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Articles

Intermolecular Michael Addition of Substituted Amines to a Sugar-Derived α,β-Unsaturated Ester: Synthesis of 1-Deoxy-D-*gluco*- and -L-*ido*-homonojirimycin, 1-Deoxy-castanospermine and 1-Deoxy-8a-*epi*-castanospermine

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The synthesis of polyhydroxylated piperidine alkaloids, namely, 1-deoxy-D-g*luco*-homonojirimycin **3a**, 1-deoxy-L-i*do*-homonojirimycin **3b,** and indolizidine alkaloids 1-deoxy-castanospermine **5a** and 1-deoxy-8a-*epi*-castanospermine **5b**, has been achieved. The key step involved is the intermolecular Michael addition of benzylamine to α,β-unsaturated ester **1**, derived from D-*glucose*, which afforded diastereomeric mixture of β-amino esters **6a** and **6b** with D-*gluco*- and L-*ido*- configuration at C5, respectively. Attempts were made to increase and/or alter the diastereoselectivity at the newly generated stereocenter. The high stereoselectivity, in favor of L-*ido*-isomer **6b**, was achieved under kinetically controlled conditions by using lithium *N*-benzyl amide as a Michael donor. The β-amino esters **6a** and **6b** represent common intermediates to target molecules. Thus, LAH reduction of **6a** and **6b**, individually, gave β-amino alcohol **7a** and **7b.** Sequential hydrogenolysis, selective protection of the amino group, followed by hydrolysis of the 1,2-acetonide functionality, and hydrogenation gave **3a** and **3b**, respectively. On the other hand, the β-amino ester **6a** was converted to γ-amino ester **13a** by Arndt−Eistert synthesis, which on hydrogenolysis and treatment with sodium acetate gave γ-lactam **14a**. The LAH reduction afforded pyrrolidene. The *N*-protection−hydrolysis−hydrogenation cascade successfully executed, and 1-deoxy-castanospermine **5a** was obtained in good yield. The same sequence of reactions was applied to β-amino ester **6b**, which afforded 1-deoxy-8a-*epi*-castanospermine **5b**.

Introduction

Among the strategies available for the asymmetric synthesis of β-amino esters, one of the most attractive is the stereoselective intra-[1] or inter-[2] molecular Michael addition of an ammonia equivalent to an α,β-unsaturated ester. In general, these routes make use of chiral amines and achiral α,β-unsaturated esters. However, a limited study is available with chiral Michael acceptors,[2a−d] and to our knowledge the readily accessible α,β-unsaturated

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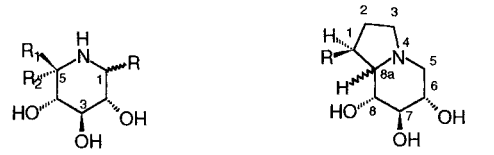


3a R = R_2 = H, R_1 = CH_2CH_2OH
3b R = R_1 = H, R_2 = CH_2CH_2OH
3c R = OH, R_1 = CH_2OH, R_2 = H

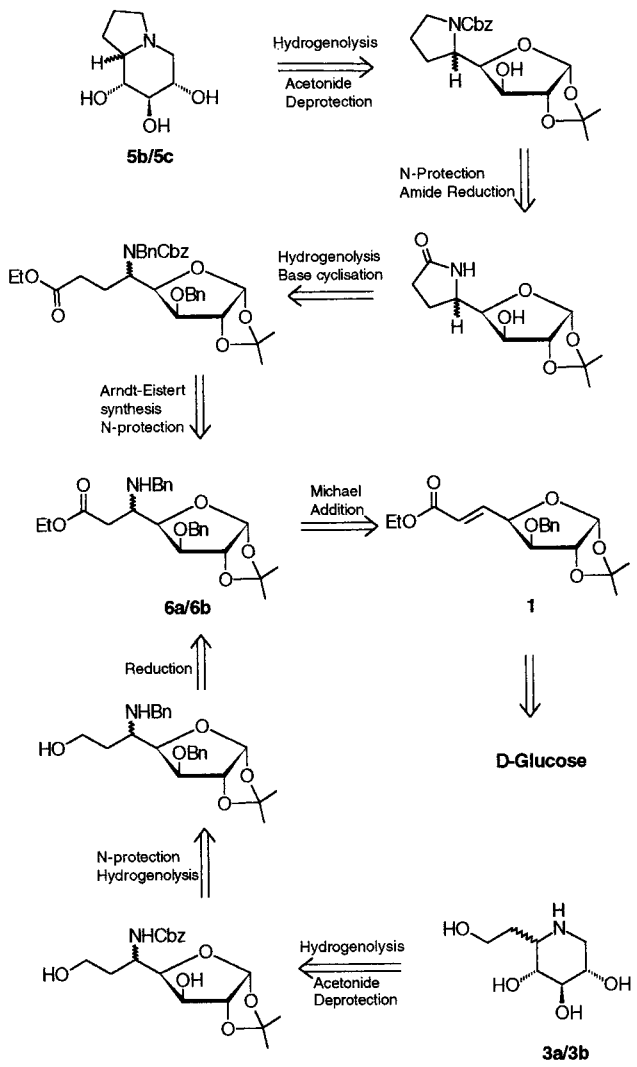
5a R = H, C8a-Hα
5b R = H, C8a-Hβ
5c R = OH, C8a-Hα

Figure 1.

ester **1**, derived from D-*glucose*, has been exploited only by our group.[3a] In this context, we recently reported a highly diastereoselective intramolecular conjugate addition strategy for the synthesis of 1-deoxy-L-*ido*-homonojirimycin (**3b**)[3a] utilizing intermediate **1**. This class of compounds, in particular nojirimycin (**3c**) and castanospermine (**5c**) (Figure 1), has attracted considerable attention because of their promising glycosidase inhibitory activity.[4] In the search for structure−activity relationships, a number of natural and unnatural derivatives of nojirimycin[5] and castanospermine[6] have been synthesized and evaluated for glycosidase inhibition in the treatment of various diseases such as diabetes,[7] cancer,[8] and viral infections, including AIDS.[9] As a part of our continuing interest in the synthesis of nojirimycin analogues,[3] we are now describing an altogether different strategy for the synthesis of homonojirimycin analogues **3a,b**, 1-deoxy-castanospermine (**5a**), and 1-deoxy-8a-*epi*-castanospermine (**5b**) (Figure 1). Although, a few reports are available for the synthesis of **5a**,[10] only a single asymmetric pathway for the synthesis of **5b** has been reported.[11,12]

As shown in the retrosynthetic analysis (Scheme 1),

Scheme 1



the key intermediate in our approach, common to both types of target molecules, is the sugar-based β-amino

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Table 1. Intermolecular Conjugate Addition Reaction of Amines to Sugar-Derived α,β-Unsaturated Esters 1a−d.

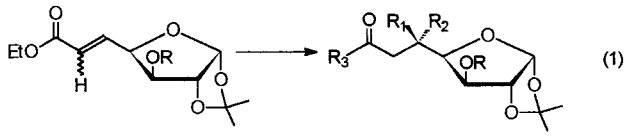
				reaction conditions				
entry	substrate	amine (equiv)	solvent	temp (°C)	time	product	yield[a] (%)	ratio
1	**1a**	$PhCH_2NH_2$ (2.5)		25	12 h	**6a** and **6b**	90	30/70
2	**1a**	$PhCH_2NH_2$ (2.5)	THF	25	3 d	**6a** and **6b**	80	25/75
3	**1a**	$PhCH_2NH_2$ (2.5)	CH_2Cl_2	25	3 d	**6a** and **6b**	82	28/72
4	**1a**	$PhCH_2NH_2$ (2.5)	MeOH	25	3 d	**6a** and **6b**	78	30/70
5	**1a**	$PhCH_2NH_2$ (2.5)		−10	4 d	**6a** and **6b**	70[b]	30/70
6	**1a**	$PhCH_2NH_2$ (1.1)		25	12 h	**6a** and **6b**	65[b]	24/76
7	**1b**	$PhCH_2NH_2$ (2.5)		25	1.5 d	**6a** and **6b**	75	25/75
8	**1b**	$PhCH_2NH_2$ (2.5)	CH_2Cl_2	25	4 d	**6a** and **6b**	76	25/75
9	**1a**+**1b**	Ph_2CHNH_2 (2.5)		25	4 d	no reaction		
10	**1a**+**1b**	Ph_2CHNH_2 (2.5)	THF	25	4 d	no reaction		
11	**1a**+**1b**	$PhCH_2NHLi$ (1.1)	THF	−40	2 h	**6b**	85	0/100
12	**1a**+**1b**	$Ph_2CHNHLi$ (1.1)	THF	−40 to 25	15 h	**6c** or **6d**[c]	30[d]	
13	**1a**+**1b**	$Ph_2CHNHLi$ (2.5)	THF	−40 to 25	15 h	**6c** or **6d**	30[d]	
14	**1c**+**1d**	$PhCH_2NH_2$ (2.5)		25	15 h	**6e** and **6f**	90	20/80
15	**1c**+**1d**	$PhCH_2NH_2$ (1.1)		25	12 h	**6e** and **6f**	59[b]	
						6g	14	
16	**1c**+**1d**	$PhCH_2NH_2$ (2.5)		−5	4 d	**6g**	62	0/100
17	**1d**	$PhCH_2NH_2$ (2.5)		25	12 h	**6e** and **6f**	90	20/80
18	**1c**+**1d**	$PhCH_2NH_2$ (1.1)	THF	25	20 h	**6e** and **6f**	55[b]	20/80
						6g	15	
19	**1c**+**1d**	$PhCH_2NH_2$ (1.1)	CH_2Cl_2	25	18 h	**6e** and **6f**	56[b]	20/80
						6g	13	
20	**1c**+**1d**	$PhCH_2NH_2$ (1.1)	MeOH	25	20 h	**6e** and **6f**	55[b]	20/80
						6g	14	
21	**1d**	$PhCH_2NHLi$ (1.1)	THF	−40	2 h	complex mixture		
22	**1d**	Ph_2CHNH_2 (2.5)		25	4 d	no reaction		

[a] Yields refer to the isolated yields after chromatography. [b] Starting recovered ~20%. [c] Relative stereochemistry was not assigned. [d] Starting recovered ~50%. [e] Relative stereochemistry was tentatively assigned. [f] Stereochemistry was assigned by chemical co-relation.

ester **6** that could be derived from the stereoselective intermolecular Michael addition of substituted amines to α,β-unsaturated ester **1**, derived from D-*glucose*. An attractive feature of this strategy lies in its inherent flexibility. The stereoselectivity at the prochiral β-carbon atom could be controlled either by making use of differentially protected sugar derived α,β-unsaturated esters derived from D-*glucose* or by appropriately substituted amines. Our efforts in the successful implementation of this methodology for the formation of homoazasugars **3a,b** and indolizidine alkaloids **5a,b** are reported herein.

Results and Discussion

Stereoselective Michael Addition of Substituted Amines to Sugar-Derived α,β-Unsaturated Esters. The present synthetic route starts with α,β-unsaturated esters **1a** +**1b**, prepared as we have previously reported.[3a] Having both the *Z* and the *E* isomers in hand, the conjugate addition reaction with a variety of substituted amines was studied (eq 1). As shown in Table 1, the



(1)

1a R = Bn (*Z*)
1b R = Bn (*E*)
1c R = H (*Z*)
1d R = H (*E*)

6a R = Bn, R_1 = NHBn, R_2 = H, R_3 = OEt
6b R = Bn, R_1 = H, R_2 = NHBn, R_3 = OEt
6c R = Bn, R_2 = H, R_1 = R_3 = $NHCHPh_2$
6d R = Bn, R_1 = H, R_2 = R_3 = $NHCHPh_2$
6e R = R_2 = H, R_1 = R_3 = NHBn
6f R = R_1 = H, R_2 = R_3 = NHBn
6g R = R_1 = H, R_2 = NHBn, R_3 = OEt

Michael addition of *N*-benzylamine with **1a** (*Z*-isomer), at 25 °C for 12 h in the absence of solvent, afforded **6a** (D-*gluco*) and **6b** (L-*ido*) in a 3:7 ratio (entry 1). To improve the stereoselectivity at the prochiral C5 center, various reaction conditions (e.g., change of solvent, temperature and stoichiometry of reactants, etc.) were tried. Changing the solvent had no effect on the stereoselectivity (entries 2−4). The reaction at −10 °C for 4 days was sluggish and afforded **6a** and **6b** in poor yield with no significant change in the stereoselectivity (entry 5).

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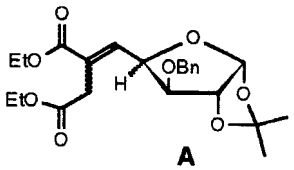
(11) (a) Denis, Y. S.; Chan, T-H. *J. Org. Chem.* **1992**, *57*, 3078. In this paper, Denis and Chan reported the synthesis of **5b** and three other stereoisomers of 1-deoxy-castanospermine wherein the stereochemical assignment using ^{1}H NMR was erroneous. Only recently they have revised the stereochemistry and corrected their assignment, see: Denis, Y. S.; Chan T-H. *Can. J. Chem.* **2000**, *78*, 776. We are thankful to one of the referees for providing this reference.

(12) A report by Martin et al. also claimed the first synthesis of 1-deoxy-8a-*epi*-castanospermine **5b**. However, a subsequent paper from the same group stated that the compound reported was not **5b** but its diastereomer, namely, 1-deoxy-8-*epi*-castanospermine, see: (a) Martin, S. F.; Chen, H.; Yang C−P. *J. Org. Chem.* **1993**, *58*, 2867. (b) Martin, S. F.; Chen, H.; Lynch, V. M. *J. Org. Chem.* **1995**, *60*, 276.

(13) Since only one diastereomer, either **6c** or **6d**, was in hand, we were not able to assign the configuration at C5 on the basis of ^{1}H NMR data.

(14) We have also performed the 1,4 addition reaction of *N*-benzylamine and diphenylmethylamine, in the absence and in the presence of solvent with D-*glucose*-derived α,β-unsaturated ester **A**. The reactions in methanol (rt, 5 days or reflux, 12 h) did not give product.



A

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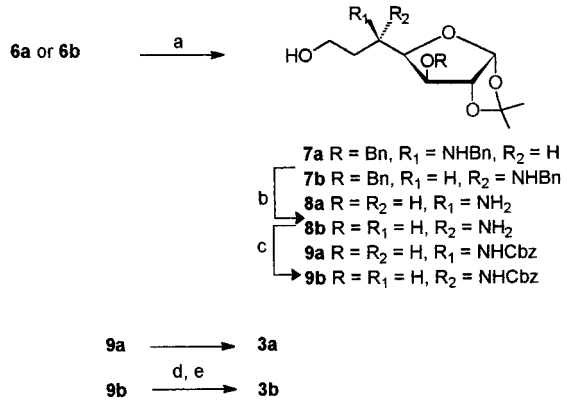
Change in the stoichiometry of the reactants (i.e., decreasing the amine−ester ratio) lowered the combined yield with marginal increase of the diastereomer **6b** (entry 6). To understand the effect of double bond geometry on the stereoselectivity, the reactions were also performed with **1b** (*E*-isomer). Under identical reaction conditions as above, no appreciable change was observed in the stereoselectivity (entries 7 and 8), but the reactions were sluggish as compared to **1a** (*Z*-isomer). These findings led us to make use of the mixture of **1a** and **1b** for further studies.[2b]

The effect of size of the amino substituent was studied in the above reaction using diphenylmethylamine. The reaction of diphenylmethylamine with a mixture of **1a** and **1b** at 25 °C was found to be very slow, and a large amount of the starting material (88%) was recovered, even after 4 days (entry 9). The use of THF as the solvent in the above reaction failed to give the product (entry 10). This study thus precluded the use of other bulky amino derivatives as Michael donors. Subsequently, we thought of using lithium *N*-benzylamide as more nucleophilic Michael donor. The reaction of lithium *N*-benzylamide (1.1 equiv) with a mixture of **1a** and **1b** in THF at −40 °C for 2 h afforded **6b** (L-*ido* isomer) as the only isolable diastereomer in 85% yield (entry 11). On the other hand, lithium diphenylmethyl amide (1.1 equiv) at −40 to 25 °C for 15 h gave either **6c** or **6d** (eq 1) in 30% yield[13] along with the starting material (entry 12). Use of a high molar ratio of lithium diphenylmethyl amide (2.5 equiv) did not provide an appreciable change in the course of the reaction (entry 13).

In an attempt to alter the stereochemistry at C5, we changed the Michael acceptor[14] by replacing the bulky −OBn group at C3 in **1a/1b** with an −OH group. For this, ethyl 1,2-*O*-isopropylidine-5,6-dideoxy-hept-5-eno-furanuranate (**1c**/**1d**) was prepared as per the literature procedure.[15] The reaction of 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdose with $Ph_3P{=}CHCOOEt$ in acetonitrile under reflux for 15 min afforded an inseparable mixture of **1c** and **1d** (*Z*:*E* = 55:45).[16] The same Wittig reaction in acetonitrile (reflux for 2 h) yielded **1d** (*E*-isomer) and its lactone (by cyclization of *Z*-isomer **1c**)[17] in 42% and 40% yield, respectively. The conjugate addition reactions with **1c**/**1d** were then studied. The reaction of *N*-benzylamine (2.5 equiv) with a mixture of **1c** and **1d** at 25 °C for 15 h afforded an inseparable diastereomeric mixture of amides **6e** and **6f** (eq 1) in 90% yield (entry 14), wherein an intermolecular Michael addition and aminolysis of ester functionality had occurred simultaneously. Use of 1.1 equiv of *N*-benzylamine with a mixture of **1c** and **1d** at 25 °C for 12 h afforded the *N*-benzylamides **6e** and **6f** as a major products and the intermolecular Michael addition product **6g** as the minor product (entry 15). Performing the same reaction at −5 °C for 4 days afforded **6g** (L-*ido*-isomer) as the only isolable product in 62% yield (entry 16). Using **1d** as a substrate, the above reaction led to identical results (compare entries 17 and 14). Changing the solvent was less effective (entries 18−20). Using lithium *N*-benzylamide with **1c**/**1d** (at −40 °C) led to a complex mixture of products (entry 21). The reaction of **1c**/**1d** with diphenylmethylamine did not proceed at 25 °C, even after 4 days (entry 22).

Scheme 2[a]

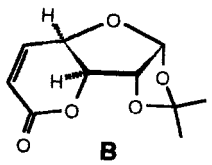


[a] (a) $LiAlH_4$, THF, rt, 2 h; (b) $HCOONH_4$, MeOH, 10%Pd/C, reflux, 2 h; (c) CbzCl, $NaHCO_3$, EtOH−H_2O (1:1), 4 h; (d) TFA−H_2O (3:2), rt, 2 h; (e) 10%Pd/C, H_2, MeOH, 45 psi.

Assignment of the Relative Stereochemistry at C5 of the β-Amino Esters 6a, 6b, and 6g. It was difficult to assign the relative stereochemistry at C5 in **6a** and **6b** at this stage, so the stereochemical assignments were then made in the subsequent stage. The reduction of the ester functionality in **6a** and **6b**, separately, with LAH in THF afforded the β-amino alcohols **7a** and **7b** in 87% and 84% yield, respectively (Scheme 2). The comparative ^1H NMR data of the C5-epimeric pair **7a** and **7b** turned out to be informative. It is known that for a given C5-epimeric pair, derived from D-*gluco*-furanose, the $J_{4,5}$ in the L-*ido* isomer (*threo*-relationship) is consistently larger than that of the corresponding D-*gluco* isomer (*erythro*-relationship).[18] The higher value of $J_{4,5}$ observed in the diastereomer **7b** (9.5 Hz), as compared to **7a** (6.9 Hz) indicated the L-*ido* configuration for **7b** and the D-*gluco* configuration for **7a**. This assignment was further supported by a comparison of the chemical shifts of H3 in both the isomers. The chemical shift of H3 is reported to be diagnostic such that, in the L-*ido*-isomer, it is significantly upfield (δ ∼3.6) as compared to that in the D-*gluco* (δ ∼4.0).[18] In **7b**, H3 appeared upfield at δ 3.86 as compared to **7a** at 4.03 δ, further supporting the D-*gluco*- and L-*ido*- configuration at C5 to **7a** and **7b**, respectively. This fixed the configurations at C5 in **6a** and **6b** as 5*R* and 5*S*, respectively. This assignment was confirmed by the conversion of **6a** and **6b** to compounds of known configuration (vide infra). The configuration at C5 in **6g** was assigned by chemical correlation as follows. The hydrogenolysis of **6b** (L-*ido*-isomer) and **6g**, separately, using 10% Pd/C and ammonium formate in methanol (eq 2) followed by *N*-Cbz

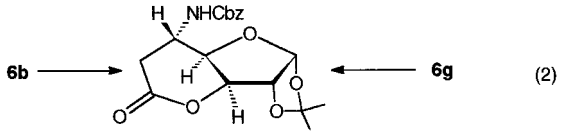
(16) The reaction of 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdose with $Ph_3P{=}CHCOOEt$ in acetonitrile at reflux is reported to yield **1d** (*E*-isomer) as a major product in 86% yield after 2 h (ref 14b). However, we have noticed that the reaction is complete after 15 min.

(17) The analytical and spectral data of lactone **B** was consistent with the reported data, see: Baskaran, S.; Trivedi, G. K. *Ind. J. Chem.* **1994**, *33B*, 562.



B

(18) Cornia, M.; Casiraghi, G. *Tetrahedron* **1989**, *45*, 2869.



protection afforded identical six-membered δ-lactones that were characterized by analytical and spectral methods.[19] Since **6b** and **6g** afforded the same δ-lactone and as **6b** had 5*S* configuration, the same stereochemistry was therefore assigned to compound **6g** (5*S*).

Explanation for the Observed Stereoselectivity in the Michael Addition. The observed stereoselectivity in the conjugate addition to **1a**−**d** could be rationalized in terms of Felkin−Anh like transition states.[20] As shown in Figure 2, four transition states **I**, **II**, **III**, and **IV** were considered for **1a**−**d**. In conformations **I** and **II**, the more electronegative C−O group of the furanose ring, whereas in **III** and **IV** the largest C3-benzyloxy substituent were placed at right angles to the C=C bond. In the Felkin−Anh like model it is known that, the nucleophile should attack from the side opposite to the group perpendicular to the C=C. In the case of **1a,b**, the *re* face attack in conformer **I** (to give D-*gluco*-isomer) and *si* face attack in conformer **II** (to give L-*ido*-isomer) is hindered by the C3-benzyloxy group. Therefore, we considered conformers **III** and **IV**. We presumed that the conformer **III** has the preference over **IV** due to the favorable alkene−arene π-stacking effect[2k] wherein the *si* face attack of the lithium *N*-benzylamide (or *N*-benzylamine), by chelation with furanose ring oxygen, explains the formation of L-*ido*-isomer. In the C3-hydroxy compounds **1c,d**, the alkene−arene π-stacking stabilization effect is absent; therefore, we believe that the furanose C−O bond will adopt the perpendicular position[21] favoring the conformers **I** and **II**. The nucleophilic attack along the Burg−Dunitz trajectory to **I** or **II** would then lead to the product formation, as there is no hindrance in the absence of benzyl group. Although conformer **I** is free from steric interactions, the conformation **II** is likely to be more stabilized through hydrogen bonding of C3−OH with the carbonyl group of carboethoxy functionality (particularly in case of **1c**). The *si* face attack of *N*-benzylamine, which is free from steric hindrance, provides the L-*ido*-isomer in excess.

Synthesis of 1-Deoxy-D-*gluco*-homonojirimycin and 1-Deoxy-L-*ido*-homonojirimycin 3a and 3b. The utility of **6a** and **6b** was initially demonstrated in the formation of the corresponding iminosugars **3a** and **3b**. As shown in Scheme 2, reduction of the ester group in **6a** with LAH in THF afforded alcohol **7a** in 87% yield. Hydrogenolysis of **7a** gave the debenzylated amino

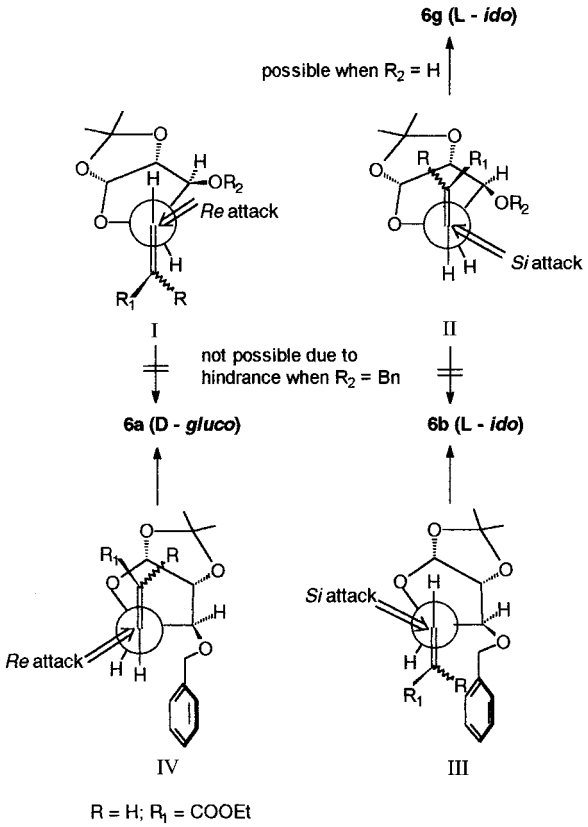


Figure 2. Felkin−Anh like transition states for **1a**−**d**.

alcohol **8a**, and selective protection of the amino group with CbzCl gave **9a** (90% yield in the two steps). Deprotection of the 1,2-acetonide functionality in **9a** with TFA−water followed by hydrogenation afforded 1-deoxy-D-*gluco*-homonojirimycin (**3a**) in 90% yield. The same sequence of reactions with **6b** gave 1-deoxy-L-*ido*-homonojirimycin (**3b**) (72% from **6b**). Compounds **8a,b**, **9a,b**, **3a** and **3b** were characterized by spectral and analytical techniques. The data were found to be in agreement with the corresponding compounds that we have reported earlier.[3d]

Synthesis of 1-Deoxy-castanospermine 5a and 1-Deoxy-8a-*epi*-castanospermine 5b. The positions and the configurations of the hydroxyl groups (at C2, C3, and C4) in **6a** and **6b** were noticed to be identical with those in castanospermine **5c** (at C6, C7, and C8). It was obvious that elaboration of **6a**, with D-*gluco*-configuration at C5, would lead to 1-deoxy-castanospermine (**5a**) and elaboration of **6b**, with L-*ido*-configuration at C5, would give 1-deoxy-8a-*epi*-castanospermine (**5b**).

The protection of amino group in **6a** with CbzCl afforded **10a** in 95% yield[22] (Scheme 3). Hydrolysis of the ester functionality in **10a** with LiOH in aqueous methanol gave the acid **11a** in 96% yield. In the next step, conversion of **11a** to mixed anhydride followed by reaction with diazomethane in ether gave α-diazo ketone **12a** in 69% yield. Wolff rearrangement[23] of **12a** using silver benzoate and Et_3N in methanol afforded the γ-amino

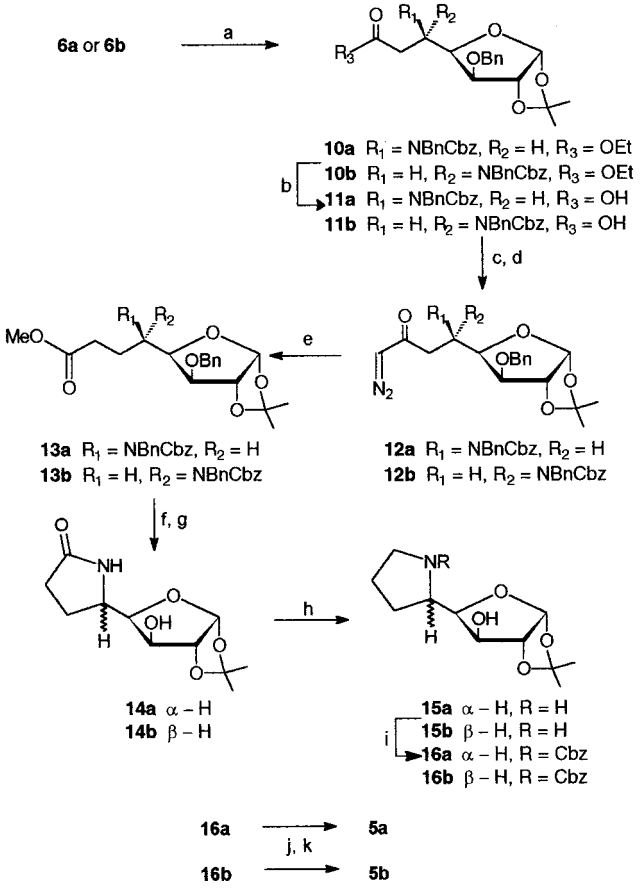
(19) Spectral data for lactone: IR (neat) 3358, 1727 (broad band); ^{1}H NMR ($CDCl_3$, 300 MHz) 1.31 (s, 3H), 1.48 (s, 3H), 1.52−1.80 (bs, 1H, exchanges with D_2O), 2.68 (dd, J = 17.1, 6.6 Hz, 1H), 2.82 (dd, J = 17.1, 5.1 Hz, 1H), 4.10−4.18 (m, 2H), 4.28−4.39 (m, 1H), 4.53 (d, J = 3.5 Hz, 1H), 5.10 (ABq, J = 12.3 Hz, 2H), 5.93 (d, J = 3.5 Hz, 1H), 7.20−7.40 (m, 5H). Anal. Calcd for $C_{18}H_{21}NO_7$: C, 59.49; H, 5.83. Found C, 59.65; H, 5.98.

(20) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2201. (c) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2205. (d) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145.

(21) As per Houck's explanation, the most electronegative group adopts the perpendicular position (C−O bond in our case) and such conformation is stabilized through the mixing of the C=C π* orbital with the lowest energy σ* orbital of a most electronegative substituent, see: Houck, K. N.; Paddon-Row: N. M.; Rondon, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, C. D.; Metz, J. T.; Li, Y. L.; Loncharich, R. J. *Science* **1986**, *231*, 1108.

(22) The ^{1}H and ^{13}C NMR spectra of compounds **10a**, **11a**, **12a**, **13a** and **10b**, **11b**, **12b**, **13b**, in which a *N*-Cbz group is present, showed doubling of signals. This was due to isomerization by restricted rotation around C=N, see: *Applications of NMR Spectroscopy in Organic Chemistry*; Jackman, L. M., Sternhell, S., Eds.; Pergamon Press: Elmsford, NY, 1978; p 361. An analogous observation was also noticed by others (ref 11a).

Scheme 3[a]



[a] (a) CbzCl, $NaHCO_3$, EtOH−H_2O (9:1), rt, 4 h; (b) LiOH, MeOH−H_2O (4:1), rt, 4 h; (c) EtOCOCl, NEt_3, THF, 0 °C, 30 min; (d) CH_2N_2, Et_2O, 0 to 25 °C, 1.5 h; (e) PhCOOAg, NEt_3, MeOH, rt, 1.5 h; (f) 10%Pd/C, H_2, MeOH; (g) CH_3COONa, MeOH, reflux, 4 h; (h) $LiAlH_4$, THF, reflux, 20 h; (i) CbzCl, $NaHCO_3$, EtOH, rt, 1.5 h; (j) TFA−H_2O (3:2), rt, 2 h; (k) 10%Pd/C, H_2, MeOH.

ester **13a** in 85% yield. Next, **13a** was subjected to hydrogenolysis[24] (10% Pd/C in methanol). The product obtained was refluxed with sodium acetate in methanol to give the γ-lactam **14a** in 80% yield.[25] The reduction of the lactam functionality in **14a** with LAH in THF gave the pyrrolidine **15a,** which on reaction with CbzCl gave **16a**. The observed rotation value of **16a** was consistent with the reported value.[10b] The ^{1}H and ^{13}C NMR spectra were also found to be in good agreement with the structure.[26] In subsequent steps, opening of the 1,2-acetonide group followed by hydrogenation and purification by chromatography afforded 1-deoxy-castanospermine (**5a**) as a white solid. The physical and the spectral

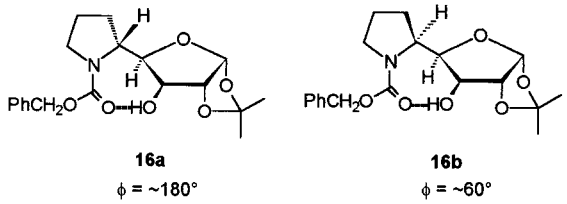


Figure 3.

data as well as the optical rotation for **5a** were consistent with that reported.[10] Synthesis of **5a** thus confirmed our assignment of the relative stereochemistry for compounds **6a** and **6b** as D-*gluco*-and L-*ido*-isomers, respectively.

The reaction sequence was repeated for **6b** as above (Scheme 3). The corresponding C5-epimeric compounds **10b**, **11b**, **12b**, **13b**, and **14b** were isolated and characterized by spectral and analytical data.[22] Subsequently, the lactam functionality in **14b** was reduced with LAH in THF to provide pyrrolidine **15b**, which was converted to the *N*-Cbz protected pyrrolidine compound **16b**. Comparison of the ^{1}H NMR spectra of C5-epimeric compounds **16a** and **16b** led to an interesting observation. In general, the relative configuration at C5, for such types of epimeric compounds, is revealed by $J_{4,5}$, and it is known that, for the given C5-epimeric pair, the $J_{4,5}$ is larger for L-*ido*-isomer than for the corresponding D-*gluco*-isomer[18] (vide supra). However, in the case of **16a** (D-*gluco*) the observed $J_{4,5}$ (10.2 Hz) is larger than the $J_{4,5}$ (3.0 Hz) in **16b**. This finding is opposite to that reported and could be attributed to the possible hydrogen bonding between C3−OH and carbonyl oxygen of *N*-Cbz group by rotation about the C4−C5 bond (Figure 3). In this situation the molecule is held in such a way that, for the hydrogen bonded D-*gluco* isomer **16a**, the dihedral angle between H4 and H5 is ~180° and that for L-*ido* isomer **16b** is ~60° thus resulting in the observed coupling constants. We confirmed the assignment by converting **16a** into the known compound **5a**.

Targeting the synthesis of 1-deoxy- 8a-*epi*-castanospermine (**5b**), compound **16b** was reacted with TFA/H_2O to cleave the 1,2-*O*-isopropylidene functionality, and the product obtained was subjected to hydrogenation. The crude product was purified by chromatography to get **5b** as a semisolid. The rotation and ^{13}C NMR[11,27] data of **5b** was also in accordance with the reported data. However, our ^{1}H NMR data differed from that reported.[28] We have independently characterized the compound **5b**. The comparison of ^{1}H NMR data of **5a** and **5b** is given in Figure 4. In 1-deoxy-castanospermine **5a**, the appearance of two triplets at 3.91 and 3.86 δ (J = 8.6 Hz), one doublet of doublet at 3.43 δ (J = 10.5 and 5.2 Hz), and a triplet at 2.30 δ (J = 10.5 Hz) clearly indicated the *trans*-diaxial relationship between the H5a, H6, H7, H8, and H8a. The large coupling constants indicated the $^8C_5$ conformation

(23) Tilekar, J. N.; Patil, N. T.; Dhavale, D. D. *Synthesis* **2000**, *3*, 395. Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513.

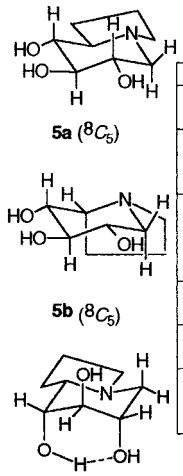
(24) The IR spectrum of the hydrogenolysis product showed two carbonyl frequencies, one at 1735 and the other at 1661 cm^{-1} indicating the presence of open chain *N*- and *O*-debenzylated γ-amino ester and pyrrolidone **14a**.

(25) At this stage, we have made another attempt to convert **13a** into **5a**. Thus, opening of the 1,2-acetonide group in **13a** followed by hydrogenolysis using 10% Pd/C should give the required ring skeleton. However, this approach failed in our hands and led to a complex mixture of products.

(26) In case of compounds **16a,b**, the isomerization by rotation about the formal C=N appears to be sufficiently rapid resulting into an averaged, well resolved spectra. We could not correlate our ^{1}H NMR spectrum, recorded at 298 °K, with the reported one for **16a** that was recorded at 328 °K.

(27) ^{13}C NMR data: (125 MHz, pyridine-d_5) 21.1, 24.5, 54.7, 55.5, 64.6, 70.5, 70.7, 70.9. Reported:[11a] (methanol-d_4) 22.4, 25.9, 56.4, 56.8, 66.6, 71.6, 71.8, 71.9.

(28) ^{1}H NMR data of compound **5b:** ^{1}H NMR (300 MHz, pyridine-d_5 + D_2O)1.72−2.00 (m, 3H), 2.22−2.40 (m, 1H), 2.84−3.00 (m, 1H), 3.44 (bd, J = 12.3 Hz, 1H), 3.49−3.67 (m, 2H), 3.69 (bd, J = 12.3 Hz, 1H), 4.42 (bs, 2H), 4.55 (bs, 1H). Reported:[11] (methanol-d_4) 2.33−2.50 (m, 4H), 3.24 (q, J = 9.4 Hz, 1H), 3.49 (dd, J = 2.0, 12.4 Hz, 1H), 3.62 (t, J = 6.2 Hz, 1H), 3.78 (dd, J = 2.6, 12.4 Hz, 1H), 4.32−4.49 (m, 3H), 4.85 (m, 1H). It may be noted that methanol-d_4 itself shows two signals at 3.31 and δ 4.80, which would obscure the signals due to compound **5b**. In addition, exchange of −OH protons of **5b** with CD_3OD would give HDO, which also shows the signal at δ 4.80.



	5a	5b
H5a	2.30 (t) $J_{5a,5e} = J_{5a,6a} = 10.5$ Hz	3.44 (bd) $J_{5a,5e} = 12.3$ Hz
H5e	3.43 (dd) $J_{5a,5e} = 10.5$ Hz $J_{5e,6a} = 5.2$ Hz	3.69 (bd) $J_{5a,5e} = 12.3$ Hz
H6	4.33 (ddd) $J_{6,5e} = 5.2$ Hz $J_{6,5a} = 10.5$ Hz $J_{6,7} = 8.6$ Hz	4.55 (bs, 1H)
H7	3.91 (t) $J_{6,7} = J_{7,8} = 8.6$ Hz	4.42 (bs, 2H)
H8	3.86 (t) $J_{7,8} = J_{8,8a} = 8.6$ Hz	
H8a	2.94 (dt) $J_{8,8a} = J_{8a,1a} = 8.6$ Hz $J_{8a,1e} = 2.0$ Hz	3.49-3.67 (m, 2H)

Figure 4. The comparison of ^{1}H NMR data of **5a** and **5b**.

for **5a**. However, in the ^{1}H NMR spectra of **5b**, the downfield shift of all the protons, with respect to the corresponding protons in **5a,** indicated the *equatorial* orientation of these protons as opposed to the *axial* orientation in **5a**. The coupling constant $J_{8,8a}$ is important for the determination of the configuration at C8a, while the conformation of **5b** would be determined by the coupling constant values between H5, H6, H7, and H8. The initial geometry in the precursor **16b** ensures that in the product **5b** the substituents at C6, C7 and C7, C8 should be *trans*. The low values for the coupling constants ($W_H \approx 6.0$ Hz) for H6, H7, and H8 indicated that the protons at these carbons are *equatorial*.[29] This suggested the $^5C_8$ conformation for the bicyclic indolizidine **5b**. The small value of $W_H \approx 6$ Hz for H8, along with the *axial* orientation of C8−OH, indicated that the C8a substituent is *equatorial* with the 8a*S* configuration. This observation was supported by two broad doublets at 3.69 and 3.44 δ ($J_{5e,5a} = 12.3$ Hz) corresponding to the protons H5a and H5e. The small $W_H \approx 5$ Hz suggested that H6 is *equatorial* and bisecting the H5 protons (dihedral angle ~55°) thus confirming the $^5C_8$ conformation. From an empirical calculation of the energy difference between the two conformations $^8C_5$ and $^5C_8$ (Figure 4) it is evident that in the $^8C_5$ conformation the 1,3-diaxial interaction between C5−Ha and C8a−C1 and between C7−H and C8a−C1 destabilize this conformation. On the contrary, in the conformation $^5C_8$, both of the 1,3-diaxial interactions (between H and C1-alkyl substituent) are absent and, in addition, the conformation $^5C_8$ is stabilized by the intramolecular hydrogen bonding in the six-member transition state as shown in Figure 4.[30] This explains the preferential orientation of **5b** in $^5C_8$ conformation, which is in agreement with the observed spectra. It may be noted that conversion of $^8C_5$ to $^5C_8$ should give *N*-C3 bond axial, but as a result of nitrogen flipping, this bond would have the more stable equatorial geometry as shown in Figure 4.

(29) In the ^{1}H NMR spectrum of **5b**, recorded with a 500 MHz instrument, the chemical shifts for H7 and H8 were equivalent. In ^{13}C NMR the C6, C7, and C8 carbons appeared in the close vicinity (δ 70.5, 70.7, and 70.9) indicating nearly identical electronic environment for these carbons.

(30) Such type of $^5C_8$ conformations for other isomers of castanospermine are also known, see: Hendry D.; Hough, L.; Richardson, A. C. *Tetrahedron* **1988**, *44*, 6153.

Conclusion

In summary, the intermolecular Michael addition of amines to D-*glucose*-derived α,β-unsaturated ester **1** afforded β-amino ester **6a** (D-*gluco*-isomer) as a minor and **6b** (L-*ido*-isomer) as a major product. The high stereoselectivity in favor of L-*ido*-isomer was achieved under kinetically controlled conditions using lithium-*N*-benzylamide. The utility of sugar β-amino esters **6a** and **6b** was successfully demonstrated in the synthesis of 1-deoxy-D-*gluco*-homonojirimycin (**3a**), 1-deoxy-L-*ido*-homonojirimycin (**3b**), and indolizidine alkaloids 1-deoxy-castanospermine (**5a**) and 1-deoxy-8a-*epi*-castanospermine (**5b**).

Experimental Section

General Methods. Melting points were recorded with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded with FTIR as a thin film or in Nujol mull or with KBr pelletes and are expressed in cm^{-1}. ^{1}H (300, 500 MHz) and ^{13}C (75, 125 MHz) NMR spectra were recorded in $CDCl_3$ as a solvent unless otherwise stated. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard. Elemental analyses were carried out with a C,H-analyzer. Optical rotations were measured using a polarimeter at 25 °C. Thin-layer chromatography was performed on precoated plates (0.25 mm, silica gel 60 F_{254}). Flash chromatography was performed on silica gel (200−400 mesh), and column chromatography was carried out with silica gel (100−200 mesh). Whenever required, the reactions were carried out in oven-dried glassware under dry N_2. Diazomethane and silver benzoate were prepared as per the literature procedure. *N*-Benzylamine and diphenylmethylamines were distilled before use. Diethyl ether, THF, ethyl acetate, dichloromethane, *n*-hexane, and methanol were purified and dried before use. Petroleum ether that was used is a distillation fraction between 40 and 60 °C. *N*-Benzylamine, *n*-BuLi (1.6 M solution in hexane), LAH, CbzCl, 10% Pd/C were purchased from Aldrich and/or Fluka. After work up the organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated at reduced pressure. Ethyl 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-5-eno-heptofuranuranoate **1a,b** and ethyl 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-5-eno-heptofuranuranoate **1c,d** were prepared as per literature procedure.[14] For the experimental detail of the compounds **3a,b**, **8a,b**, **9a,b**, see ref 3d.

General Procedure for Intermolecular Addition of Amines to α,β-Unsaturated Ester 1. In a two-neck round-bottom flask, compound **1** (1.00 mmol) and amine (1.10 or 2.50 mmol) were mixed together in the presence or absence of the solvent under dry N_2. The reaction mixture was stirred at appropriate temperature and time (Table 1). After completion of the reaction, the solvent (if used) was evaporated under reduced pressure (if used), and the residue thus obtained was purified by column/flash chromatography.

Ethyl-3-*O*-benzyl-5-(*N*-benzylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranuronate (6a) and Ethyl-3-*O*-benzyl-5-(*N*-benzylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranuronate (6b). A solution of **1a,b** (1.00 g, 2.87 mmol) and *N*-benzylamine (0.76 g, 7.18 mmol) was stirred at room temperature under N_2. After 24 h the reaction mixture was directly loaded on a flash chromatography column. Elution first with petroleum ether/ethyl acetate 98/2 afforded β-amino ester **6a** (0.35 g, 27%) as a thick liquid: $R_f = 0.47$ (*n*-hexane/ethyl acetate 6/4); $[\alpha]_D = -42.16$ (*c* 0.44, $CHCl_3$); IR (neat) 3330, 1730; ^{1}H NMR (300 MHz) 1.27 (t, $J = 7.2$ Hz, 3H), 1.33 (s, 3H), 1.50 (s, 3H), 1.66 (bs, 1H, exchanges with D_2O), 2.61 (dd, $J = 6.7$, 15.7 Hz, 1H), 2.83 (dd, $J = 4.2$, 15.7 Hz, 1H), 3.55 (ddd, $J = 4.2$, 6.7, 8.8 Hz 1H), 3.75 (d, $J = 12.8$ Hz, 1H), 3.87 (d, $J = 12.8$ Hz, 1H), 4.12 (d, $J = 3.0$ Hz, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 4.20 (dd, $J = 3.0$, 8.8 Hz, 1H), 4.56 (d, $J = 11.6$ Hz, 1H), 4.62 (d, $J = 3.7$ Hz, 1H), 4.70 (d, $J = 11.6$ Hz, 1H), 5.92 (d, $J = 3.7$ Hz, 1H), 7.15−

7.35 (m, 10H); ^{13}C NMR (75 MHz) 14.2, 26.3, 26.8, 35.7, 51.2, 52.5, 60.2, 72.0, 81.6, 81.7, 82.0, 104.7, 111.5, 126.8, 127.7, 127.8, 128.0, 128.2, 128.4, 137.4, 140.5, 172.3. Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30. Found: C, 68.79; H, 7.55.

Further elution with petroleum ether/ethyl acetate 95/5 gave **6b** (0.82 g, 63%) as a pale yellow solid: mp 70−72 °C; R_f = 0.36 (*n*-hexane/ethyl acetate 6/4); $[\alpha]_D$ = −26.25 (*c* 0.32, $CHCl_3$); IR (Nujol) 3337, 1731; ^{1}H NMR (300 MHz) 1.25 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 3H), 1.51 (s, 3H), 1.80 (bs, 1H, exchanges with D_2O), 2.33 (dd, *J* = 6.7, 14.8 Hz, 1H), 2.45 (dd, *J* = 4.6, 14.8 Hz, 1H), 3.55 (ddd, *J* = 4.6, 6.7, 8.8 Hz, 1H), 3.86 (ABq, *J* = 12.7 Hz, 2H), 3.97 (d, *J* = 3.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.26 (dd, *J* = 3.1, 8.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.67 (d, *J* = 3.9 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 5.97 (d, *J* = 3.9 Hz, 1H), 7.22−7.45 (m, 10H); ^{13}C NMR (75 MHz) 14.0, 26.1, 26.6, 36.3, 51.4, 53.6, 60.2, 71.2, 81.5, 81.6, 82.1, 104.7, 111.4, 126.6, 127.7, 127.8, 128.0, 128.1, 128.3, 136.9, 140.4, 171.5. Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30. Found: C, 68.72; H, 7.40.

General Procedure Using Lithium *N*-Benzyl Amide or Lithium *N*-Diphenylmethyl Amide. To a stirred solution of amine (0.69 mmol) in dry THF (3 mL) at −10 °C under dry N_2 was added *n*-BuLi (1.6 M in hexane, 0.43 mL, 0.69 mmol), and the mixture was stirred at the same temperature for 10 min. The reaction mixture was cooled to −40 °C, and a solution of **1a**−**d** (0.574 mmol) in dry THF (2 mL) was added over a period of 10 min. The mixture was stirred for 2 h at the same temperature, quenched with saturated solution of aqueous NH_4Cl, diluted with water, and extracted with ethyl acetate (5 mL × 3). Work up and purification by column chromatography afforded the Michael addition product.

Ethyl-5-*N*-(benzylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranuronate (6g) and 5,6-Dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzylamino)-β-L-*ido*-heptofuranuro-(*N*-benzyl)-amide (6f). A solution of **1c**−**d** (0.50 g, 1.94 mmol) and *N*-benzylamine (3.64 g, 2.12 mmol) was stirred at 25 °C, in the absence of solvent, under dry N_2. After 12 h the reaction mixture was directly loaded on a flash column chromatography. Elution first with petroleum ether/ethyl acetate 95/5 afforded β-amino ester **6g** (0.10 gm, 14%) as a thick liquid: R_f = 0.55 (*n*-hexane/ethyl acetate 1/1); $[\alpha]_D$ = +5.8 (*c* 1.0, $CHCl_3$); IR (Nujol) 3150−3300 (broad band), 1718; ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) 1.27 (t, *J* = 7.1 Hz, 1H), 1.30 (s, 3H), 1.45 (s, 3H), 2.72 (dd, *J* = 7.5, 15.4 Hz, 1H), 2.80 (dd, *J* = 4.7, 15.4 Hz, 1H), 3.58 (ddd, *J* = 1.4, 4.7, 7.5 Hz, 1H), 3.70 (d, *J* = 12.3 Hz, 1H), 3.91 (d, *J* = 12.3 Hz, 1H), 4.14 (dd, *J* = 1.4, 2.9 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 2.9 Hz, 1H), 4.46 (d, *J* = 3.5 Hz, 1H), 5.89 (d, *J* = 3.5 Hz, 1H), 7.25−7.36 (m, 5H); ^{13}C NMR (125 MHz) 14.1, 26.3, 26.9, 36.2, 50.4, 54.1, 60.9, 77.4, 78.7, 85.8, 104.9, 111.6, 127.7, 128.5, 128.7, 137.8, 171.4. Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45. Found: C, 62.35; H, 7.40.

Further elution with petroleum ether/ethyl acetate 9/1 afforded a diastereomeric mixture of **6e** and **6f** in the ratio 20:80 (0.49 g, 59%) as a thick liquid: R_f = 0.2 (*n*-hexane/ethyl acetate 6/4); IR (neat) 3200−3300, 1644; for major isomer **6f**: ^{1}H NMR (300 MHz) 1.29 (s, 3H), 1.38 (s, 3H), 2.49 (dd, *J* = 14.2, 8.7 Hz, 1H), 2.77 (dd, *J* = 14.2, 4.3 Hz, 1H), 3.63−3.70 (m, 1H), 3.75 (d, *J* = 12.5 Hz, 1H), 3.90 (d, *J* = 12.5 Hz, 1H), 4.09 (t, *J* = 2.5 Hz, 1H), 4.28 (d, *J* = 2.5 Hz, 1H), 4.35 (dd, *J* = 5.3, 14.6 Hz, 1H, becomes doublet with *J* = 14.6 on D_2O exchange), 4.46 (d, *J* = 3.6 Hz, 1H), 4.51 (dd, *J* = 14.6, 6.1 Hz, 1H, becomes doublet with *J* = 14.6 on D_2O exchange), 5.88 (d, *J* = 3.6 Hz, 1H), 6.4 (bs, 1H), 7.22−7.34 (m, 12H); ^{13}C NMR (125 MHz,) 26.1, 26.8, 38.9, 43.7, 50.6, 54.5, 77.2, 78.7, 85.8, 104.7, 111.5, 127.5, 127.8, 128.3, 128.6, 128.7, 137.8, 138.3, 170.2. Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 69.71; H, 7.56. Found: C, 69.67; H, 7.76. The ^{1}H and ^{13}C NMR spectra showed additional peaks (20%) corresponding to D-*gluco* isomer **6e**.

3-*O*-Benzyl-5,6-dideoxy-5-(*N*-benzylamino)-1,2-*O*-isopropylidene-α-D-*gluco*-hepto-1,4-furanose (7a). To an ice-cooled suspension of LAH (0.20 g, 5.49 mmol) in dry THF (5 mL) was added a solution of **6a** (0.5 g, 1.1 mmol) in dry THF (5 mL) over a period of 10 min. The reaction mixture was warmed to room temperature and stirred for 2 h. Ethyl acetate (10 mL) was added at 0 °C, stirred for 10 min, and quenched with a saturated solution of NH_4Cl (2 mL). The solution was filtered, and the residue was washed with ethyl acetate (3 mL × 3). The organic layer was evaporated and purified by column chromatography ($CHCl_3$/MeOH 98/2) to gave **7a** (0.4 g, 87%) as a thick liquid: R_f = 0.77 ($CHCl_3$/MeOH 9/1); $[\alpha]_D$ = −30.38 (*c* 0.65, $CHCl_3$); IR (Nujol) 3750−3340 (broad); ^{1}H NMR (300 MHz) 1.33 (s, 3H), 1.50 (s, 3H), 1.77−1.83 (m, 2H), 2.85−2.90 (bs, 2H, exchanges with D_2O), 3.32−3.40 (m, 1H), 3.79 (d, *J* = 12.3 Hz, 1H), 3.75−3.90 (m, 2H), 3.94 (d, *J* = 12.3 Hz, 1H), 4.03 (d, *J* = 3.3 Hz, 1H), 4.20 (dd, *J* = 3.3, 6.9 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 3.8 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 5.95 (d, *J* = 3.8 Hz, 1H), 7.15−7.35 (m, 10H); ^{13}C NMR (75 MHz) 26.2, 26.8, 31.9, 51.8, 56.9, 62.5, 71.8, 81.4, 81.6, 82.2, 104.7, 111.5, 127.1, 127.5, 128.0, 128.2, 128.5, 128.7, 136.8, 139.8. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H 7.56. Found: C, 69.59; H, 7.40.

3-*O*-Benzyl-5,6-dideoxy-5-*N*-(benzylamino)-1,2-*O*-isopropylidene-β-L-*ido*- hepto-1,4-furanose (7b). The reaction of **6b** (0.5 g, 1.10 mmol) with LAH (0.20 g, 5.49 mmol) was performed under the same conditions as reported for **6a**. Flash chromatography ($CHCl_3$/MeOH 96/4) afforded **7b** (0.95 g, 84%) as a thick liquid: R_f = 0.48 ($CHCl_3$/MeOH 9/1); $[\alpha]_D$ = −32.65 (*c* 0.65, $CHCl_3$); IR (neat) 3250−3600 (broad); ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) 1.33 (s, 3H), 1.50 (s, 3H), 1.38−1.65 (m, 2H), 3.38 (m, 1H), 3.69−3.82 (m, 2H), 3.86 (d, *J* = 3.1 Hz, 1H), 3.89 (ABq, *J* = 12.1 Hz, 2H), 4.24 (dd, *J* = 3.1, 9.5 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 3.8 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 5.96 (d, *J* = 3.8 Hz, 1H), 7.21−7.39 (m, 10H); ^{13}C NMR (75 MHz) 26.2, 26.8, 29.5, 50.8, 56.8, 62.3, 71.8, 81.4, 81.7, 81.9, 104.8, 111.7, 127.1, 128.1, 128.2, 128.5, 128.6, 136.9, 139.7. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56. Found: C, 69.70; H, 7.40.

Ethyl 3-*O*-Benzyl-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranuronate (10a). To a stirred solution of **6a** (1.00 g, 2.19 mmol) and sodium bicarbonate (0.75 g, 8.93 mmol) in ethanol−water (2 mL, 1:1) was added benzyloxycarbonyl chloride (0.45 g, 2.64 mmol) at 0 °C. The mixture was stirred at 30 °C for 3 h. Water (5 mL) was added, and reaction mixture was extracted with chloroform (10 mL × 3). Workup and purification by column chromatography (petroleum ether/ethyl acetate 95/5) gave **10a** (1.37 g, 97%) as a thick liquid: R_f = 0.48 (*n*-hexane/ethyl acetate 6/4); $[\alpha]_D$ = −32.97 (*c* 2.2, $CHCl_3$); IR (neat) 1730, 1695; ^{1}H NMR (500 MHz) 1.00−1.40 (m, 9H), 2.52−2.93 (m, 2H), 3.50−4.00 (m, 3H), 4.20−4.95 (m, 7H), 5.0−5.30 (m, 2H), 5.82 (bs, 1H), 7.10−7.50 (m, 15H). Anal. Calcd for $C_{34}H_{39}NO_8$: C, 69.25; H, 6.67. Found: C, 69.35; H, 6.78.

Ethyl 3-*O*-Benzyl-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranuronate (10b). The reaction of **6b** (2.00 g, 4.39 mmol) with benzyloxycarbonyl chloride (0.90 g, 5.28 mmol) under the same conditions reported for **6a** gave **10b** (2.74 g, 97%) as a thick liquid: R_f = 0.45 (*n*-hexane/ethyl acetate 7/3); $[\alpha]_D$ = −19.6 (*c* 1, $CHCl_3$); IR (neat) 1734, 1699; ^{1}H NMR (500 MHz), 1.06 (t, *J* = 7 Hz, 3H), 1.28,1.31,1.42 (each s, 6H), 2.55, 2.90 (each m, 1H), 3.62−3.92 (m, 3H), 4.25−4.75 (m, 8H), 5.05−5.30(m, 2H), 5.76, 5.86 (each s, 1H), 7.10−7.50 (m, 15H). Anal. Calcd for $C_{34}H_{39}NO_8$: C, 69.25; H, 6.67. Found C, 69.30; H, 6.70.

Ethyl 3-*O*-Benzyl-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranuronic acid (11a). To an ice-cooled solution of **10a** (1.00 g, 1.69 mmol) in methanol/water (20 mL, 4/1) was added lithium hydroxide monohydrate (0.43 g, 10.24 mmol) at 0 °C. The mixture was brought to 25 °C and the pH of the solution was adjusted to 7 by addition of 0.5 M H_3PO_4, the solvent was evaporated, and residue thus obtained was extracted with chloroform (10 mL × 3). Purification by column chromatography (chloroform/methanol 98/2) afforded **11a** (0.95 g, 96%) as a thick liquid: R_f = 0.62 (chloroform/methanol 9/1); $[\alpha]_D$ = −33.89 (*c* 0.72, $CHCl_3$); IR (neat) 1735, 1695; ^{1}H NMR (500 MHz, $CDCl_3$ + D_2O) 1.26, 1.30, 1.38 (each s, 6H), 2.60−3.00 (m, 2H), 3.59−3.79 (bs, 1H), 4.20−4.40 (m, 2H), 4.45−4.58 (m,

5H), 5.02−5.32 (m, 2H), 5.85 (bs, 1H), 7.07−7.29 (m, 15H). Anal. Calcd for $C_{32}H_{35}NO_8$: C, 68.43; H, 6.28. Found: C, 68.40; H, 6.29.

Ethyl 3-*O*-Benzyl-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranuronic acid (11b). The reaction of **10b** (2.00 g, 3.39 mmol) with lithium hydroxide monohydrate (0.86 g, 20.49 mmol) under the same conditions reported for **10a** gave **11b** (1.9 g, 96%) as a thick liquid: R_f = 0.6 (chloroform/methanol 9/1); $[\alpha]_D$ = −25.75 (*c* 0.8, $CHCl_3$); IR (neat) 3500−3600 (broad band), 1739, 1702; ^{1}H NMR (500 MHz, $CDCl_3$ + D_2O) 1.28, 1.30, 1.44 (each singlet, 6H), 2.09 (dd, *J* = 15.0, 4.5 Hz) and 2.20 (dd, *J* = 13.0, 3.5 Hz) (each dd, 1H), 2.57−2.70, 2.87−2.98 (each m, 1H), 3.70, 3.83 (each bs, 1H), 4.30−4.52 (m, 3H), 4.55−4.75 (m, 4H), 5.13, 5.23 (each s, 2H), 5.77, 5.88 (each bs, 1H), 7.10−7.45 (m, 15H); ^{13}C NMR (125 MHz) for major isomer 26.4, 26.8, 34.5, 55.5, 67.1, 71.3, 77.0, 78.9, 80.9, 81.1, 104.7, 111.8, 126.9, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 136.4, 136.8, 138.2, 156.1, 176.0. ^{13}C NMR showed additional signals corresponding to other isomer. Anal. Calcd for $C_{32}H_{35}NO_8$: C, 68.43 H, 6.28. Found: C, 68.33; H, 6.30.

5,6,8-Trideoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-5-(*N*-benzyl-*N*-benzoxy carbonyl amino)-8-diazo-α-D-*gluco*-octo-1,4-furan-7-ulose (12a). A solution of **11a** (0.80 g, 1.42 mmol) in THF (10 mL) was cooled to 0 °C under dry N_2. Triethylamine (0.16 gm, 1.57 mmol) and ethylchloroformate (0.17 mL, 1.57 mmol) were added one after another. After 15 min, the suspension was allowed to warm to 25 °C and filtered through Celite. To the filtrate was added a freshly prepared solution of diazomethane in diethyl ether [(prepared from *N*-nitrosomethyl urea (1.02 g, 7.12 mmol) and KOH (2 g)] dropwise over a period of 30 min. The mixture was stirred for 1.5 h, during which the reaction slowly attained room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate 9/1) to give **12a** (0.52 g, 62%) as thick liquid: R_f = 0.35 (*n*-hexane/ethyl acetate 7/3); $[\alpha]_D$ = −12.2 (*c* 4.0, $CHCl_3$); IR (neat) 2106, 1696, 1642; ^{1}H NMR (500 MHz) 1.26, 1.40, 1.43 (each s, 6H), 2.52−3.10 (m, 2H), 3.74, 3.76 (each bs, 1H), 4.15−4.92 (m, 8H), 5.10−5.32 (m, 2H), 5.84 (d, *J* = 3.2 Hz, 1H), 7.10−7.50 (m, 15H); ^{13}C NMR (125 MHz) 26.2, 26.6, 41.2, 52.7, 54.7, 67.2, 67.7, 71.6, 80.5, 81.4, 82.0, 104.7, 111.6, 127.1, 127.7, 127.9, 128.4, 136.4, 137.1, 138.4, 155.9, 158.0, 191.7. ^{13}C NMR shows additional signals. Anal. Calcd for $C_{33}H_{35}N_3O_7$: C, 67.68; H, 6.02. Found: C, 67.78; H, 6.32.

5,6,8-Trideoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-5-(*N*-benzyl-*N*-benzoxy carbonyl amino)-8-diazo-β-L-*ido*-octo-1,4-furan-7-ulose (12b). The reaction of **11b** (1.60 g, 2.85 mmol) with ethylchloroformate (0.34 g, 3.14 mmol) and then with diazomethane [(prepared from *N*-nitrosomethyl urea (2.04 g, 14.24 mmol) and KOH (4 g)] under the same conditions reported for **11a** gave **12b** (1.08 g, 65%) as a yellow solid: mp 98−99 °C; R_f = 0.26 (*n*-hexane/ethyl acetate 7/3); $[\alpha]_D$ = −26.00 (*c* 0.5, $CHCl_3$); IR (Nujol) 2106, 1697, 1640; ^{1}H NMR (500 MHz) 1.43, 1.31, 1.33, 1.29 (each s, 6H), 2.00−2.15 (m, 1H), 2.40−2.98 (m, 1H), 3.75, 3.8 (each bs, 1H), 4.25−4.50 (m, 3H), 4.52−4.75 (m, 4H), 4.80 (bs, 1H), 5.11, 5.23 (each ABq, *J* = 12.6 Hz, 1H), 5.82, 5.88 (each d, *J* = 2.5 Hz, 1H), 7.10−7.50 (m, 15H); ^{13}C NMR (125 MHz) 26.3, 26.7, 40.5, 54.7, 66.9, 67.5, 70.9, 71.2, 79.1, 80.9, 81.6, 104.6, 111.7, 127.0, 127.4, 127.7, 127.9, 128.0, 128.2, 128.4, 136.5, 136.8, 138.2, 155.9, 191.7. ^{13}C NMR showed additional peaks corresponding to other isomer. Anal. Calcd for $C_{33}H_{35}N_3O_7$: C, 67.68 H, 6.02. Found: C, 67.91; H, 6.25.

Methyl 3-*O*-Benzyl-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-5,6,7-trideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-octo-1,4-furanuronate (13a). To a solution of α-diazo ketone **12a** (0.5 g, 0.85 mmol) in anhydrous MeOH (12 mL) was added dropwise a solution of silver benzoate (0.06 g, 0.27 mmol) in triethylamine (1 mL) under dry N_2. The mixture was stirred at 25 °C for 1.5 h. The solvent was evaporated, and the residue was purified by column chromatography (petroleum ether/ethyl acetate 95/5) to give **13a** (0.42 g, 83%) as a thick liquid: R_f = 0.46 (*n*-hexane/ethyl acetate 7/3); $[\alpha]_D$ = −50.87 (*c* 3.0, $CHCl_3$); IR (neat) 1736, 1695; ^{1}H NMR (500 MHz) 1.25, 1.32 (each singlet, 6H), 1.90−2.42 (m, 4H), 3.52−3.56 (two singlets, 3H), 3.90−5.10 (m, 8H), 5.12−5.32 (m, 2H), 5.84 (bs, 1H), 7.10−7.30 (m, 15H); ^{13}C NMR (125 MHz) 26.1, 26.6, 30.8, 31.0, 51.3, 67.3, 69.7, 71.8, 80.8, 81.4, 81.8, 104.7, 111.4, 127.2, 127.6, 127.9, 128.0, 128.4, 136.1, 137.2, 138.5, 172.1, 173.0. ^{13}C NMR showed additional signals corresponding to other isomer. Anal. Calcd for $C_{34}H_{39}NO_8$: C, 69.25; H, 6.67. Found: C, 69.36; H, 6.60.

Methyl 3-*O*-Benzyl-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-5,6,7-trideoxy-1,2-*O*-isopropylidene-β-L-*ido*-octo-1,4-furanuronate (13b). The reaction of **12b** (0.8 g, 1.37 mmol) for **12a** gave **13b** (0.69 g, 85%) as a white solid: mp 102−103 °C; R_f = 0.34 (*n*-hexane/ethyl acetate 7/3); $[\alpha]_D$ = −20.5 (*c* 0.4, $CHCl_3$); IR (Nujol) 1740, 1695; ^{1}H NMR (500 MHz) 1.28,1.30 (each s, 6H), 1.34−1.48 (m, 2H), 1.97−2.18 (m, 2H), 3.48 (s, 1.8H), 3.52 (s, 1.2H), 3.78 (m, 0.4H), 3.85 (m, 0.6H), 4.20−4.40 (bm, 1H), 4.40−4.55 (m, 2H), 4.58−4.78 (m, 3H), 5.14 (s, 1.2H), 5.19(s, 0.8H), 5.85 (s, 0.4H), 5.92 (s, 0.6H), 7.20−7.50 (m, 2H). ^{13}C NMR showed additional signals corresponding to other isomer. Anal. Calcd for $C_{34}H_{39}NO_8$: C, 69.25; H, 6.67. Found: C, 69.45; H, 6.75.

5,6,7-Trideoxy-5,8-imino-1,2-*O*-isopropylidene-α-D-*gluco*-oct-1,4-furan-8-ulose (14a). A mixture of **13a** (0.4 g, 0.68 mmol) and 10% Pd/C (0.05 g) in methanol (10 mL) was hydrogenolysed at 80 psi for 12h. The catalyst was filtered through Celite and washed with methanol. To the filtrate, anhydrous sodium acetate (0.06 g, 0.23 mmol) was added, and the mixture was refluxed for 6,h. The pH of the solution was adjusted to 8 by addition of 1 N NaOH. Methanol was removed, and the solution was extracted with chloroform (5 mL × 5). The chloroform layer was dried and evaporated to give a gummy solid ,which was purified by column chromatography (chloroform/methanol 4/1) to give **14a** (0.13 g, 80%) as a yellow solid: mp 152−153 °C; R_f = 0.56 (chloroform/methanol 98/2); $[\alpha]_D$ = −3.04 (*c* 0.46, $CHCl_3$); IR (Nujol) 3147, 1661; ^{1}H NMR (300 MHz, DMSO-d_6) 1.23 (s, 3H), 1.38 (s, 3H), 1.64−1.80 (m, 1H), 2.02−2.22 (m, 3H), 3.67−3.76 (m, 1H), 3.78 (dd, *J* = 8.4, 2.3 Hz, 1H), 4.02 (bd, *J* = 2.3 Hz, 1H becomes doublet with *J* = 2.3 Hz on D_2O exchange), 4.40 (d, *J* = 3.6 Hz, 1H), 5.40 (d, *J* = 4.9 Hz, 1H, disappears on D_2O exchange), 5.85 (d, *J* = 3.6 Hz, 1H), 7.57 (bs, 1H, disappears on D_2O exchange); ^{13}C NMR (125 MHz, DMSO-d_6) 24.6, 26.8, 27.3, 30.5, 53.3, 74.4, 83.6, 85.9, 105.4, 112.6, 180.9. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04. Found: C, 54.55; H, 7.14.

5,6,7-Trideoxy 5,8-imino-1,2-*O*-isopropylidene-β-L-ido-oct-1,4-furan-8-ulose (14b). A solution of **13b** (0.60 g, 1.02 mmol) in methanol (10 mL) hydrogenated in the presence of 10% Pd/C under the same conditions reported for **13a** gave **14b** (0.20 g, 80%) as a white solid: mp 168−170 °C; R_f = 0.5 (chloroform/methanol 4/1); $[\alpha]_D$ = −104.35 (*c* 0.40, MeOH); IR (Nujol) 3321 (broad band), 1681; ^{1}H NMR (300 MHz, DMSO-d_6) 1.23 (s, 3H), 1.38 (s, 3H), 1.62−1.78 (m, 1H), 2.02−2.20 (m, 3H), 3.63−3.80 (m, 2H), 4.02−4.06 (m, 1H, became bd, *J* = 2.3 Hz on D_2O exchange), 4.42 (d, *J* = 3.6 Hz, 1H), 5.40 (d, *J* = 4.9 Hz, 1H disappear on D_2O exchange), 5.85 (d, *J* = 3.6 Hz, 1H), 7.58 (s, 1H, exchanges with D_2O); ^{13}C NMR (125 MHz, DMSO-d_6) 23.0, 25.1, 25.8, 29.5, 54.2, 74.5, 83.6, 85.7, 105.0, 111.5, 180.0. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04. Found: C, 54.25; H, 7.12.

5,6,7,8-Tetradeoxy-5,8-(*N*-benzoxycarbonylimino)-1,2-*O*-isopropylidene-α-D-*gluco*-oct-1,4-furanose (16a). To an ice-cooled suspension of LAH (0.93 g, 2.45 mmol) in dry THF (4 mL) was added a solution of **14a** (0.12 g, 0.49 mmol) in dry THF (6 mL) over a period of 10 min. The mixture was refluxed for 18 h. Ethyl acetate (10 mL) was added at 0 °C and stirred for 10 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl (2 mL) and filtered, and the residue was rinsed with ethyl acetate (5 mL). Work up gave **15a** as thick liquid. To a stirred solution of **15a** in ethanol/water (2 mL, 1/1) were added sodium bicarbonate (0.17 g, 1.97 mmol) and benzyloxycarbonyl chloride (0.10 g, 0.59 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. Workup followed with extraction with chloroform (5 mL × 3). The chloroform layer was dried and evaporated to afford a thick liquid that

was purified by column chromatography (petroleum ether/ethyl acetate 92/8) to give **16a** (0.13 g, 74%) as a thick liquid: R_f = 5.5 (*n*-hexane/ethyl acetate 6/4); $[\alpha]_D$ = +29.00 (*c* 0.56, $CHCl_3$) [reported +28.30 (c,1.1, $CHCl_3$)];[10b] IR (neat) 3366, 1675; ^{1}H NMR (300 MHz) 1.31 (s, CH_3), 1.49 (s, CH_3), 1.84−2.05 (m, 3H), 2.09−2.15 (m, 1H), 3.38−3.45 (m, 2H), 3.80 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.02 (d, *J* = 1.8 Hz, 1H), 4.14 (, *J* = 10.2, 6.2 Hz, 1H), 5.26 (bs, 1H, exchanges with D_2O), 4.59 (d, *J* = 3.7 Hz, 1H), 5.14 (ABq, *J* = 12.5 Hz, 2H), 5.90 (d, *J* = 3.7 Hz, 1H), 7.26−7.38 (m, 5H), ^{13}C NMR (75 MHz) 23.0, 26.1, 27.1, 28.2, 48.8, 59.9, 68.1, 73.9, 81.0, 85.0, 105.2, 112.3, 128.0, 128.4, 129.1, 136.0, 157.1. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93. Found: C, 62.68; H, 6.81.

5,6,7,8-Tetradeoxy-5,8-(*N*-benzoxycarbonylimino)-1,2-*O*-isopropylidene-*β*-L-*ido*-oct-1,4-furanose (16b). The reaction of **14b** (0.20 g, 0.82 mmol) with LAH (0.16 g, 4.1 mmol) under the same conditions reported for **14a** gave **15b** as a thick liquid that on treatment with benzyloxycarbonyl chloride (0.16 g, 0.94 mmol) under the same conditions reported for **15a** gave **16b** (0.22 g, 74%) as a thick liquid: R_f = 0.42 (*n*-hexane/ethyl acetate 6/4); $[\alpha]_D$ = −72.27 (*c* 0.44, $CHCl_3$); IR (neat) 3390, 1693; ^{1}H NMR (300 MHz) 1.30 (s, 3H), 1.48 (s, 3H), 1.82−1.94 (m, 2H), 1.96−2.20 (m, 2H), 3.42−3.58 (m, 2H), 4.0 (t, *J* = 3.0 Hz, 1H), 4.13 (d, *J* = 2.9 Hz 1H), 4.26−4.34 (m, 1H), 4.48 (d, *J* = 3.6 Hz, 1H), 5.13 (ABq, *J* = 12.3 Hz, 2H), 5.87 (d, *J* = 3.6 Hz 1H), 7.24−7.42 (m, 5H); ^{13}C NMR (75 MHz) 23.6, 26.1, 26.7, 29.7, 47.2, 55.5, 67.5, 75.7, 84.0, 85.0, 104.5, 111.2, 127.8, 128.0, 128.4, 136.3, 158.7. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93. Found: C, 62.80; H, 6.79.

(6*S*,7*R*,8*R*,8a*R*)-6,7,8-Trihydroxy-indolizidine (5a). A solution of **16a** (0.10 g, 0.28 mmol) in TFA/H_2O (2 mL, 3/2) was stirred at 25 °C for 2 h. Trifluroacetic acid was coevaporated with benzene to furnish a thick liquid, which was directly used in the next reaction. A solution of the above product in methanol (5 mL) was added 10% Pd/C (0.01 g), and the solution was hydrogenated at 80 psi for 16 h. The catalyst was filtered and washed with methanol and the filtrate concentrated to get a sticky solid which was purified by column chromatography (chloroform/methanol 9/1) to give **5a** (0.04 g, 90%) as a white solid: mp 176−178 °C (reported 178−181 °C)[10b]; R_f = 0.45 (chloroform/methanol 9/1) $[\alpha]_D$ = +50.10 (*c* 0.7, MeOH) [reported +50.6 (*c* 0.2, MeOH)];[10b] IR (KBr pellet) 3380, 3270 (broad band); ^{1}H NMR (300 MHz, pyridine-d_5 + D_2O) 1.39−1.58 (m, 1H), 1.64−1.82 (m, 2H), 1.93−2.06 (m, 1H), 2.10−2.24 (m, 2H), 2.30 (t, *J* = 10.5 Hz, 1H), 2.94 (dt, *J* = 8.6, 2.0 Hz, 1H), 3.43 (dd, *J* = 5.2, 10.5 Hz, 1H), 3.86 (t, *J* = 8.6 Hz, 1H), 3.91 (t, *J* = 8.6 Hz, 1H), 4.33 (ddd, *J* = 10.5, 8.6, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, pyridine-d_5) 21.9, 28.6, 53.2, 56.9, 68.3, 71.5, 75.9, 80.9. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73. Found: C, 55.77; H, 8.98.

(6*S*,7*R*,8*R*,8a*S*)-6,7,8-Trihydroxy-indolizidine (5b). The reaction of **16b** (0.16 g, 0.44 mmol) with TFA/H_2O (2 mL, 3/2) under the same conditions reported for **16a** gave the corresponding hemiacetal as a thick liquid, which on hydrogenation with 10% Pd/C (0.02 g) in methanol under the same conditions reported for **16a** gave **5b** as a thick liquid. Column chromatography using chloroform/methanol 8/2 as an eluent gave (0.065 g, 87%) as a semisolid: R_f = 0.2 (chloroform/methanol 1/1); $[\alpha]_D$ = +23.0 (*c* 0.72, MeOH) [reported +22.5 (*c* 1.13, MeOH)[11]]; IR (KBr pellet) 3360−3250 (broad band); ^{1}H NMR (300 MHz, pyridine-d_5 + D_2O) 1.72−2.00 (m, 3H), 2.22−2.40 (m, 1H), 2.84−3.00 (m, 1H), 3.44 (bd, *J* = 12.3 Hz, 1H), 3.49−3.67 (m, 2H), 3.69 (bd, *J* = 12.3 Hz, 1H), 4.42 (bs, 2H), 4.55 (bs, 1H); ^{13}C NMR (125 MHz, pyridine-d_5) 21.1, 24.5, 54.7, 55.5, 64.6, 70.5, 70.7, 70.9. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73. Found: C, 55.80; H, 9.02.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3a,b**, **5a,b**, **6a,b**, **6g, 7a,b**, **10a,b**, **14a,b**, and **16a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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