,3-dipolar cycloaddition (DC) of nitronone with olefin, leading to the formation of isoxazolidine, followed by N–O bond reductive cleavage is a useful strategy in the synthesis of amino compounds—the key intermediates to nitrogen heterocycles.¹ Among nitronones, the sugar-derived nitronones represent versatile substrates as they provide a polyhydroxylated carbon framework with multiple avenues of chirality as well as an access for amino group transformation required for the synthesis of polyhydroxylated piperidine, pyrrolidine, pyrrolizidine, indolizidine, and quinolizidine alkaloids.² This class of compounds, commonly known as azasugars, namely nojirimycin **1** and castanospermine **2** (Figure 1), have attracted considerable attention because of their promising glycosidase inhibitory activity.³ In the search for a structure–activity relationship, a number of natural and unnatural derivatives of castanospermine have been synthesized⁴ and evaluated for glycosidase inhibition in the treatment of various diseases such as diabetes,⁵

cancer,⁶ and viral infections, including AIDS.⁷ As a part of our continuing interest in the synthesis of azasugars,⁸ we have now studied the intermolecular 1,3-DC reaction of D-glucose-derived nitronone **4** with allyl alcohol, as a key step, in the formation of sugar-substituted isoxazolidines that are elaborated in the synthesis of 2-hydroxy-1-deoxycastanospermine analogues **3a,d**.⁹

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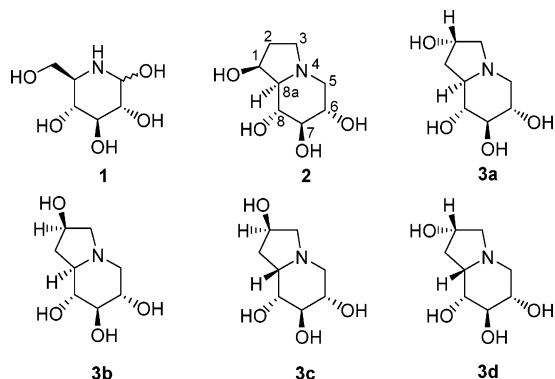
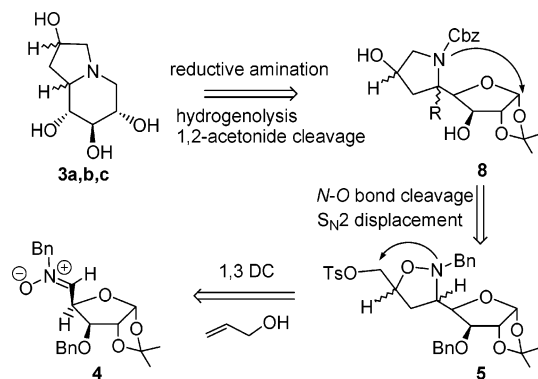


FIGURE 1. Azasugars and analogues.

SCHEME 1. Retrosynthetic Analysis



Results and Discussion

Retrosynthetic Analysis. As shown in the retrosynthetic analysis (Scheme 1), the requisite bicyclic ring skeleton of the 2-hydroxy-1-deoxycastanospermine could be built up by 1,2-acetonide cleavage of **8** followed by

hydrogenation (one-pot hydrogenolysis and reductive aminocyclization). The N–O bond reductive cleavage of tosyloxylated isoxazolidine **5** and concomitant nucleophilic displacement of the –O-tosyl group, by in situ generated secondary amino functionality, will give an access to **8**. Thus, the isoxazolidine **5** is the key intermediate that could be derived from the 1,3-DC of D-glucose-derived nitrone **4** with the allyl alcohol followed by tosylation. Our visualization relies on the fact that the 1,3-DC of nitrones with the allyl alcohol occur with perfect regioselectivity, wherein the oxygen of the 1,3-dipole attacks the more highly substituted carbon of the double bond to produce the corresponding cycloadduct in excellent yield.¹⁰ We assume that the same regioselectivity would be obtained with the sugar nitrone **4** and as far as the regioselectivity is perfect, the π -facial stereoselectivity will not be a serious problem as the *Re* face cycloaddition will provide D-*gluco*-configured isoxazolidines while the *Si* facial selectivity will afford L-*ido*-configured isoxazolidines and all the stereomers, if obtained, could be converted to 2-hydroxy-1-deoxycastanospermine **3a,b** and 2-hydroxy-1-deoxy-8a-*epi*-castanospermine **3c,d**, respectively. Although a few reports are available on the use of 1,3-DC of the nitrones with allyl alcohol,¹¹ the application of this strategy with nitrone **4** toward the synthesis of castanospermine analogues, to the best of our knowledge, is not known. Our efforts in the successful implementation of this methodology for the synthesis of 2-hydroxy-1-deoxycastanospermine analogues **3a–d** are reported herein.

Regioselective 1,3-Dipolar Cycloaddition of Nitrone **4 with Allyl Alcohol.** The requisite *Z*-nitro **4** was prepared from the D-glucose as reported earlier by us.^{8a} The 1,3-DC of **4** with the allyl alcohol in acetone at 30 °C for 7 days was sluggish; however, refluxing for 48 h afforded an inseparable mixture of isoxazolidines in

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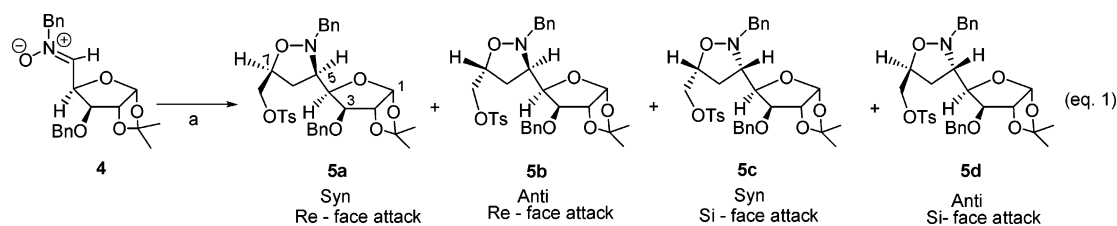
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(9) The synthesis of 2-hydroxy-1-deoxy castanospermine **3a** and **3b** has been reported wherein the assignment of absolute configuration at C-2 is not given. The authors have reported only the ¹³C NMR values: Compennolle, F.; Joly, G.; Peeters, K.; Toppet, S.; Hoomaert, G. *Tetrahedron* **1997**, *53*, 12739–12754. The compounds **3c,d** are not reported so far.

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SCHEME 2^a

^a Reaction conditions: (a) (i) allyl alcohol, acetone, 70 °C, 48 h, 95% (ii) TsCl, pyridine, 0 to 25 °C, 2 h, 87% (syn:anti 76:24).

95% yield (after chromatographic purification) which on further treatment with *p*-toluenesulfonyl chloride in pyridine followed by careful separation of the crude mixture by flash chromatography afforded tosyloxylated isoxazolidines **5a–d** in 49%, 07%, 17%, and 14% yield, respectively (87% combined yield), with complete regioselectivity (Scheme 2). Our attempts to improve the stereoselectivity at the prochiral C-5 nitronium carbon under various reaction conditions such as change of solvent, temperature, stoichiometry of reactants, and different Lewis acids were unsuccessful.¹² Thus, the 1,3-DC of **4** with the allyl alcohol and subsequent tosylation afforded a mixture of the syn and anti isomers in the ratio 3:1 in which the products **5a** and **5b** were formed by the addition of the allyl alcohol to the *Re* face while **5c** and **5d** were formed by the addition of the allyl alcohol to the *Si* face of the nitronium **4**.¹³

Assignment of the Relative Stereochemistry at C-5 and C-7 in Isoxazolidines 5a–d. Fortunately, the *O*-tosylated isoxazolidines **5a** and **5d** were obtained as crystalline solids. The single-crystal X-ray analysis of **5a** (Figure 2) and **5d** (Figure 3) established the absolute configurations at newly generated C5 and C7 stereocenters as (5*R*,7*S*) and (5*S*,7*S*), defining these as *D*-*gluco* and *L*-*ido* derivatives, respectively. However, the stereochemical assignments in **5b** and **5c** were derived from the correlation study. For this, **5a–d** were individually subjected to N–O bond reductive cleavage with use of Zn-acetic acid, which afforded corresponding pyrrolidines **6a–d** in good yields (Scheme 3). This one-pot two-step reaction of **5** probably involves in situ generation of β -amino alcohol that concomitantly undergoes nucleophilic displacement of the *-O*-tosyl group leading to the formation of the 7-hydroxy-pyrrolidine-ring skeleton. At this stage, we thought of oxidizing the C7 hydroxyl group, in **6a–d**, to the corresponding keto functionality, which is expected to give only two C5 epimeric 7-keto products. This will enable us to get the absolute configuration at C5 in **6**, and from X-ray data correlation of **5a** and **5d** one can assign the relative stereochemistry at C7 in **6**.

(12) The cycloaddition reaction in benzene and toluene at reflux had little effect on stereoselectivity and the use of dichloromethane and acetonitrile at reflux did not afford the products. The same reaction, in the absence of solvent, was complete in 4 h affording only three isoxazolidines **5a:5c:5d** in the ratio 3.2:1.2:1.0. The 1,3-DC with Lewis acids such as Cu(OTf)₂ or TBDMSOTf (0.5 and 1.0 equiv), either in acetone or in dichloromethane at the elevated temperature, furnished a complex mixture of products, probably due to the cleavage of the 1,2-acetonide group, thus precluding the use of Lewis acids in the 1,3-DC reaction of sugar nitronium.

(13) The isomers **5a** and **5c** are often referred as *exo* while **5b** and **5d** are called *endo*.^{1a,f} However since *exo* and *endo* are more correctly used for bicyclic systems, we have dropped this terminology as suggested by one of the referees. We are thankful to the referee for his comments.

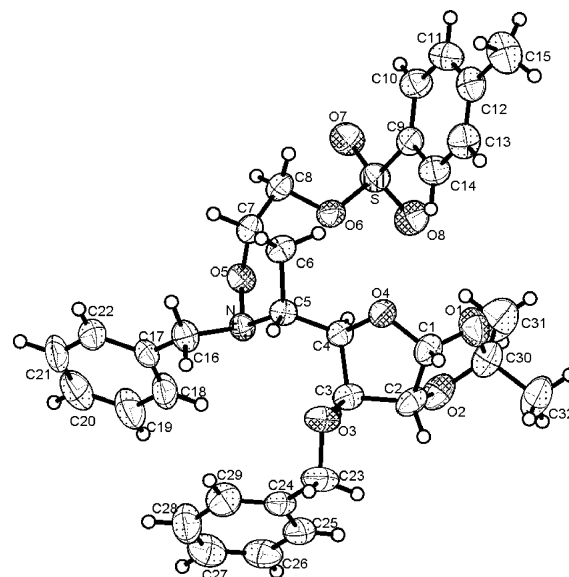


FIGURE 2. ORTEP drawing of compound **5a**.

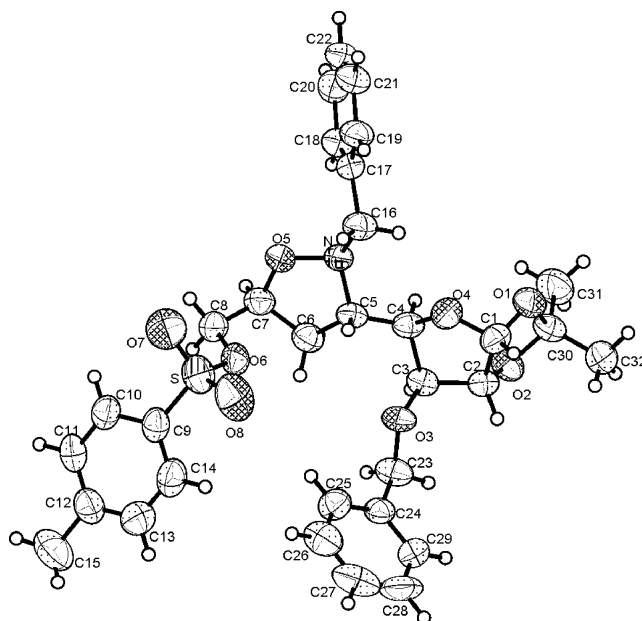
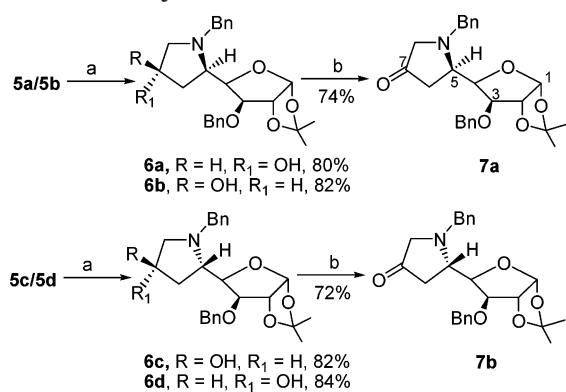


FIGURE 3. ORTEP drawing of compound **5d**.

Thus, individual Swern oxidation of **6a** and **6b** afforded *D*-*gluco*-configured 7-keto compound **7a** as a thick oil (Scheme 3) while **6c** and **6d** gave *L*-*ido*-configured 7-keto product **7b** as a colorless solid in good yields.¹⁴ The absolute configuration at C5 in **6a** and **6d** was established as (5*R*) and (5*S*) from the corresponding X-ray

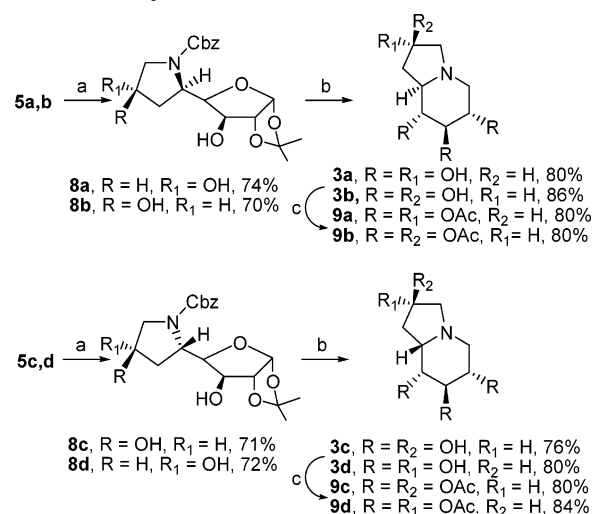
SCHEME 3^a Determination of Absolute Stereochemistry

^a Reaction conditions: (a) Zn, Cu(OAc)₂, AcOH, 70 °C, 1 h; (b) DMSO, (COCl)₂, (Et)₃N, -78 to 25 °C, 3 h.

structure of **5a** and **5d**; therefore, the same absolute configuration (5*R*) and (5*S*) was assigned in **6b** and **6c**, respectively. The absolute configuration at C7 in **6a** and **6d** was noticed to be (7*S*) and as the **6a/6b** and **6c/6d** were found to be C7-epimeric alcohols, the C7-configuration in **6b** and **6c** was therefore assigned as (7*R*). As **6b** and **6c** were derived from **5b** and **5c**, respectively, the same relative stereochemistry (5*R*,7*R*) and (5*S*,7*R*) was assigned to the corresponding precursor isoxazolidines **5b** and **5c**.

Synthesis of 2-Hydroxy-1-deoxycastanospermine Analogues 3a–d. Treatment of **5a** with ammonium formate and 10% Pd/C followed by selective amine protection, with benzyl chloroformate, afforded *N*-Cbz protected diol **8a** in 70% yield (Scheme 4). This one-pot three-step hydrogenation reaction resulted in *N*–O bond cleavage, intramolecular aminocyclization to form the pyrrolidine ring skeleton, and the removal of *N*- and *O*-benzyl groups. Subsequently, deprotection of 1,2-acetone functionality in **8a** with TFA–water followed by hydrogenation (H₂, 10% Pd/C) afforded 2-(*S*)-hydroxy-1-deoxycastanospermine **3a**. The same sequence of reactions with **5b**, **5c**, and **5d** gave 2-(*R*)-hydroxy-1-deoxycastanospermine **3b**, 2(*R*)-hydroxy-1-deoxy-8*a*-*epi*-castanospermine **3c**, and 2(*S*)-hydroxy-1-deoxy-8*a*-*epi*-castanospermine **3d**, respectively. The *N*-Cbz protected diols **8a–d** and target molecules **3a–d** were characterized by spectral and analytical techniques and the data were found to be in agreement with the structures. The individual reactions of **3a–d** with Ac₂O in pyridine afforded corresponding acetyl derivatives **9a–d**, which were characterized by spectral and analytical methods.

Conformational Assignments of 3a–d. We have recently reported that the 1-deoxycastanospermine and 1-deoxy-8*a*-*epi*-castanospermine exist in ⁵C₅ and ⁵C₈ conformations, respectively.^{8b} The conformational aspects of **3a–d** were studied by using ¹H NMR data wherein the assignment of signals and coupling constants information were obtained from decoupling experiments and

SCHEME 4^a Synthesis of 3a–d

^a Reaction conditions: (a) (i) HCOONH₄, Pd/C, MeOH, 80 °C, 1 h; (ii) CbzCl, NaHCO₃, MeOH, 0 to 25 °C, 2 h; (b) (i) TFA–H₂O (3:2), 25 °C, 2 h; (ii) H₂, Pd/C, MeOH, 80 psi, 25 °C, 12 h; (c) Ac₂O, pyridine, DMAP, 0 to 25 °C, 12 h.

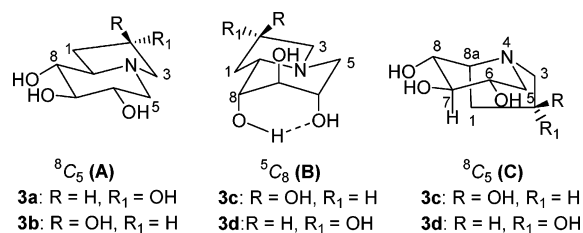
are given in Table 1. In case of **3a**, the appearance of two triplets for H7 and H8 at δ 3.23 and 3.14 (*J* = 9.3 Hz), one doublet of doublet for H6 at δ 3.51 (*J* = 11.0, 9.3, and 5.4 Hz) and a triplet for H5a at δ 2.25 (*J* = 11.0 Hz) clearly indicated the *trans*-diaxial relationship between the H5a, H6, H7, H8, and H8a. The large coupling constants of these protons require axial orientation and indicated the ⁸C₅ conformation (**A**) (Figure 4) for **3a**. Similarly, in the case of **3b**, the appearance of two triplets at δ 3.20 and 3.39 (*J* = 9.3 Hz) corresponding to H7 and H8 indicated the *trans*-diaxial orientation of H6a, H7, and H8. In addition, the H5a resonated as triplet at δ 2.29 with a large coupling constant (*J*_{5a,6a} = *J*_{5a,6a} = 11.0 Hz) that requires *trans*-diaxial disposition of H6a and H5a. The axial arrangements of these protons thus indicated ⁸C₅ conformation (**A**) for **3b**.

The ¹H NMR spectra of **3c,d** were found to be different wherein H6, H7, and H8 protons were deshielded as compared to the corresponding protons in **3a** and **3b**. This downfield shift indicated the *equatorial* orientation of these protons as opposed to the *axial* orientation in **3a,b**. The initial geometry in the precursor **5c,d** ensures that, in the product **3c,d**, the substituents at C6, C7, and C8 should be *trans*. The low values for the coupling constants between H6, H7, and H8 in **3c** (5.6 Hz) and **3d** (*W*_H = 3.0 Hz) supported the fact that these protons are *equatorial*. This suggested the ⁵C₈ conformation (**B**) for both the bicyclic indolizidines **3c,d**. The doublet of doublet for H-8 at δ 3.69 (*J* = 5.6, 3.6 Hz) in **3c** and narrow multiplet at δ 3.73–3.85 (*W*_H = 3.0 Hz) in **3d** indicated that the C8a substituent is *equatorial* with (8a*S*) absolute configuration. From an empirical calculation of the energy difference between the two conformations ⁵C₈ and ⁸C₅, (**B**) and (**C**), respectively, it is evident that in the ⁸C₅ conformation (**C**) the 1,3-diaxial interactions between C5–Ha and C8a–C1 and between C7–H and C8a–C1 destabilize this conformation. On the contrary, in the ⁵C₈ conformation (**B**), both the 1,3-diaxial interactions are absent and, in addition, the conformation ⁵C₈ is stabilized by the intra-

(14) The formation of keto product **7a** obtained separately from **6a/6b** was found to be identical on the basis of super imposable IR and other spectral and analytical data. Similarly, the keto product **7b** derived from **6c/6d** was found to be identical on the basis of mp, mixed mp, and super imposable IR and other spectral and analytical data.

TABLE 1. ^1H – ^1H Coupling Constant Values of Compounds **3a–d**

	H2	H5a	H5e	H6	H7	H8	H8a
3a	δ 4.34–4.44 (m)	2.25 (t) ($J_{5a,5e} =$ $J_{5a,6a} = 11.0$ Hz)	3.12 (dd) ($J_{5e,6a} = 5.4$ Hz)	3.51 (ddd) ($J_{6a,5a} = 11.0$ Hz, $J_{6a,5e} = 5.4$ Hz, $J_{6,7} = 9.3$ Hz)	3.23 (t) ($J_{7,6} =$ $J_{7,8} = 9.3$ Hz)	3.14 (t) ($J_{8,7} = J_{8,8a} =$ 9.3 Hz)	2.54 (ddd) ($J_{8a,1a} = 7.3$ Hz, $J_{8a,1b} = 6.4$ Hz)
3b	δ 4.38–4.48 (m)	2.29 (t) ($J_{5a,5e} =$ $J_{5a,6a} = 11.0$ Hz)	3.24 (dd) ($J_{5e,6a} = 5.0$ Hz)	3.61 (ddd) ($J_{6a,5a} = 11.0$ Hz, $J_{6a,5e} = 5.0$ Hz, $J_{6,7} = 9.3$ Hz)	3.20 (t) ($J_{7,6} =$ $J_{7,8} = 9.3$ Hz)	3.35 (t) ($J_{8,7} = J_{8,8a} =$ 9.3 Hz)	2.45 (ddd) ($J_{8a,1a} = 8.4$ Hz, $J_{8a,1b} = 6.3$ Hz)
3c	δ 4.47–4.58 (m)	2.72 (dd) ($J_{5a,6e} = 5.6$ Hz, $J_{5a,5e} = 12.2$ Hz)	2.65 (dd) ($J_{5e,6e} = 3.3$ Hz)	3.82 (dt) ($J_{6e,5a} =$ $J_{6,7} = 5.6$ Hz, $J_{6e,5e} = 3.3$ Hz)	3.74 (t) ($J_{7,6} =$ $J_{7,8} = 5.6$ Hz)	3.69 (dd) ($J_{8,7} = 5.6$ Hz, $J_{8,8a} = 3.6$ Hz)	3.04 (ddd) ($J_{8a,1a} = 6.0$ Hz, $J_{8a,1b} = 12.0$ Hz)
3d	δ 4.45–4.50 (narrow multiplet)	2.9–3.05 (narrow multiplet)	3.08–3.25 (m)	3.74–3.85 (narrow multiplet) ($W_H = 3.0$ Hz)			3.08–3.25 (m)

FIGURE 4. Conformations of **3a–d**.TABLE 2. IC_{50} Values for Compounds **3a–d**^a

enzyme	IC_{50} (mM)			
	3a	3b	3c	3d
α -galactosidase (almond)	NI	9.76	3.93	4.6
β -galactosidase (bovine)	16.53	6.45	ND	4.26
α -mannosidase (Jack bean)	20.00	36.23	4.28	NI
α -glucosidase (yeast)	28.56	NI	8.48	10.97
β -glucosidase (almond)	3.71	2.96	4.59	7.94

^a NI = inhibition not observed under assay conditions. ND = not determined. Data are the average of three sets of assay performed.

molecular hydrogen bonding in a six-membered transition state as shown in Figure 4.¹⁵ It may be noted that conversion of conformation (C) to (B) should give the N–C3 bond *axial*; however, this bond would attain the more stable equatorial geometry due to the nitrogen lone pair flipping that further assists in releasing the 1,3-diaxial interaction of the N–C3 bond with C6 and C8–OH.

Glycosidase Inhibitory Study. The castanospermine **2** is a potent but nonselective inhibitor of many glycohydrolases including the intestinal disaccharidases.¹⁶ The castanospermine analogues **3a–d** thus obtained were tested for inhibitory activity against glycosidases, namely α -galactosidase (E.C. 3.2.1.22), β -galactosidase (E.C. 3.2.1.23), α -mannosidase (E.C. 3.2.1.24), α -glucosidase (E.C. 3.2.1.20), and β -glucosidase (E.C. 3.2.1.21). All the compounds showed inhibition in micromolar ranges and the results obtained are summarized in Table 2. The inhibitory profile of **3a–d** also corroborates the nonselective nature of inhibition as in the case of castanospermine **2**.

(15) Such types of 5C_8 conformations for other isomers of castanospermine are also known, see: Hendry D.; Hough, L.; Richardson, A. C. *Tetrahedron* **1988**, *44*, 6153–6168.

(16) Rhinehart, B. L.; Robinson, K. M.; King, C. H.; Liu, P. S. *Biochem. Pharmacol.* **1990**, *39*, 1537–1543.

Conclusions

In summary, the 1,3-DC of D-glucose-derived nitrone **4** with allyl alcohol followed by tosylation afforded tosyloxylated isoxazolidines **5a–d** with complete regioselectivity in high yield. The utility **5a–d** was demonstrated in the synthesis of 2-hydroxy-1-deoxycastanospermine analogues **3a–d**. The conformational study of **3a–d** indicated that the C2–OH functionality has no effect on conformational preference as **3a/3b** attains 8C_5 while **3c/d** have 5C_8 conformations analogous to 1-deoxycastanospermine and 1-deoxy-8a-*epi*-castanospermine, respectively. The glycosidase inhibitory study showed that compound **3b** is more potent toward β -glucosidase.

Experimental Section

1,2-O-Isopropylidene-3-O-benzyl-4R-[(3'R,5'S)-N-benzyl-5'-tosyloxymethyl-3'-isoxazolidinyl]- α -L-threo-1,4-furanose (5a), 1,2-O-Isopropylidene-3-O-benzyl-4R-[(3'R,5'R)-N-benzyl-5'-tosyloxymethyl-3'-isoxazolidinyl]- α -L-threo-1,4-furanose (5b), 1,2-O-Isopropylidene-3-O-benzyl-4R-[(3'S,5'R)-N-benzyl-5'-tosyloxymethyl-3'-isoxazolidinyl]- α -L-threo-1,4-furanose (5c), and 1,2-O-Isopropylidene-3-O-benzyl-4R-[(3'S,5'S)-N-benzyl-5'-tosyloxymethyl-3'-isoxazolidinyl]- α -L-threo-1,4-furanose (5d). Nitron **4** (2.0 g, 5.2 mmol), allyl alcohol (3.5 g, 52.0 mmol), and acetone (10 mL) were refluxed at 70 °C for 48 h. The solvent was removed under reduced pressure and purification by column chromatography with *n*-hexane/ethyl acetate 70/30 afforded the mixture of cycloadducts as a thick liquid (2.2 g, 95%). To a mixture of cycloadducts (2.0 g, 4.5 mmol) in dry pyridine (5 mL) cooled at 0 °C was added *p*-toluenesulfonyl chloride (1.03 g, 5.4 mmol), then the mixture was stirred at room temperature for 4 h. Quenching with cold water followed by the usual workup and extraction with ethyl acetate (3 \times 30 mL) afforded a thick oil. Separation by flash column chromatography and elution first with *n*-hexane/ethyl acetate (95/5) gave **5a** (1.31 g, 49%) as a white solid; mp 119–120 °C; R_f 0.57 (*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D +8.0$ (c 0.25, CHCl_3); IR (Nujol) 1595, 1495, 1358 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.28 (s, 3H), 1.44 (s, 3H), 2.11–2.24 (m, 1H), 2.46 (s, 3H), 2.60 (dt, $J = 13.3$, 8.4 Hz, 1H), 3.68–3.80 (m, 1H), 3.76 (d, $J = 13.5$ Hz, 1H), 3.94 (d, $J = 13.5$ Hz, 1H), 4.00–4.12 (m, 3H), 4.15 (dd, $J = 10.2$, 3.9 Hz, 1H), 4.33 (d, $J = 12.0$ Hz, 1H), 4.44–4.58 (m, 1H), 4.55 (d, $J = 12.0$ Hz, 1H), 4.58 (d, $J = 3.9$ Hz, 1H), 5.87 (d, $J = 3.9$ Hz, 1H), 7.20–7.42 (m, 12H), 7.81 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.6, 26.2, 26.7, 33.5, 60.7, 62.4, 70.2, 71.7, 74.3, 81.2, 81.7, 82.0, 104.8, 111.7, 127.4, 127.5, 127.8, 128.0 (s), 128.3 (s), 128.4 (s), 129.8 (s), 132.6, 137.0, 137.3, 144.8. Anal. Calcd for $\text{C}_{32}\text{H}_{37}\text{NO}_8\text{S}$: C, 64.52; H, 6.26. Found: C, 64.68; H, 6.38. Further elution with *n*-hexane/ethyl acetate (95/5) afforded **5b** (0.19 g, 7%) as a thick liquid; R_f 0.54

(*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D +6.6$ (*c* 0.30, CHCl_3); IR (Neat) 1590, 1445, 1355 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.28 (s, 3H), 1.44 (s, 3H), 2.37 (ddd, $J = 12.9, 8.7, 8.4$ Hz, 1H), 2.43 (s, 3H), 2.55 (ddd, $J = 12.9, 8.8, 1.7$ Hz, 1H), 3.71–3.82 (m, 1H), 3.81 (d, $J = 13.7$ Hz, 1H), 3.89 (d, $J = 13.7$ Hz, 1H), 4.0–4.17 (m, 4H), 4.30 (d, $J = 11.5$ Hz, 1H), 4.25–4.37 (m, 1H), 4.52 (d, $J = 11.5$ Hz, 1H), 4.56 (d, $J = 3.9$ Hz, 1H), 5.86 (d, $J = 3.9$ Hz, 1H), 7.15–7.34 (m, 12H), 7.75 (d, $J = 8.5$ Hz, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 21.7, 26.2, 26.8, 32.2, 62.3, 62.8, 68.9, 71.9, 77.2, 79.0, 81.6, 82.1, 104.9, 111.9, 127.8 (s), 128.0 (s), 128.4 (s), 128.5 (s), 129.6 (s), 129.9 (s), 132.4, 137.1, 145.1. Anal. Calcd for $\text{C}_{32}\text{H}_{37}\text{NO}_5$: C, 64.52; H, 6.26. Found: C, 64.70; H, 6.42. Next elution with *n*-hexane/ethyl acetate (90/10) afforded **5c** (0.47 g, 17%) as a thick liquid; R_f 0.50 (*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D -10.6$ (*c* 1.5, CHCl_3); IR (Neat) 1588, 1450, 1360 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.32 (s, 3H), 1.47 (s, 3H), 2.33 (ddd, $J = 9.3, 5.1, 1.8$ Hz, 1H), 2.45 (s, 3H), 2.59 (ddd, $J = 9.3, 9.0, 1.8$ Hz, 1H), 3.75–3.78 (m, 1H), 3.78 (d, $J = 13.5$ Hz, 1H), 3.91 (d, $J = 13.5$ Hz, 1H), 4.16 (d, $J = 3.0$ Hz, 1H), 4.10–4.17 (m, 3H), 4.29–4.38 (m, 1H), 4.32 (d, $J = 11.7$ Hz, 1H), 4.55 (d, $J = 11.7$ Hz, 1H), 4.59 (d, $J = 3.9$ Hz, 1H), 5.90 (d, $J = 3.9$ Hz, 1H), 7.20–7.38 (m, 12H), 7.81 (d, $J = 8.5$ Hz, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 21.6, 26.1, 26.7, 32.1, 62.5, 62.7, 69.5, 71.7, 76.2, 79.5, 81.5, 81.9, 104.8, 111.6, 127.2, 127.5 (s), 127.8, 127.9 (s), 128.2 (s), 128.4 (s), 128.9 (s), 129.8 (s), 132.5, 137.2, 137.2, 144.9. Anal. Calcd for $\text{C}_{32}\text{H}_{37}\text{NO}_5$: C, 64.52; H, 6.26. Found: C, 64.60; H, 6.48. Further elution with *n*-hexane/ethyl acetate (85/15) afforded **5d** (0.37 g, 14%) as a white solid; mp 133–134 °C; R_f 0.42 (*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D -110.0$ (*c* 1.0, CHCl_3); IR (Nujol) 1598, 1454, 1365 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.36 (s, 3H), 1.53 (s, 3H), 1.93 (dt, $J = 12.3, 8.7$ Hz, 1H), 2.04–2.15 (m, 1H), 2.46 (s, 3H), 3.24 (dd, apparent quartet $J = 8.7$ Hz, 1H), 3.67 (d, $J = 14.4$ Hz, 1H), 3.90 (d, $J = 3.0$ Hz, 1H), 3.96 (d, $J = 4.5$ Hz, 2H), 4.09–4.19 (m, 1H), 4.22 (dd, $J = 8.7, 3.0$ Hz, 1H), 4.47 (d, $J = 11.7$ Hz, 1H), 4.53 (d, $J = 14.4$ Hz, 1H), 4.65 (d, $J = 3.9$ Hz, 1H), 4.74 (d, $J = 11.7$ Hz, 1H), 6.01 (d, $J = 3.9$ Hz, 1H), 7.20–7.54 (m, 12H), 7.80 (d, $J = 8.1$ Hz, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 21.5, 26.2, 26.6, 34.0, 61.8, 63.8, 69.6, 71.6, 73.1, 80.9, 81.6, 82.5, 104.4, 111.7, 126.8, 127.9 (s), 128.0 (s), 128.3 (s), 128.3, 128.7 (s), 129.0 (s), 129.8 (s), 132.6, 136.6, 137.9, 144.8. Anal. Calcd for $\text{C}_{32}\text{H}_{37}\text{NO}_5$: C, 64.52; H, 6.26. Found: C, 64.78; H, 6.50.

General Procedure for the Conversion of 5 to 6. Zinc dust (0.30 g, 4.6 mmol) was added to a solution of copper(II) acetate (0.01 g, 0.007 mmol) in glacial acetic acid (1 mL) under nitrogen atmosphere and the mixture was stirred at room temperature for 10 min until the color disappeared. Compound **5** (0.50 g, 0.93 mmol) in glacial acetic acid (0.7 mL) and water (0.3 mL) was successively added and the reaction mixture was heated at 70 °C for 1 h. On cooling to room temperature, sodium salt of EDTA (0.1 g) was added and the mixture was stirred for 10 min and then made alkaline to pH 10 by addition of 3 N NaOH. The resulting solution was extracted with chloroform (3 × 10 mL) and the combined organic layer was evaporated under reduced pressure.

5,6,8-Trideoxy-5,8-(*N*-benzylimino)-1,2-*O*-isopropylidene-3-*O*-benzyl-7(*S*)-hydroxy- α -*D*-glycero-*D*-gluco-oct-1,4-furanose (6a). Purification by column chromatography (*n*-hexane/ethyl acetate = 70/30) afforded **6a** (0.29 g, 81%) as a thick oil; R_f 0.58 (ethyl acetate); $[\alpha]_D -17.8$ (*c* 0.41, CHCl_3); IR (Neat) 3540–3200, 1632, 1458 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, $\text{CDCl}_3 + \text{D}_2\text{O}$) δ 1.38 (s, 3H), 1.55 (s, 3H), 2.00–2.12 (m, 1H), 2.30 (dt, $J = 13.5, 6.3$ Hz, 1H), 2.50 (dd, $J = 10.5, 3.9$ Hz, 1H), 3.14 (d, $J = 10.5, 5.4$ Hz, 1H), 3.57 (ddd, apparent quartet $J = 6.6, 6.3$ Hz, 1H), 3.71 (d, $J = 13.2$ Hz, 1H), 4.01 (d, $J = 3.3$ Hz, 1H), 4.03 (d, $J = 13.2$ Hz, 1H), 4.16 (dd, $J = 6.0, 3.3$ Hz, 1H), 4.36–4.44 (m, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.65 (d, $J = 3.3$ Hz, 1H), 4.68 (d, $J = 12.0$ Hz, 1H), 5.94 (d, $J = 3.3$ Hz, 1H), 7.21–7.42 (m, 10H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 26.2, 26.7, 38.0, 59.7, 60.6, 61.1, 70.6, 71.4, 81.6, 82.0, 82.2, 104.6, 111.5, 127.0, 127.6 (s), 127.9, 128.3 (s), 128.4 (s), 128.7 (s),

137.1, 138.7. Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_5$: C, 70.57; H, 7.34. Found: C, 70.62; H, 7.39.

5,6,8-Trideoxy-5,8-(*N*-benzylimino)-1,2-*O*-isopropylidene-3-*O*-benzyl-7(*R*)-hydroxy- α -*L*-glycero-*D*-gluco-oct-1,4-furanose (6b). Purification by column chromatography (*n*-hexane/ethyl acetate = 70/30) afforded **6b** (0.30 g, 84%) as a white solid; mp 93–94 °C; R_f 0.60 (ethyl acetate); $[\alpha]_D -40.0$ (*c* 0.25, CHCl_3); IR (Nujol) 3550–3200, 1612, 1454 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, $\text{CDCl}_3 + \text{D}_2\text{O}$) δ 1.35 (s, 3H), 1.44 (s, 3H), 2.19–2.38 (m, 2H), 2.39 (dd, $J = 10.2, 3.6$ Hz, 1H), 3.01 (d, $J = 10.2$ Hz, 1H), 3.08–3.12 (m, 1H), 3.60 (d, $J = 13.2$ Hz, 1H), 3.87 (d, $J = 3.3$ Hz, 1H), 3.94 (d, $J = 13.2$ Hz, 1H), 4.12–4.20 (m, 1H), 4.25 (t, $J = 3.3$ Hz, 1H), 4.46 (d, $J = 12.0$ Hz, 1H), 4.62 (d, $J = 3.9$ Hz, 1H), 4.69 (d, $J = 12.0$ Hz, 1H), 6.00 (d, $J = 3.9$ Hz, 1H), 7.20–7.32 (m, 10H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 26.4, 26.9, 36.2, 58.8, 61.0, 61.8, 70.6, 71.5, 81.5, 82.3 (s), 104.7, 111.8, 127.0, 127.3 (s), 127.8, 128.3 (s), 128.4 (s), 128.8 (s), 137.3, 138.8. Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_5$: C, 70.57; H, 7.34. Found: C, 70.71; H, 7.30.

5,6,8-Trideoxy-5,8-(*N*-benzylimino)-1,2-*O*-isopropylidene-7(*R*)-hydroxy- β -*L*-glycero-*L*-ido-oct-1,4-furanose (6c). Purification by column chromatography (*n*-hexane/ethyl acetate = 60/40) afforded **6c** (0.28 g, 79%) as a thick liquid; R_f 0.34 (ethyl acetate); $[\alpha]_D -80.0$ (*c* 0.27, CHCl_3); IR (neat) 3550–3200, 1618, 1450 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.34 (s, 3H), 1.55 (s, 3H), 1.60–1.82 (m, 2H), 2.38 (dd, $J = 10.7, 4.6$ Hz, 1H), 2.66 (br s, exchanges with D_2O , 1H), 3.29 (dd, $J = 10.7, 5.8$ Hz, 1H), 3.44 (ddd, apparent quartet, $J = 8.5$ Hz, 1H), 3.60 (d, $J = 13.2$ Hz, 1H), 3.88 (d, $J = 3.0$ Hz, 1H), 4.28–4.42 (m, 2H), 4.46 (d, $J = 11.5$ Hz, 1H), 4.54 (d, $J = 13.2$ Hz, 1H), 4.61 (d, $J = 3.9$ Hz, 1H), 4.69 (d, $J = 11.7$ Hz, 1H), 6.03 (d, $J = 3.9$ Hz, 1H), 7.20–7.41 (m, 10H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 26.3, 26.6, 37.2, 59.1, 61.0, 61.5, 69.0, 71.7, 80.8, 83.1, 83.5, 105.4, 111.6, 127.3, 127.8 (s), 128.0, 128.2 (s), 128.4 (s), 129.8 (s), 137.0. Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_5$: C, 70.57; H, 7.34. Found: C, 70.82; H, 7.52.

5,6,8-Trideoxy-5,8-(*N*-benzylimino)-1,2-*O*-isopropylidene-7(*S*)-hydroxy- β -*D*-glycero-*L*-ido-oct-1,4-furanose (6d). Purification by column chromatography (*n*-hexane/ethyl acetate = 65/35) afforded **6d** (0.29 g, 82%) as a thick liquid; R_f 0.44 (ethyl acetate); $[\alpha]_D -48.5$ (*c* 0.70, CHCl_3); IR (Neat) 3600–3200, 1628, 1454 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.37 (s, 3H), 1.40–1.55 (m, 1H), 1.57 (s, 3H), 2.23–2.38 (m, 2H), 2.47 (br s, exchanges with D_2O , 1H), 2.88 (d, $J = 10.2$ Hz, 1H), 2.98 (ddd, apparent quartet, $J = 8.5$ Hz, 1H), 3.37 (d, $J = 13.5$ Hz, 1H), 3.96 (d, $J = 3.0$ Hz, 1H), 4.08–4.18 (m, 1H), 4.34 (dd, $J = 8.7, 3.0$ Hz, 1H), 4.48 (d, $J = 11.7$ Hz, 1H), 4.58 (d, $J = 13.5$ Hz, 1H), 4.63 (d, $J = 3.9$ Hz, 1H), 4.72 (d, $J = 11.7$ Hz, 1H), 6.05 (d, $J = 3.9$ Hz, 1H), 7.15–7.50 (m, 10H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 26.3, 26.7, 38.3, 58.7, 60.9, 62.4, 69.9, 71.7, 80.9, 83.6, 85.5, 105.5, 111.5, 126.7, 127.9 (s), 128.0 (s), 128.5 (s), 129.2 (s), 137.0, 138.9. Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_5$: C, 70.57; H, 7.34. Found: C, 70.67; H, 7.42.

5,6,8-Trideoxy-5,8-(*N*-benzylimino)-1,2-*O*-isopropylidene- α -*D*-gluco-oct-1,4-furan-7-olose (7a). To a solution of oxalyl chloride (0.033 g, 0.26 mmol) in CH_2Cl_2 (1 mL) at –78 °C was added DMSO (0.04 g, 0.51 mmol) and the mixture was stirred for 15 min, a solution of alcohol **6a/6b** (0.1 g, 0.23 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was stirred at –78 °C for an additional 1 h. Triethylamine (0.12 g, 1.1 mmol) was added, and the mixture was allowed to warm to room temperature. The usual workup followed by purification by column chromatography (*n*-hexane/ethyl acetate = 90/10) afforded **7a** (0.07 g, 70%) as a thick liquid; R_f 0.70 (*n*-hexane/ethyl acetate = 5/5); $[\alpha]_D -26.6$ (*c* 0.30, CHCl_3); IR (Neat) 1749, 1654 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.35 (s, 3H), 1.55 (s, 3H), 2.58 (dd, $J = 19.0, 7.5$ Hz, 1H), 2.80 (dd, $J = 19.0, 7.0$ Hz, 1H), 2.83 (d, $J = 17.4$ Hz, 1H), 3.31 (d, $J = 17.4$ Hz, 1H), 3.51–3.58 (m, 1H), 3.52 (d, $J = 13.8$ Hz, 1H), 4.04 (d, $J = 3.3$ Hz, 1H), 4.08 (d, $J = 13.8$ Hz, 1H), 4.47 (d, $J = 11.8$ Hz, 1H), 4.47–4.52 (m, 1H), 4.67 (d, $J = 3.8$ Hz, 1H), 4.73 (d, $J = 11.8$ Hz, 1H), 5.97 (d, $J = 3.8$ Hz, 1H), 7.20–7.50 (m, 10 H); ^{13}C

NMR (75 MHz, CDCl₃) δ 26.2, 26.8, 40.3, 58.6, 59.6, 60.6, 71.6, 79.6, 81.7, 82.6, 104.7, 111.6, 127.3, 127.6 (s), 128.0, 128.4 (s), 128.6 (s), 137.0, 137.9, 214.6. Anal. Calcd for C₂₅H₂₉NO₅: C, 70.90; H, 6.90. Found: C, 71.01; H, 6.72.

5,6,8-Trideoxy-5,8-(*N*-benzoylimino)-1,2-*O*-isopropylidene- β -*L*-ido-oct-1,4-furan-7-ulose (7b). The reaction of oxalyl chloride (0.026 g, 0.20 mmol), DMSO (0.032 g, 0.41 mmol), alcohol **6c/6d** (0.08 g, 0.18 mmol), and triethylamine (0.09 g, 0.9 mmol) in CH₂Cl₂ (2 mL) was performed under the same conditions as mentioned for **7a**. Purification by column chromatography (*n*-hexane/ethyl acetate = 90/10) afforded **7b** (0.058 g, 74%) as a white solid; mp 129–130 °C; *R*_f 0.64 (*n*-hexane/ethyl acetate = 1/1); [α]_D –123.0 (*c* 0.32, CHCl₃); IR (Nujol) 1745, 1650 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.38 (s, 3H), 1.57 (s, 3H), 2.15 (dd, *J* = 18.0, 10.5 Hz, 1H), 2.41 (dd, *J* = 18.0, 6.6 Hz, 1H), 2.72 (d, *J* = 18.0 Hz, 1H), 3.28 (d, *J* = 18.0 Hz, 1H), 3.35–3.47 (m, 1H), 3.46 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 2.7 Hz, 1H), 4.37 (dd, *J* = 7.8, 2.7 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.65 (d, *J* = 3.9 Hz, 1H), 4.69 (d, *J* = 13.2 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 6.07 (d, *J* = 3.9 Hz, 1H), 7.20–7.48 (m, 10 H); ¹³C NMR (75 MHz, CDCl₃) δ 26.4, 26.8, 40.6, 59.3, 60.5, 61.8, 71.8, 80.6, 83.4, 84.5, 105.6, 111.8, 127.1, 128.0 (s), 128.4 (s), 128.7 (s), 129.0, 136.8, 138.3, 212.6. Anal. Calcd for C₂₅H₂₉NO₅: C, 70.90; H, 6.89. Found: C, 70.98; H, 7.04.

General Procedure for the Conversion of 5 to 8. A solution of compound **5** (0.30 g, 0.50 mmol), 10% Pd/C (0.075 g), and ammonium formate (0.19 g, 3.0 mmol) in methanol (4 mL) was refluxed for 1 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to give a thick oil. To a solution of amino alcohol (0.12 g, 0.50 mmol) in methanol–water (10 mL, 9:1) cooled to 0 °C was added benzylchloroformate (0.1 g, 0.60 mmol) and sodium bicarbonate (0.126 g, 1.5 mmol) and the solution was stirred for 2.5 h. Methanol was evaporated under reduced pressure and the aqueous layer was extracted with chloroform (3 × 15 mL). After the usual workup the chloroform layer was evaporated under reduced pressure.

5,6,8-Trideoxy-5,8-(*N*-benzoxycarbonylimino)-1,2-*O*-isopropylidene-7(*S*)-hydroxy- α -*D*-glycero-*D*-gluco-oct-1,4-furanose (8a). Purification by column chromatography (*n*-hexane/ethyl acetate = 80/20) gave **8a** (0.137 g, 72% overall) as a white solid; mp 115–116 °C; *R*_f 0.62 (ethyl acetate); [α]_D +64.0 (*c* 0.25, CHCl₃); IR (Nujol) 3600–3250, 1670, 1427 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + D₂O) δ 1.38 (s, 3H), 1.47 (s, 3H), 2.21 (ddd, *J* = 13.8, 7.8, 6.0 Hz, 1H), 2.35 (dt, *J* = 13.8, 4.8 Hz, 1H), 3.50 (dd, *J* = 11.9, 5.1 Hz, 1H), 3.69 (dd, *J* = 11.9, 2.7 Hz, 1H), 3.76 (dd, *J* = 9.9, 2.1 Hz, 1H), 4.07 (d, *J* = 2.1 Hz, 1H), 4.33 (ddd, *J* = 9.9, 7.8, 6.0 Hz, 1H), 4.47–4.58 (m, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 5.17 (ABq, *J* = 12.3 Hz, 2H), 5.91 (d, *J* = 3.6 Hz, 1H), 7.32–7.42 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 25.9, 26.7, 38.3, 53.8, 54.4, 67.8, 69.5, 73.7, 83.0, 84.9, 104.5, 111.4, 128.0 (s), 128.3, 128.6 (s), 135.8, 157.1. Anal. Calcd for C₁₉H₂₅NO₇: C, 60.15; H, 6.64. Found: C, 60.30; H, 6.82.

5,6,8-Trideoxy-5,8-(*N*-benzoxycarbonylimino)-1,2-*O*-isopropylidene-7(*R*)-hydroxy- α -*L*-glycero-*D*-gluco-oct-1,4-furanose (8b). Purification by column chromatography (*n*-hexane/ethyl acetate = 80/20) afforded **8b** (0.143 g, 75%) as a thick liquid; *R*_f 0.67 (ethyl acetate); [α]_D +40.0 (*c* 0.40, CHCl₃); IR (Neat) 3600–3200, 1674, 1421, 1346 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + D₂O) δ 1.26 (s, 3H), 1.50 (s, 3H), 2.14 (ddd, *J* = 13.9, 8.4, 4.7 Hz, 1H), 2.36 (d, *J* = 13.9 Hz, 1H), 3.49 (d, *J* = 12.3 Hz, 1H), 3.67 (dd, *J* = 12.3, 3.9 Hz, 1H), 4.12 (d, *J* = 2.1 Hz, 1H), 4.23 (dd, *J* = 9.9, 8.4 Hz, 1H), 4.42 (dd, *J* = 9.9, 2.1 Hz, 1H), 4.54 (dd, *J* = 4.7, 3.9 Hz, 1H), 4.62 (d, *J* = 3.9 Hz, 1H), 5.16 (s, 2H), 5.91 (d, *J* = 3.9 Hz, 1H), 7.25–7.44 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 26.2, 26.6, 36.7, 54.8, 55.6, 67.6, 70.5, 73.6, 81.9, 85.1, 104.3, 111.5, 127.9 (s), 128.2, 128.5 (s), 135.9, 156.7. Anal. Calcd for C₁₉H₂₅NO₇: C, 60.15; H, 6.64. Found: C, 60.24; H, 6.78.

5,6,8-Trideoxy-5,8-(*N*-benzoxycarbonylimino)-1,2-*O*-isopropylidene-7(*R*)-hydroxy- β -*L*-glycero-*L*-ido-oct-1,4-

furanose (8c). Purification by column chromatography (*n*-hexane/ethyl acetate = 70/30) afforded **8c** (0.135 g, 73%) as a thick liquid; *R*_f 0.54 (ethyl acetate); [α]_D –58.0 (*c* 0.275, CHCl₃); IR (Neat) 3570–3230, 1678, 1438, 1354 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.37 (s, 3H), 1.54 (s, 3H), 2.17–2.25 (m, 2H), 3.00 (br s, exchanges with D₂O, 2H), 3.57 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.76 (br d, *J* = 11.5 Hz, 1H), 4.00–4.12 (m, 1H), 4.41 (d, *J* = 3.0 Hz, 1H), 4.47–4.57 (m, 2H), 4.58–4.70 (m, 1H), 5.20 (ABq, *J* = 12.4 Hz, 2H), 5.96 (d, *J* = 3.9 Hz, 1H), 7.26–7.44 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 26.0, 26.7, 29.3, 54.9, 55.0, 67.6, 69.6, 75.2, 83.4, 85.0, 104.5, 111.3, 127.8 (s), 128.0, 128.4 (s), 136.1, 157.6. Anal. Calcd for C₁₉H₂₅NO₇: C, 60.15; H, 6.64. Found: C, 60.41; H, 6.60.

5,6,8-Trideoxy-5,8-(*N*-benzoxycarbonylimino)-1,2-*O*-isopropylidene-7(*S*)-hydroxy- β -*D*-glycero-*L*-ido-oct-1,4-furanose (8d). Purification by column chromatography (*n*-hexane/ethyl acetate = 60/40) afforded **8d** (0.145 g, 76%) as a white solid; mp 168–169 °C; *R*_f 0.39 (ethyl acetate); [α]_D –96.0 (*c* 0.50, CHCl₃); IR (Nujol) 3550–3200, 1674, 1421, 1346 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + D₂O) δ 1.33 (s, 3H), 1.50 (s, 3H), 2.00 (d, *J* = 14.1 Hz, 1H), 2.45 (ddd, *J* = 14.0, 9.6, 5.8 Hz, 1H), 3.44 (d, *J* = 12.3 Hz, 1H), 3.85 (dd, *J* = 12.3, 6.3 Hz, 1H), 4.23 (d, *J* = 2.0 Hz, 1H), 4.29 (d, *J* = 2.0 Hz, 1H), 4.32–4.42 (m, 2H), 4.54 (d, *J* = 3.3 Hz, 1H), 5.18 (ABq, *J* = 12.3 Hz, 2H), 5.95 (d, *J* = 3.3 Hz, 1H), 7.20–7.40 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 26.2, 26.9, 41.4, 55.6, 57.4, 68.0, 70.0, 74.9, 83.6, 84.8, 104.3, 112.1, 128.0 (s), 128.3, 128.5 (s), 135.8, 157.5. Anal. Calcd for C₁₉H₂₅NO₇: C, 60.15; H, 6.64. Found: C, 60.32; H, 6.78.

General Procedure for the Conversion of 8 to 3. A solution of **8** (0.10 g, 0.26 mmol) in TFA–H₂O (3 mL, 2:1) was stirred at 25 °C for 2.5 h. Trifluoroacetic acid was coevaporated with benzene to furnish a thick liquid. To a solution of the above product in methanol (5 mL) was added 10% Pd/C (0.05 g) and the solution was hydrogenated at 80 psi for 12 h. The catalyst was filtered and washed with methanol and the filtrate was concentrated.

(2*S*,6*S*,7*R*,8*R*,8*aR*)-2,6,7,8-Tetrahydroxyindolizidine (3a). Purification by column chromatography (chloroform/methanol = 80/20) afforded **3a** (0.04 g, 80%) as a white solid; mp 205–207 °C dec; *R*_f 0.40 (chloroform/methanol 1/1); [α]_D +44.4 (*c* 0.21, MeOH); IR (Nujol) 3676–3250 cm⁻¹; ¹H NMR (300 MHz, D₂O) δ 1.79 (ddd, *J* = 14.0, 10.5, 7.3 Hz, 1H), 1.88 (ddd, *J* = 14.0, 6.4, 1.8 Hz, 1H), 2.25 (t, *J* = 11.0 Hz, 1H), 2.28 (dd, *J* = 10.5, 5.0 Hz, 1H), 2.54 (ddd, *J* = 9.3, 7.3, 6.4 Hz, 1H), 3.12 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.14 (t, *J* = 9.3 Hz, 1H), 3.23 (t, *J* = 9.3 Hz, 1H), 3.40 (dd, *J* = 10.5, 6.9 Hz, 1H), 3.51 (ddd, *J* = 11.0, 9.3, 5.4 Hz, 1H), 4.34–4.44 (m, 1H); ¹³C NMR (75 MHz, D₂O) δ 37.7, 54.0, 60.7, 65.0, 68.4, 69.4, 73.3, 77.7. Anal. Calcd for C₈H₁₅NO₄: C, 50.75; H, 7.98. Found: C, 50.89; H, 8.04.

(2*R*,6*S*,7*R*,8*R*,8*aR*)-2,6,7,8-Tetrahydroxyindolizidine (3b). Purification by column chromatography (chloroform/methanol = 75/25) afforded **3b** (0.04 g, 80%) as a thick liquid; *R*_f 0.33 (chloroform/methanol 1/1); [α]_D +40.0 (*c* 0.60, MeOH); IR (Neat) 3429–3230 cm⁻¹; ¹H NMR (300 MHz, D₂O) δ 1.45 (ddd, *J* = 12.9, 8.4, 2.7 Hz, 1H), 2.29 (t, *J* = 11.0 Hz, 1H), 2.45 (ddd, *J* = 9.3, 8.4, 6.3 Hz, 1H), 2.51 (ddd, *J* = 12.9, 6.3, 1.4 Hz, 1H), 2.74 (dd, *J* = 11.5, 6.3 Hz, 1H), 3.03 (br d, *J* = 11.5 Hz, 1H), 3.20 (t, *J* = 9.3 Hz, 1H), 3.24 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.35 (t, *J* = 9.3 Hz, 1H), 3.61 (ddd, *J* = 10.9, 9.3, 5.0 Hz, 1H), 4.38–4.48 (m, 1H); ¹³C NMR (75 MHz, D₂O) δ 37.9, 54.6, 61.4, 66.4, 69.0, 69.9, 74.2, 78.0. Anal. Calcd for C₈H₁₅NO₄: C, 50.75; H, 7.98. Found: C, 50.82; H, 8.12.

(2*R*,6*S*,7*R*,8*R*,8*aS*)-2,6,7,8-Tetrahydroxyindolizidine (3c). Purification by column chromatography (chloroform/methanol = 50/50) afforded **3c** (0.04 g, 80%) as a thick liquid; *R*_f 0.39 (methanol); [α]_D –32.0 (*c* 0.37, MeOH); IR (Neat) 3450–3200 cm⁻¹; ¹H NMR (300 MHz, D₂O) δ 1.66 (ddd, *J* = 13.7, 6.0, 1.4 Hz, 1H), 2.16 (ddd, *J* = 13.7, 12.0, 8.2 Hz, 1H), 2.35 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.65 (dd, *J* = 12.2, 3.3 Hz, 1H), 2.72 (dd, *J* = 12.2, 5.6 Hz, 1H), 3.04 (ddd, *J* = 12.0, 6.0, 3.6 Hz, 1H), 3.34 (dd, *J* = 11.5, 7.1 Hz, 1H), 3.69 (dd, *J* = 5.6, 3.6

Hz, 1H), 3.74 (t, $J = 5.6$ Hz, 1H), 3.82 (dt, $J = 5.6, 3.3$ Hz, 1H), 4.47–4.58 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 33.3, 52.8, 60.6, 62.0, 68.2, 69.2, 69.6, 70.5. Anal. Calcd for $\text{C}_8\text{H}_{15}\text{NO}_4$: C, 50.75; H, 7.98. Found: C, 50.92; H, 8.16.

(2S,6S,7R,8R,8aS)-2,6,7,8-Tetrahydroxyindolizidine (3d). Purification by column chromatography (chloroform/methanol = 30/70) afforded **3d** (0.039 g, 79%) as a thick liquid; R_f 0.18 (methanol); $[\alpha]_D +35.5$ (c 0.45, MeOH); IR (Neat) 3435–3220 cm^{-1} ; ^1H NMR (300 MHz, D_2O) δ 1.34 (dt, $J = 14.2, 4.8$ Hz, 1H), 2.33 (dt, $J = 14.2, 7.5$ Hz, 1H), 2.90–3.06 (m, 2H), 3.08–3.25 (m, 3H), 3.74–3.85 (narrow m, 3H), 4.45–4.50 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 33.1, 53.0, 61.4, 63.2, 67.3, 68.0(s), 68.8. Anal. Calcd for $\text{C}_8\text{H}_{15}\text{NO}_4$: C, 50.75; H, 7.98. Found: C, 50.86; H, 8.08.

General Procedure for 3 to 9. To an ice-cooled solution of **3** (0.03 g, 0.15 mmol) in dry pyridine (0.4 g, 4.4 mmol) was added acetic anhydride (1.0 g, 10.0 mmol) and DMAP (0.0019 g, 0.015 mmol) and the mixture was stirred for 12 h at room temperature. The reaction was decomposed with cold water (2 mL) and extracted with chloroform (3×5 mL). The usual work up afforded a thick oil.

(2S,6S,7R,8R,8aR)-2,6,7,8-Tetraacetoxyindolizidine (9a). Purification by column chromatography (*n*-hexane/ethyl acetate = 80/20) afforded tetraacetate **9a** (0.045 g, 80%) as a white solid; mp 105–106 °C; R_f 0.25 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D +17.1$ (c 1.05, CHCl_3); IR (Nujol) 1732 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.88–2.20 (m, 2H), 2.04 (s, 12H), 2.24 (t, $J = 10.5$ Hz, 1H), 2.32 (dd, $J = 10.0, 4.5$ Hz, 1H), 2.53 (dt, $J = 9.3, 6.3$ Hz, 1H), 3.30 (dd, $J = 10.5, 5.1$ Hz, 1H), 3.60 (dd, $J = 10.0, 6.9$ Hz, 1H), 4.84 (t, $J = 9.3$ Hz, 1H), 5.01 (ddd, $J = 15.0, 9.9, 5.4$ Hz, 1H), 5.09 (t, $J = 9.3$ Hz, 1H), 5.13–5.22 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.7 (s), 20.8, 21.0, 36.5, 51.9, 59.3, 63.2, 70.3, 72.6, 73.4, 74.3, 169.8, 170.0, 170.3, 170.5. Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_8$: C, 53.78; H, 6.49. Found: C, 53.90; H, 6.61.

(2R,6S,7R,8R,8aR)-2,6,7,8-Tetraacetoxyindolizidine (9b). Purification by column chromatography (*n*-hexane/ethyl acetate = 80/20) afforded **9b** (0.045 g, 80%) as a thick liquid; R_f 0.29 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D +13.3$ (c 0.45, CHCl_3); IR (Neat) 1738 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.71 (ddd, $J = 13.8, 9.6, 3.8$ Hz, 1H), 2.02 (s, 6H), 2.03 (s, 3H), 2.06 (s, 3H), 2.11 (t, $J = 10.5$ Hz, 1H), 2.27 (ddd, $J = 9.3, 7.8, 6.6$ Hz, 1H), 2.43 (ddd, $J = 13.8, 7.8, 6.6$ Hz, 1H), 2.56 (dd, $J = 11.0, 6.3$ Hz, 1H), 3.12 (d, $J = 11.0$ Hz, 1H), 3.33 (dd, $J = 10.5, 4.6$ Hz, 1H), 4.98 (t, $J = 9.3$ Hz, 1H), 5.09 (t, $J = 9.3$ Hz, 1H), 5.05–5.18 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.7 (s), 20.8, 21.1, 36.4, 52.1, 59.4, 64.6, 70.3, 72.5, 73.4, 74.6, 169.9, 170.0, 170.4, 171.4. Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_8$: C, 53.78; H, 6.49. Found: C, 53.87; H, 6.52.

(2R,6S,7R,8R,8aS)-2,6,7,8-Tetraacetoxyindolizidine (9c). Purification by column chromatography (*n*-hexane/ethyl acetate = 70/30) afforded **9c** (0.048 g, 86%) as a thick liquid; R_f 0.56 (ethyl acetate); $[\alpha]_D +5.7$ (c 0.70, CHCl_3); IR (Neat) 1730 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.81 (ddd, $J = 13.7, 5.5, 1.1$ Hz, 1H), 2.05 (ddd, $J = 13.7, 11.2, 8.0$ Hz, 1H), 2.07 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 2.21 (dd, $J = 10.5,$

4.3 Hz, 1H), 2.64 (dd, $J = 13.2, 2.5$ Hz, 1H), 2.79 (ddd, $J = 8.0, 5.5, 2.0$ Hz, 1H), 3.23 (br d, $J = 13.2$ Hz, 1H), 3.71 (dd, $J = 10.5, 6.7$ Hz, 1H), 4.94 (dd, $J = 5.0, 3.2$ Hz, 1H), 5.00–5.08 (m, 2H), 4.15–4.24 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.9 (s), 21.1, 21.3, 33.1, 51.9, 58.7, 60.5, 67.0, 67.3, 67.7, 71.2, 168.5, 170.1 (s), 170.6. Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_8$: C, 53.78; H, 6.49. Found: C, 54.00; H, 6.62.

(2S,6S,7R,8R,8aS)-2,6,7,8-Tetraacetoxyindolizidine (9d). Purification by column chromatography (*n*-hexane/ethyl acetate = 70/30) afforded **9d** (0.047 g, 85%) as a thick liquid; R_f 0.28 (*n*-hexane/ethyl acetate 1/1); $[\alpha]_D -5.3$ (c 0.75, CHCl_3); IR (Neat) 1726 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.75 (ddd, $J = 13.2, 11.7, 5.4$ Hz, 1H), 2.07 (s, 3H), 2.12 (s, 3H), 2.19 (s, 3H), 2.21 (s, 3H), 2.29 (ddd, $J = 13.2, 8.4, 5.7$ Hz, 1H), 2.45–2.56 (m, 3H), 3.18 (d, $J = 11.1$ Hz, 1H), 3.20 (dd, $J = 13.5, 1.5$ Hz, 1H), 4.91 (d, $J = 1.5$ Hz, 1H), 4.99 (t, $J = 1.8$ Hz, 1H), 5.03 (t, $J = 2.7$ Hz, 1H), 5.17 (dd, $J = 13.5, 6.0$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.8, 20.8, 21.1, 21.2, 32.8, 51.9, 60.0, 60.1, 67.1, 67.2, 67.8, 71.3, 168.4, 170.0, 170.1, 171.0. Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_8$: C, 53.78; H, 6.49. Found: C, 53.82; H, 6.59.

Procedure for Inhibition Assay. Inhibition potencies of the castanospermine analogues **3a–d** were determined by measuring the residual hydrolytic activities of the glycosidases. The substrates (Purchased from Sigma Chemicals Co. USA.) *p*-nitrophenyl- α -D-glucopyranoside, *p*-nitrophenyl- β -D-glucopyranoside, *p*-nitrophenyl- β -D-galactopyranoside, and *p*-nitrophenyl- α -D-galactopyranoside, of 2 mM concentration, were prepared in 0.025 M citrate buffer with pH 6.0, and *p*-nitrophenyl- α -D-mannopyranoside, of 2 mM concentration, was prepared in 0.025 M citrate buffer with pH 4.0. The test compound (of various concentrations of 0.5 μM to 1 mM) was preincubated with the enzyme, buffered at its optimal pH, for 1 h at 25 °C. The enzyme reaction was initiated by the addition of 100 μL of substrate. Controls were run simultaneously in the absence of test compound. The reaction was terminated at the end of 10 min by the addition of 0.05 M borate buffer (pH 9.8) and absorbance of the liberated *p*-nitrophenol was measured at 405 nm with a Shimadzu Spectrophotometer UV-1601. One unit of glycosidase activity is defined as the amount of enzyme that hydrolyzed 1 μmol of *p*-nitrophenyl pyranoside per minute at 25 °C.

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Supporting Information Available: General experimental methods, crystallographic data for **5a** and **5d**, and copies of ^1H and ^{13}C NMR spectra of compounds **3a–d**, **5a–d**, **6a–d**, **7a,b**, **8a–d**, and **9a–d**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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