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Stereocontrolled 1,3-addition reaction of silyl ketene acetal to sugar nitrone: synthesis of D-gluco-homo-1-deoxynojirimycin and L-ido-homo-1-deoxynojirimycin

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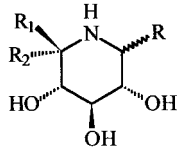
Abstract—The 1,3-addition reaction of silyl ketene acetal **6** to D-glucose derived nitrone **7** followed by reductive cleavage of the N–O bond afforded D-gluco- and L-ido-β-amino ester derivatives of **9a** and **9b**. The diastereoselectivity in addition reaction was improved as well as altered by making use of different Lewis acids. Reduction of the ester group in **9a** followed by hydrogenolysis gave amino alcohol **12a**. Selective *N*-Cbz protection, hydrolysis and intramolecular reductive amination afforded D-*gluco*-homo-1-deoxynojirimycin **1d**. Analogously, β-amino ester **9b** was converted to L-*ido*-homo-1-deoxynojirimycin **1c**.

1. Introduction

The term 'iminosugars' is currently being used to describe monosaccharide analogues having a nitrogen atom instead of the ring oxygen atom. These iminosugars (azasugars), namely nojirimycin **1a** and 1-deoxynojirimycin **1b** (Fig. 1) are glycosidase inhibitors with promising medicinal applications in the treatment of diabetes, obesity and viral infections including HIV-1, the virus responsible for AIDS.[1] The worldwide intense search for potential drugs against AIDS has resulted in the development of new methodologies enabling the synthesis of a plethora of natural and unnatural nojirimycin analogues.[2]

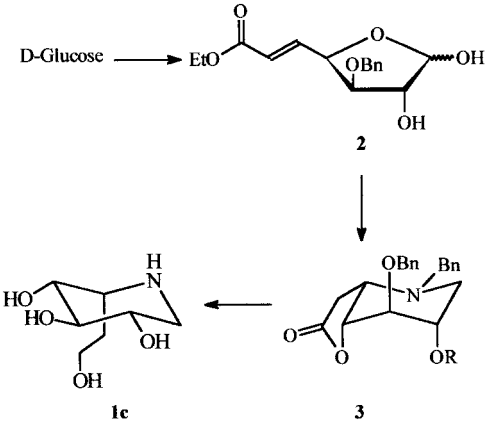
In recent years, synthesis and evaluation of homoazasugars with a CH_2-homologation either at C1 or at C5 have received much attention.[3] In this context, we have recently reported the synthesis of 1-deoxy-L-ido-homonojirimycin **1c**.[4a] Our approach (Scheme 1) involved highly diastereoselective intramolecular Michael addition of in situ generated *N*-benzyl substituted sugar amine, from D-glucose derived hemiacetal **2**, to α,β-unsaturated ester and domino lactonisation to yield lactone **3** as the only isolable product with the homoazasugar ring skeleton having $^1C_4$ conformations. Reduction of the lactone functionality and removal of the protecting groups afforded 1-deoxy-L-ido-homonojirimycin **1c** with $^4C_1$ conformation. As a part of our continuing interest in this area,[4] we are now describing a divergent synthetic route to **1c** and 1-deoxy-D-gluco-homonojirimycin **1d**.

We visualized that, the 1-deoxy piperidine ring skeleton with requisite homologated side chain could be built up



1a R = OH, $R_1 = CH_2OH$, R_2 = H
1b R = H, $R_1 = CH_2OH$, R_2 =H
1c R = H, R_1 = H, $R_2 = CH_2CH_2OH$
1d R = H, $R_1 = CH_2CH_2OH$, R_2 = H

Figure 1.



Scheme 1.

Keywords: piperidines; alkaloids; amino sugars; enzymes inhibitors; nitrones.

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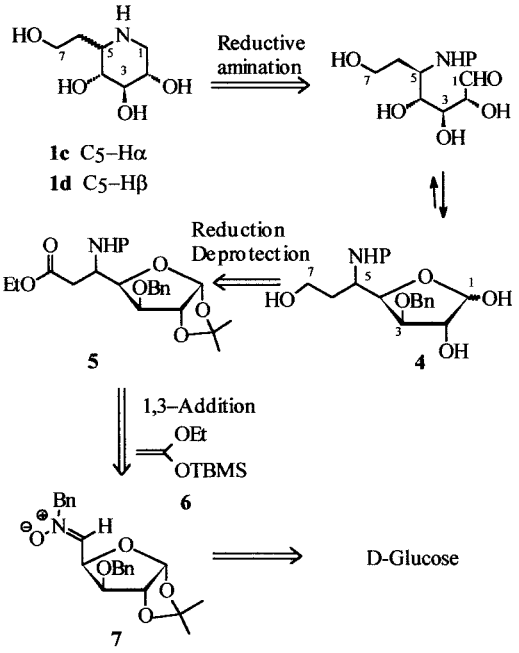


Scheme 2.

by the reductive amination of C_1 aldehyde with the C5 amino group of the hemiacetal **4** (Scheme 2). The compound **4** could be obtained by the reduction of the ester group and the cleavage of acetonide group in **5**. The synthesis of sugar β-amino ester **5** would thus be the key step in the process. It is possible that this can be achieved by 1,3-addition reaction of silyl ketene acetal **6** with sugar nitrone **7** which in turn could be easily derived from D-glucose. It remained a matter of practicability whether the addition reaction could be performed stereoselectively to obtain the sugar β-aminoester **5** with required D-gluco or L-ido diastereomer in excess.

After evaluation of the addition reactions of silyl ketene acetals to chiral and achiral nitrones, performed by us[5] and reported by others,[6–8] it was felt that the configuration at the pro-chiral nitrone carbon could be influenced if the reaction system was properly designed. In view of this, we have anticipated that the addition of silyl ketene acetal **6** to nitrone **7** could be stereocontrolled under different chelation and non-chelation conditions by the use of suitable Lewis acids. The chelation-controlled pathway should favour one configuration while the Felkin–Anh stereoselectivity should lead to the other configuration at the newly generated C5 asymmetric carbon centre.

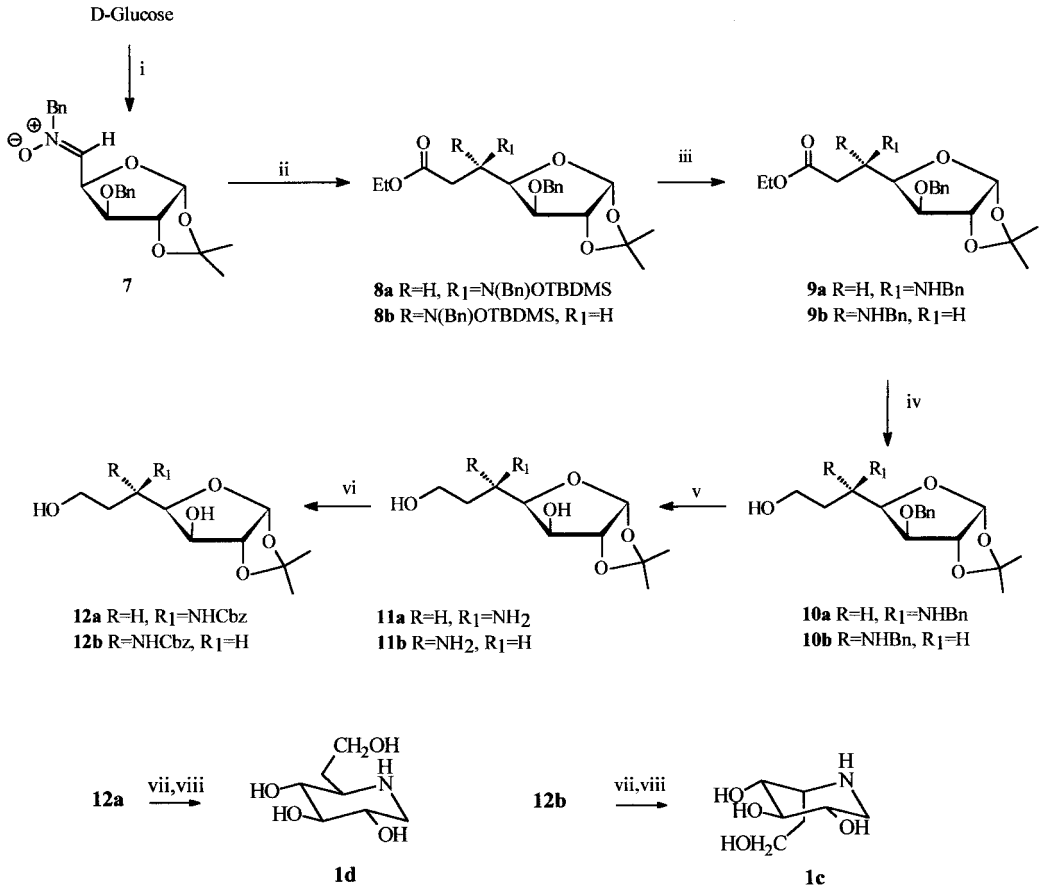
Although, nitrones are widely used as the starting compounds in the synthesis of natural and unnatural amino compounds,[7] their utility in the synthesis of polyhydroxylated indolizidine, pyrrolidine and piperidine alkaloids have received limited attention.[8] In this context, we have recently reported on the diastereoselective nucleophilic addition of methylmagnesium chloride to D-glucose derived nitrone **7** to give 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-5-(*N*-hydroxy)benzylamino-α-D-*gluco*-furanose. The D-gluco derivative which was obtained in major amount (D-gluco:L-ido=88:12) was subsequently elaborated to 6-deoxynojirimycin.[4c] The other aspect of nitrone chemistry i.e. the [3+2] cycloaddition reactions have also been exploited by us.[5] In particular, the TMSOTf catalysed [3+2] cycloaddition of aldonitrones with silylated nucleophiles for the synthesis of isooxazolidines has been studied in detail. There, we have observed that the transfer of silyl group from TMSOTf to nitrone oxygen leads to the formation of *N*-silyloxyiminium ions wherein, the activation energy for the formation of C–C bond has been reduced considerably leading to regio- and stereo-selective cycloaddition of electron rich alkenes under mild conditions. We have now studied the 1,3-addition reaction of silyl ketene acetal **6** to nitrone **7** under different reaction conditions and demonstrated its applicability in the synthesis of homo-1-deoxynojirimycins **1c** and **1d**.

2. Results and discussion

The desired sugar nitrone **7** was readily prepared by the reaction of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-pento-dialdose with *N*-benzylhydroxylamine hydrochloride, in the presence of sodium acetate in ethanol–water, as reported earlier by us[4c] (Scheme 3). The 1,3-addition reaction of silyl ketene acetal **6** to nitrone **7** in dichloromethane at 25°C for 24 h afforded an inseparable diastereomeric mixture of *O*-silyloxy-β-amino esters **8a** and **8b** (D-gluco:L-ido=36:64)[9] in 95% yield (Table 1, entry 1). The product showed single spot on TLC (R_f=0.69, hexane/ethyl acetate=3/1) but the ^{1}H NMR (300 MHz) was not assignable due to the overlap of signals. The formation of β-silyloxyamino ester, indicated by strong ester carbonyl stretching frequency at 1740 cm^{-1} in the IR spectrum, precludes the formation of isoxazolidine in the reaction sequence.

Performing the reactions using CH_3CN as a solvent at different reaction temperature (0°C to reflux temperature) led to a moderate change of stereoselectivity in favour of L-ido-isomer (Table 1, entry 2,3). In order to increase or alter the diastereoselectivity, we investigated the influence of solvent and various Lewis acids. In this respect, the effect of TMSOTf was first examined. As shown in Table 1, the individual reactions of **6** with **7** were performed in the presence of 0.1 or 1.2 equiv. of TMSOTf using either CH_2Cl_2 or CH_3CN as the solvent (Table 1, entries 4–7). Excellent chemical yield with good diastereoselectivity (D-gluco:L-ido=23:77), in favour of L-ido isomer, was achieved by using 1.2 equiv. of TMSOTf in a binary mixture of CH_2Cl_2 and CH_3CN at −78°C (entry 5). We presumed that these TMSOTf promoted cycloaddition reactions proceed with the formation of *O*-silyloxy intermediate leading to the product formation in a non-chelation controlled manner.[10]

The sugar nitrone **7** possesses two alkoxy substituents namely the furanose ring oxygen at the α-position and benzyloxy group (at C3) at the β-position with respect to C=N bond. These alkoxy substituents are considered to be promising chelating groups prone to enhance or alter the stereoselectivity of the cycloaddition reactions.[5,7] This prompted us to make use of metal chelating Lewis acids such as $ZnCl_2$, ZnI_2 and $MgBr_2$ in the subsequent reactions. The use of either $ZnCl_2$ or ZnI_2, under various conditions of



Scheme 3.

temperature, solvent and mole proportions did not alter the diastereoselectivity (preponderance of L-ido isomer **8b**) however, the observed stereoselectivity was poor (Table 1, entries 8–15). Surprisingly, the replacement of $ZnCl_2$ with $MgBr_2$ altered the stereochemical course of the addition reaction (Table 1, entries 16–19). The best result was obtained by the use of 2.5 equiv. of $MgBr_2$ in a binary mixture of CH_2Cl_2 and CH_3CN at $-10°C$ which afforded **8a** as the major product (**8a**:**8b**=76:24) in 94% yield (entry 18). No significant effect was observed when

Table 1. Lewis acid catalysed addition of silyl ketene acetal **6** to nitrone **7**

Run	Lewis acid (equiv.)	Solvent[a]	Conditions		Yield[b] (%)	**8a**:**8b**
			Temp. °C	time h		
1	–	CH_2Cl_2	25	24	95	36:64
2	–	CH_3CN	25	20	95	34:66
3	–	CH_3CN	80	4	80	30:70
4	TMSOTf (1.2)	CH_2Cl_2	−78	1.5	94	34:66
5	TMSOTf (1.2)	CH_2Cl_2+CH_3CN	−78	1.5	93	23:77
6	TMSOTf (0.1)	CH_2Cl_2+CH_3CN	−78	15	96	31:69
7	TMSOTf (0.1)	CH_3CN	25	2.0	93	25:75
8	$ZnCl_2$ (1.2)	CH_2Cl_2	−78	24	No reaction	
9	$ZnCl_2$ (1.2)	CH_2Cl_2	−40	2.0	94	40:60
10	$ZnCl_2$ (1.2)	CH_2Cl_2+CH_3CN	−40	2.0	96	42:58
11	$ZnCl_2$ (3.0)	CH_2Cl_2+CH_3CN	−40	2.0	85	45:55
12	ZnI_2 (1.2)	CH_2Cl_2	−78	24	No reaction	
13	ZnI_2 (1.2)	CH_2Cl_2	−40	2.0	92	50:50
14	ZnI_2 (1.2)	CH_2Cl_2+CH_3CN	−40	2.0	91	46:54
15	ZnI_2 (3.0)	CH_2Cl_2+CH_3CN	−40	2.0	83	46:54
16	$MgBr_2$ (1.2)	CH_2Cl_2	−78	24	No reaction	
17	$MgBr_2$ (1.2)	CH_2Cl_2	−10	2.0	90	60:40
18	$MgBr_2$ (2.5)	CH_2Cl_2+CH_3CN	−10	2.0	94	76:24
19	$MgBr_2$(2.5)	CH_3CN	−10	2.0	90	74:26

[a] CH_2Cl_2+CH_3CN in the ratio 1:1.
[b] Yields refer to the isolated yields after column chromatography.

the reaction was performed in CH_3CN as a solvent (entry 19).

The determination of the D-gluco/L-ido diastereomeric ratio, at the newly generated C5 stereocentre, in the 1,3-addition reaction of **6** and **7** was not possible with the inseparable mixture of β-silyloxy amino esters **8a** and **8b**. Therefore, the crude mixture of β-silyloxy amino esters **8a** and **8b** was subjected to N–O bond reductive cleavage by treatment with zinc/copper couple in acetic acid–water at 70°C for 1 h and the diastereomeric mixture of *N*-benzyl β-amino esters **9a** and **9b** was separated by flash chromatography (91% yield). Although, β-amino esters **9a** and **9b** were isolated in the pure form, their ^{1}H NMR data could not discriminate the D-gluco and L-ido isomers. As a result, the configurational assignment at C5 was made in the next stage. Thus, reduction of the ester functionality in β-amino esters **9a** and **9b**, individually, with LAH in THF afforded β-aminoalcohols **10a** and **10b**, respectively. Assignment of the configuration at C5 was made on the basis of comparison of their ^{1}H NMR spectra. It is known that, for a series of given C5 epimeric pairs, derived from D-gluco-furanose, the vicinal coupling constants between H4 and H5 in L-ido isomers (threo-relationship) are constantly larger than those of the corresponding D-gluco isomers (erythro relationship).[11] The higher value of $J_{4,5}$ observed in diastereomer **10b** (9.5 Hz) as compare to **10a** (6.9 Hz) indicated the L-ido configuration for **10b** and D-gluco configuration for **10a**. This assignment was further supported by comparison of the H3 chemical shifts in both the isomers. The chemical shift of H3 is reported to be diagnostic such that in the L-ido- the H3 resonates significantly upfield ($\delta\sim3.6$) as compared to that in the D-gluco-configuration ($\delta\sim4.0$).[11] In **10b**, H3 appeared considerably upfield (at δ 3.86) as compare to **10a** (at δ 4.03) further supporting the L-ido- and D-gluco-configuration at C5 to **10b** and **10a**, respectively.

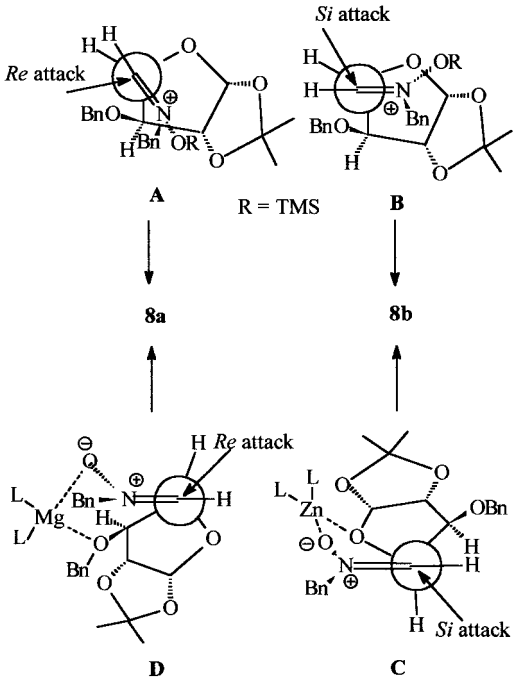


Figure 2.

2.1. Explanation for the observed diasteroselectivity

According to Felkin–Anh[12] model two conformations **A** and **B** (Fig. 2) were considered. Although, transition state **A** is preferred over **B**,[13] the attack of the bulky silyl ketene acetal, along the Bürgi–Dunitz trajectory[14] from the *Re* face is disfavored by the C3-benzyloxy substituent. This explains why D-gluco isomer **8a** is obtained as a minor product. However, in the alternate transition state **B**, the attack of the silyl ketene acetal from the opposite face of the bulky C3-benzyloxy group (*Si* face) is strongly favored due to the minimised steric non-bonded interactions, leading to the preferential formation of the L-ido-isomer **8b** as the major product.

The stereochemical outcome in the bivalent metal assisted reaction could be explained by considering the chelated transition states involving the metal complexation with nitrone oxygen and proximate alkoxy groups.[6] Two conformations **C** and **D** (Fig. 2) are therefore considered. The α-chelation of nitrone oxygen with furanose ring oxygen, in a six membered transition state, is represented in model **C** while the β-chelation with the benzyloxy substituent at C3 resembles the model **D**. For the reaction in the presence of $MgBr_2$, we assume that the reactive transition state that resembles the complexation of magnesium hydroxylamine with the C3 benzyloxy group prevails (β-chelated model **D**) wherein; *Re* facial nucleophilic addition, from the small group, gives the observed D-gluco stereoselectivity (anti-product). In the case of $ZnCl_2$ and ZnI_2 mediated addition reactions with nitones, with α- and β-alkoxy substituents in the proximity, earlier workers have shown that the α-chelation model explains the observed stereoselectivity.[6] Thus, nucleophilic attack from the preferred *Si* face in conformer **C** affords the syn-adduct albeit in poor selectivity. Other workers also noted an analogous observation wherein a bidentate Lewis acid precomplex the nitrones and α-chelated conformation leads to syn-adducts while the β-chelated one affords the anti-adducts.[7g]

2.2. Synthesis of D-gluco- and L-ido-homo-1-deoxynojirimycins

The C5 amino alcohols **10a** and **10b** with respective D-gluco- and L-ido-configurations are the true intermediates for the synthesis of higher homologues of 1-deoxynojirimycin. Thus, in the subsequent steps, the one pot deprotection of *N*- and *O*-benzyl groups in **10a**, by treatment with 10% Pd/C in the presence of ammonium formate as a hydrogen donor in methanol, afforded amino alcohol **11a** in 91% yield. The removal of the 1,2-*O*-isopropylidene functionality in **11a** with TFA–water followed by hydrogenation with 10% Pd/C resulted into a complex mixture of products. Therefore, C5–NH_2 functionality in **11a** was protected with Cbz group using benzyl chloroformate in the presence of sodium bicarbonate in ethanol–water to obtain *N*-Cbz protected amino alcohol **12a** in 95% yield. Finally, hydrolysis of **12a** with TFA–water at 0°C to 25°C for 2 h afforded a hemiacetal which was directly subjected to hydrogenolysis using 10% Pd/C wherein deprotection of the *N*-Cbz group, intramolecular amine cyclisation, imine formation and reduction of the imino group in one pot gave D-gluco-homo-1-deoxynojirimycin **1d** as a pale yellow

solid. In the ^{1}H NMR spectra, appearance of two triplets with large coupling constants- one at δ 3.08 corresponds to H4 ($J_{4,5}$=$J_{3,4}$=9.5 Hz) and other at δ 3.27 for H3 ($J_{3,4}$=$J_{2,3}$=9.5 Hz) indicated *trans* diaxial relation with the adjacent protons. In the amino alcohol **10a** the relative stereochemistry of the substituents at C2, C3 and C3, C4 is *trans* and the same stereochemistry is retained in the product formation. The appearance of eight line pattern (ddd) at 2.51 δ corresponding to H5 with $J_{4,5}$=9.5 Hz, $J_{5,6}$=8.8 Hz and $J_{5,6'}$=3.3 Hz confirmed the trans diaxial relative disposition of H4 and H5 protons. This confirms that the C5 substituent (–CH_2CH_2OH) is oriented equatorially [(5*R*)-configuration] and the compound **1d** has the $^4C_1$ conformation.

In an analogous reaction sequence, the pure *N*-benzyl amino alcohol **10b** on hydrogenolysis gave **11b**, which on selective *N*-protection afforded *N*-Cbz-amino alcohol **12b**. In the next step, removal of the acetonide group followed by the hydrogenolysis afforded L-ido-homo-1-deoxynojirimycin **1c** in 78% yield from **10b**. Since the ^{1}H NMR spectrum of **1c** is very different from **1d**, it was thought that **1c** could exit in the $^1C_4$ conformation. However, appearance of two distinct doublet of doublets for H1a at δ 2.62 ($J_{1a,1e}$=13.3 Hz; $J_{1a,2}$=8.2 Hz) and for H1e at δ 2.88 ($J_{1e,1a}$=13.3 Hz; $J_{1e,2}$=4.2 Hz) were informative. The large coupling constant ($J_{1a,2}$=8.2 Hz) for the H1 axial proton requires *trans* diaxial relationship with H2 proton. This clearly requires H2 proton to be axial and suggestive of the fact that compound **1c** exits in $^4C_1$ conformation. The ^{1}H and ^{13}C NMR spectral and analytical data was also found to be in consonance with the data reported earlier by us[4a] thus confirming the $^4C_1$ conformation with (5*S*) configuration.

In conclusion, we have demonstrated that the 1,3-addition reaction of silyl ketene acetal **6** with D-glucose derived nitrone **7** can be stereocontrolled by the use of appropriate Lewis acid under chelation and non-chelated controlled pathways. The two-diastereomeric sugar β-aminoesters thus obtained were successfully utilized in the synthesis of D-gluco-homo-1-deoxynojirimycin and L-ido-homo-1-deoxynojirimycin. Work is in progress to demonstrate the applicability of this methodology in the synthesis of castanospermine.

3. Experimental

^{1}H NMR (300 MHz, 500 MHz) and ^{13}C NMR (75 MHz, 125 MHz) spectra were recorded using $CDCl_3$ as a solvent unless otherwise stated. Chemical shifts are reported in ppm (δ) relative to internal standard Me_4Si. IR spectra (ν, cm^{-1}) were measured as thin films or nujol mulls or KBr pellets. Optical rotations were recorded at 25°C. Whenever required the reactions were carried out in oven-dried glassware under dry N_2. On work up, reaction mixture was extracted with organic solvents, evaporated at reduced pressure with rotary evaporator. Thin layer chromatography was performed on 0.25 mm pre-coated silica gel; flash chromatography was carried out on silica gel 200–400 mesh and column chromatography on silica gel 100–200 mesh. The organic solvents such as n-hexane, THF, diethyl ether, methylene chloride, chloroform, petroleum ether (pet. ether, 60–70°C fraction), ethyl acetate and methanol were purified and dried before use. *N*-Benzylhydroxylamine, *N*-benzylamine, HMDS, HMPA, LAH, Cbz-Cl were purchased from Aldrich and/or Fluka. Sugar nitrone **6** was prepared from 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-pento-dialdose in 78% yield as reported earlier.[4c]

3.1. General procedure for the cycloaddition of silyl ketene acetal 6 to nitrone 7 in the presence of Lewis acid

To a solution of nitrone **7** (1 equiv.) in dichloromethane (5 mL) was added Lewis acid (0.1, 1.2 or 3.0 equiv.) at 0°C and the reaction mixture was stirred for 30 min. After cooling (−78°C or −10°C) silyl ketene acetal **6** (1.3 equiv.) in solvent (5 mL) was added and stirred for required time at specific temperature (Table 1). After completion of the reaction, as monitored by TLC, a saturated solution of aqueous NH_4Cl (2 mL) was added and the reaction mixture was extracted with organic solvent. The combined organic layer washed with water and brine and dried over anhydrous Na_2SO_4. Solvent removal afforded a diastereomeric mixture of **8a** and **8b** as a thick liquid, which was purified by column chromatography using pet. ether/ethyl acetate (7:3) as an eluent (yield 83–96%).

3.1.1. Ethyl 3-*O*-benzyl-5-aminobenzyl-1,2-*O*-isopropylidene-α-D-*gluco*-hept-furanuronate (9a). Ethyl 3-*O*-benzyl-5-aminobenzyl-1,2-*O*-isopropylidene-β-L-*ido*-hept-furanuronate (9b). Copper(II) acetate (0.02 g, 0.110 mmol) was added to a stirred solution of zinc dust (0.25 g, 3.85 mmol) in glacial acetic acid (1 mL) under N_2. The mixture was stirred at room temperature for 15 min until the colour disappeared. A mixture of **8a** and **8b** (0.45 g, 0.77 mmol) in glacial acetic acid (1 mL) and water (0.3 mL) was added, the reaction mixture was heated at 70°C for 1 h and then cooled to room temperature. After the sodium salt of EDTA (0.1 g) was added, the mixture was stirred for 10 min and then made alkaline (pH=10) by addition of 3 M NaOH. Extraction with chloroform (3×10 ml) and usual workup gave a thick oil. Flash chromatographic purification by elution with pet. ether/ethyl acetate (98/2) gave **9a** (0.109 g, 31%) as a thick colourless oil: R_f=0.47 (hexane/EtOAc=6/4); $[\alpha]_D$=−42.16 (*c* 0.44, $CHCl_3$); IR (neat) 3330, 1730; ^{1}H NMR (300 MHz) δ 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) δ 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.

Futher elution with pet. ether/ethyl acetate=95/5 gave **9b** (0.21 g, 60%) as a pale yellow solid: mp 70–72°C; R_f=0.36 (Hexane/EtOAc=6/4); $[\alpha]_D$=−26.25 (*c* 0.32, $CHCl_3$); IR (nujol) 3337, 1731; ^{1}H NMR (300 MHz) δ 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) δ 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.

3.1.2. 3-*O*-Benzyl-5,6-dideoxy-5-(*N*-benzyl)amino-1,2-*O*-isopropylidene-α-D-*gluco*-hepto-1,4-furanose 10a. To an ice cooled suspension of LAH (0.20 g, 5.49 mmol) in dry THF (5 mL) was added a solution of **9a** (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 the reaction was quenched with saturated solution of NH_4Cl (2 mL). The solution was filtered, the residue washed with ethyl acetate (5 mL) and workup as usual. Flash chromatography ($CHCl_3$/MeOH=98/2) gave **10a** (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) δ 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) δ 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, 69.49; H, 7.77.

3.1.3. 3-*O*-Benzyl-5,6-dideoxy-5-(*N*-benzyl)amino-1,2-*O*-isopropylidene-β-L-*ido*-hepto-1,4-furanose 10b. The reaction of **9b** (0.5 g, 1.1 mmol) with LAH (0.20 g, 5.49 mmol) under the same conditions as reported for **9a**. Flash chromatography ($CHCl_3$/MeOH=96/4) afforded **10b** (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) δ 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) δ 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, 69.73; H, 7.61.

3.1.4. 5,6-Dideoxy-5-amino-1,2-*O*-isopropylidene-α-D-*gluco*-hepto-1,4-furanose 11a. To a stirred suspension of **10a** (0.35 g, 0.847 mmol), 10% Pd/C (0.35 g) in dry methanol (10 mL) was added ammonium formate (0.38 g, 6.01 mmol). The reaction mixture was refluxed for 1 h and cooled to room temperature. The catalyst was filtered through celite and washed with methanol (5 mL). The filtrate was evaporated to afford oil, which was purified by column chromatography. Elution with $CHCl_3$/MeOH (95/5) gave amine **11a** (0.29 g, 91%) as a thick liquid: R_f=0.67 ($CHCl_3$/MeOH=1/1); $[\alpha]_D$=−21.6 (c 0.5, MeOH); IR (neat) 3750–3150 (broad); ^{1}H NMR (300 MHz) δ 1.36 (s, 3H), 1.51 (s, 3H), 1.75–1.85 (m, 1H), 1.92–2.03 (m, 1H), 3.42–3.49 (m, 1H), 3.78 (t, J=6.2 Hz, 1H), 4.12 (dd, J=7.3, 2.6 Hz, 1H), 4.40 (d, J=2.6 Hz, 1H), 4.70 (d, J=3.6 Hz, 1H), 6.05 (d, J=3.6 Hz, 1H); ^{13}C NMR (125 MHz) δ 27.6, 28.1, 36.1, 50.2, 61.2, 76.4, 83.8, 87.1, 107.0, 115.2. Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21. Found: C, 51.47; H, 8.41.

3.1.5. 5,6-Dideoxy-5-amino-1,2-*O*-isopropylidene-β-L-*ido*-hepto-1,4-furanose 11b. A stirred solution of **10b** (0.4 g, 0.97 mmol), 10%Pd/C (0.4 g), ammonium formate (0.43 g, 6.89 mmol) in dry methanol (10 mL) was refluxed for 1.5 h. Workup as in the case of **11a**, purification by column chromatography and eluting with $CHCl_3$/MeOH (95/5) gave **11b** (0.29 g, 89%) as a thick liquid: R_f=0.39 ($CHCl_3$/MeOH=1/1); $[\alpha]_D$=−11.14 (c 0.28, MeOH); IR (neat) 3800–3300 (broad); ^{1}H NMR (300 MHz) δ 1.32 (s, 3H), 1.48 (s, 3H), 1.75–1.90 (m, 2H), 2.50–3.00 (bs, exchanges with D_2O, 4H), 3.40–3.48 (m, 1H), 3.75–3.89 (m, 2H), 4.08 (bs, 1H), 4.28 (bd, J=2.0 Hz, 1H), 4.49 (d, J=3.3 Hz, 1H), 5.95 (d, J=3.3 Hz, 1H); ^{13}C NMR (125 MHz) δ 27.7, 28.1, 37.0, 49.6, 61.0, 76.4, 86.2, 87.5, 106.8, 115.0; Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.47; H, 8.21. Found: C, 51.38; H, 8.36.

3.1.6. 5,6-Dideoxy-5-(*N*-benzoxycarbonyl)amino-1,2-*O*-isopropylidene-α-D-*gluco*-hepto-1,4-furanose 12a. To a stirred solution of **11a** (0.12 g, 0.515 mmol) and $NaHCO_3$ (0.12g, 1.428 mmol) in ethanol–water (2 mL, 1:1), at 0°C, was added benzyl chloroformate (0.131 g, 0.770 mmol). The mixture was stirred at 25°C for 6 h, quenched with water and extracted with chloroform (3×10 mL). Usual workup and purification by column chromatography (pet ether/ethylacetate=1/1) gave **12a** as a thick liquid (0.18 g, 95%): R_f=0.71 ($CHCl_3$/MeOH=9/1); $[\alpha]_D$=+58.56 (c 0.32, MeOH); IR (neat) 3600–3300, 1693; ^{1}H NMR (300 MHz, $CDCl_3$+D_2O) δ 1.32 (s, 3H), 1.49 (s, 3H), 1.80–1.92 (m, 1H), 2.00–2.18 (m, 1H), 3.80–4.06 (m, 4H), 4.09 (bs, 1H), 4.57 (d, J=3.6 Hz, 1H), 5.10 (ABq, J=12.1 Hz, 2H), 5.91 (d, J=3.6 Hz, 1H), 7.30–7.41 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$+D_2O) δ 26.1, 26.8, 32.9, 47.6, 59.4, 67.3, 74.0, 81.7, 84.4, 104.8, 111.5, 128.1, 128.3, 128.5, 135.9, 157.8. Anal. Calcd for $C_{18}H_{25}NO_7$: C, 58.84; H, 6.86. Found: C, 58.63; H, 7.09.

3.1.7. 5,6-Dideoxy-5-(*N*-benzoxycarbonyl)amino-1,2-*O*-isopropylidene-β-L-*ido*-hepto-1,4-furanose 12b. Reaction of β-amino alcohol **11b** (0.15 g, 0.644 mmol), $NaHCO_3$ (0.15 g, 1.785 mmol) with benzyl chloroformate (0.179 g, 1.049 mmol) under the same conditions as for **11a** afforded a compound which on column chromatographic purification using pet. ether/ethyl acetate (1/1) as an eluent gave **12b** (0.19 g, 80%) as a thick liquid: R_f=0.24 ($CHCl_3$/MeOH=9/1); $[\alpha]_D$=−60.65 (c 0.25, MeOH); IR (neat) 3700–3200, 1695; ^{1}H NMR (200 MHz, $CDCl_3$+D_2O) δ 1.30 (s, 3H), 1.48 (s, 3H), 1.35–2.00 (m, 2H), 3.60–3.75 (m, 2H), 4.00–4.25 (m, 3H), 4.52 (d, J=4.0 Hz, 1H), 5.10 (AB quartet, J=12.0 Hz, 2H), 5.93 (d, J=4.0 Hz, 1H), 7.30–7.41 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$+D_2O) δ 26.0, 26.6,

35.0, 47.5, 58.4, 66.9, 74.5, 81.8, 85.3, 104.4, 111.4, 127.9, 128.0, 128.4, 136.2, 157.5; Anal. Calcd for $C_{18}H_{25}NO_7$: C, 58.84; H, 6.86. Found: C, 58.60; H, 7.04.

3.1.8. 1,5,6-Trideoxy-1,5-imino-D-*gluco*-heptitol 1d. An ice cooled solution of **12a** (0.16 g, 0.436 mmol) in TFA–H_2O (2 mL, 3:2) was warmed up to 25°C and stirred for 2 h. TFA was evaporated at high vacuum to yield a hemiacetal which was directly used in the next reaction. To a solution of hemiacetal in methanol (5 mL) was added 10% Pd/C (0.02 g) and the solution was hydrogenolysed (70 psi) at room temperature for 16 h. The catalyst was filtered, washed with methanol and the combined filtrate concentrated to a residue. The residue was washed with chloroform (3×2 mL) and then purified by column of amberlite IR 400A (OH^-) resin eluting with distilled water to yield a colorless semisolid **1d** (0.070 g, 90%): R_f=0.37 (EtOH/H_2O=3/2); $[\alpha]_D$=+8.7 (*c* 0.2, H_2O); IR (KBr) 3650–2900; ^{1}H NMR (300 MHz, $CDCl_3$+D_2O) δ 1.46–1.60 (m, 1H), 1.95–2.12 (m, 1H), 2.41 (dd, *J*=11.0, 12.5 Hz, 1H), 2.51 (ddd, *J*=3.3, 8.8, 9.5 Hz, 1H), 3.04 (dd, *J*=5.5, 12.5 Hz, 1H), 3.08 (t, *J*=9.5 Hz, 1H), 3.27 (t, *J*=9.5 Hz, 1H), 3.48 (ddd, *J*=5.5, 9.5, 11.0 Hz, 1H), 3.50–3.80 (m, 2H); ^{13}C NMR (125 MHz) δ 36.4, 51.5, 59.8, 61.5, 73.5, 77.6, 81.0. Anal. Calcd for $C_7H_{15}NO_4$: C, 47.44; H, 8.53. Found: C, 47.60; H, 8.75.

3.1.9. 1,5,6-Trideoxy-1,5-imino-L-*ido*-heptitol 1c. An ice cooled solution of **12b** (0.075 g, 0.204 mmol) in TFA–water (2 mL, 3:2) was warmed to 25°C and stirred for 2 h. After work up, as in case of **1d**, the hemiacetal was directly hydrogenolysed in methanol using 10% Pd/C (0.01 g) for 16 h. Work up as in case of **1d** afforded a foaming solid (0.034 g, 94%): mp 132–135°C; R_f=0.20 (EtOH/H_2O=3/2); $[\alpha]_D$=−13.85 (*c* 0.8, H_2O); IR (KBr) 3400–2900; ^{1}H NMR (300 MHz, $CDCl_3$+D_2O) δ 1.62–1.78 (m, 2H), 2.62 (dd *J*=8.2, 13.3 Hz, 1H), 2.88 (dd *J*=4.2, 13.3 Hz, 1H), 3.04–3.14 (m, 1H), 3.40–3.57 (m, 3H), 3.59–3.76 (m, 2H); ^{13}C NMR (125 MHz) δ 30.94, 46.73, 55.15, 62.13, 73.22, 74.51, 75.26; Anal. Calcd for $C_7H_{15}NO_4$: C, 47.44; H, 8.53. Found: C, 47.25; H, 8.74.

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9. The diastereomeric ratio was determined by converting a mixture of **8a** and **8b** to amino alcohols **10a** and **10b**. The ^{1}H NMR spectra of C5 epimeric amino alcohols **10a** and **10b** were informative in the assignment of diastereomeric ratio (*vide supra*).
10. The product of this reaction was a mixture of **8a** and **8b** along with the corresponding–OTMS derivative. We also noticed such type of scrambling of trialkylsilyl groups in the TMSOTf catalysed reaction earlier; see: Ref. 5d.
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13. We believe that the C–O bond will adopt the perpendicular position; in fact it is known that nucleophilic attack seeks the LUMO of nitrone which may be stabilized through mixing of the $\pi^*_{C=N}$ orbital with the lowest energy σ^* orbital of a substiutent, generally associated with the most electronegative substiuent. See reference: Houk, K. N.; Paddon-Row, N. M.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108.
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