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Synthesis of trihydroxy quinolizidine alkaloids: 1,3-addition reaction of allylmagnesium bromide to a sugar nitrone

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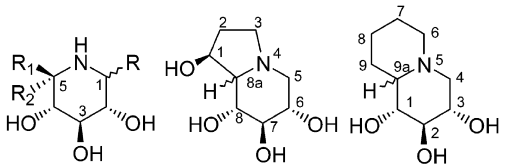
Abstract—The synthesis of (1*R*,2*R*,3*S*,9a*R*) and (1*R*,2*R*,3*S*,9a*S*) trihydroxy quinolizidine alkaloids **3a** and **3b** from D-glucose derived nitrone **4** is described. The key transformation involves the 1,3-addition of allylmagnesium bromide to nitrone **4** that afforded high diastereoselectivity in the presence of TMSOTf. The N–O bond reductive cleavage, *N*-Cbz protection, ozonolysis, Wittig olefination, lactum formation and reductive amination cascade afforded the target compounds **3a** and **3b** in good overall yield.

1. Introduction

Nitrones are becoming increasingly important in providing intermediates for the synthesis of complex molecules, including natural products and bioactive compounds.[1] In general, nitrones are employed in the 1,3-dipolar cycloaddition pathway with different olefinic compounds both in the inter- and intramolecular version. Alternatively, the reactions of nitrones as electrophiles with organometallic reagents (1,3-addition) are gaining a lot of interest in recent years.[2] Easy availability of organometallic compounds as nucleophiles (different metals combined with aryl or alkyl substituents), high electrophilicity of nitrones and feasibility to manipulate the stereoselectivity at the prochiral nitrone-carbon, under different chelation and non-chelation conditions by the use of suitable Lewis acids, made this approach versatile in organic synthesis. This approach is now finding applications in carbohydrate chemistry, especially in the synthesis of polyhydroxylated indolizidine, pyrrolidine and piperidine alkaloids.[3] In this context, we have recently reported on the diastereoselective 1,3-addition of methylmagnesium chloride and silyl ketene acetals to D-glucose derived nitrones in the synthesis of 6-deoxynojirimycin **1a** (Fig. 1) and 1-deoxy-D-*gluco*/L-*ido*-homonojirimycin, **1b**/**1c**, respectively.[4] This class of compounds, in particular polyhydroxylated piperidine (e.g. nojirimycin **1d**), indolizidine (e.g. castanospermine **2**) and quinolizidine-alkaloids **3a** and **3b** have attracted considerable attention because of their promising glycosidase inhibitory activity—the process that plays a crucial role in many biological processes, including breakdown of edible carbohydrates, eukaryotic glycoprotein processing and polysaccharide and glycoconjugate anabolism and catabolism.[5]



1a R = OH, R_1 = CH_3, R_2 = H
1b R = R_2 = H, R_1 = CH_2CH_2OH
1c R = R_1 = H, R_2 = CH_2CH_2OH
1d R = OH, R_1 = CH_2OH, R_2 = H

Figure 1.

The quinolizidine alkaloids are frequently encountered in nature especially in ant species and in the skin of frogs and toads.[6] Although a variety of structurally complex quinolizidine alkaloids are known, the synthesis of polyhydroxylated quinolizidine alkaloids and evaluation of their glycosidase inhibitory activity is a topic of current interest.[7] As part of our continuing efforts in the synthesis of azasugars,[4,8] we are now describing a synthesis of trihydroxy quinolizidine alkaloids **3a** and **3b** using the 1,3-addition reaction of allylmagnesium bromide to a D-glucose derived nitrone **4** as a key step. Although, a few reports are available for the synthesis of polyhydroxylated quinolizidine alkaloids only a single report describes the synthesis of **3b**,[9] while the synthesis of **3a** is not reported so far.

Keywords: Nitrone; Azasugar; Carbohydrate; Quinolizidine; Glycosidase; Inhibitor.
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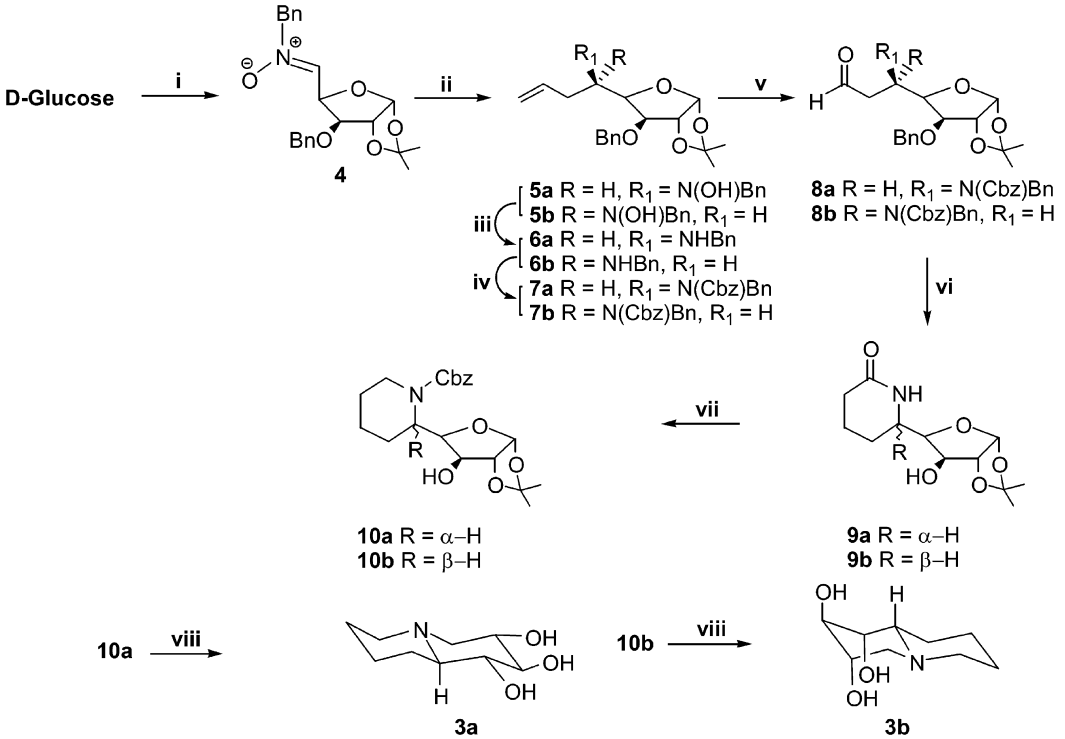
2. Results and discussion

2.1. Stereoselective 1,3-addition of allylmagnesium bromide to sugar derived nitrone 4

The desired sugar nitrone **4** was 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.[4a] The 1,3-addition of allylmagnesium bromide to **4** at −78 °C in dry THF for 2 h afforded a diastereomeric mixture of *N*-benzylhydroxylamines **5a** and **5b** in 92% yield in the ratio D-*gluco*:L-*ido*=7:3, as evident from the ^{1}H NMR spectrum of the crude product (Scheme 1). To improve the stereoselectivity at the prochiral C5 center, various reaction conditions (e.g. change of solvent, temperature and stoichiometry of reactants) were tried (Table 1). Performing the reaction using ether as solvent had no effect on the stereoselectivity while no product was obtained when dichloromethane was used (entries 2 and 3). Change in the stoichiometry of the reactants (i.e. decreasing the Grignard to nitrone ratio) lowered the combined yield with no significant change in the stereoselectivity (entries 4 and 5). In case of nitrones it is known that the presence of an oxygen atom, formally carrying a net negative charge, allows a strong complexation with Lewis acid to occur. The resulting *N*-*oxy*-immonium species thus displayed enhanced reactivity and, in some cases, different stereochemical outcomes in reaction with nucleophiles.[10] In this context, we have demonstrated the utility of trimethylsilyltriflate (TMSOTf) as a promoter that leads to good stereoselectivity with high yield under kinetic and non-chelation controlled conditions.[10d–h] Inspired by this observation, the reaction of nitrone **4** with allylmagnesium bromide (2.5 equiv.) in the presence of TMSOTf (1 equiv.) was performed. The product on desilylation afforded **5a** and **5b** in the ratio



Scheme 1. Reagents and conditions: (i) Ref. 4a 78%; (ii) Allylmagnesium bromide (2.5 equiv.), THF, −78 °C, 2 h, 93%; (iii) Zn (2 equiv.), $Cu(OAc)_2$, AcOH, 70 °C, 1 h, 78%; (iv) Cbz-Cl (1.5 equiv.), $NaHCO_3$, aq. EtOH, 2 h, 75%; (v) O_3, DCM, DMS, −40 °C, 1 h, 90%; (vi) a) Ph_3P=CHCOOEt (1.5 equiv.), MeOH, rt, 2 h; (b) H_2, 10% Pd–C, MeOH, 25 °C, 12 h; (c) CH_3COONa (4 equiv.), MeOH, reflux, 6 h, 69%; (vii) a) LAH (5 equiv.), THF, 0 °C, 1 h; (b) Cbz-Cl (1.5 equiv.), $NaHCO_3$, aq. EtOH, 2 h, 74%; (Viii) (a) TFA/H_2O (3:2), 0 °C to rt, 2.5 h; (b) H_2, 10% Pd–C, MeOH, 25 °C, 12 h, 87%.

Table 1. 1,3-Addition reaction of allylmagnesium bromide to sugar derived nitrone **4**

Entry	RMgBr R=allyl (equiv.)	Solvent	Lewis acid	Temperature (°C)	Time (h)	Product ratio[a] **5a** and **5b**	Yield[b] (%)
1	2.5	THF	—	−78	2	70/30	92
2	2.5	Et_2O	—	−30	4	65/35	94
3	2.5	CH_2Cl_2	—	−30	48	No reaction[c]	—
4	2.0	THF	—	−78	2	69/31	78[d]
5	1.5	THF	—	−78	5	65/35	48[d]
6	2.5	THF	TMSOTf	−78	2	86/14	93

[a] Ratio was calculated by ^{1}H NMR data of the crude product.
[b] Yields refer to the isolated yields after chromatography.
[c] Starting was recovered ~100%.
[d] Starting was recovered.

86:14, respectively, resulting in a significant improvement of the diastereoselective in favor of D-*gluco* isomer with high yield.

2.2. Assignment of the relative stereochemistry at C5 of the 5a and 5b

The relative stereochemistry at C5 in **5a** and **5b** was assigned on the basis of ^{1}H NMR data. It is known that for a given C5-epimeric pair, derived from the 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).[11] The higher value of $J_{4,5}$ observed in the diastereomer **5b** (9.5 Hz), as compared to **5a** (8.3 Hz) indicated the L-*ido* configuration for **5b** and the D-*gluco* configuration for **5a**. This assignment was further supported by 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, which is significantly upfield ($\delta\sim3.6$) as compared to that in the D-*gluco* ($\delta\sim4.0$).[11] In **5b** H3 appeared upfield at δ 3.84 as compared to **5a** at δ 4.01, further supporting the D-*gluco* and L-*ido* configuration at C5 to **5a** and **5b**, respectively. Thus, the absolute configurations at C-5 in **5a** and **5b** were assigned as (5*R*) and (5*S*), respectively.

2.3. Explanation for the observed stereochemistry

The observed facial selectivity in the 1,3-addition of allylmagnesium bromide to nitrone **4** could be rationalized by Felkin-Anh like transition states (TS) **A** and **B** (Fig. 2). According to Felkin-Anh model[12] the large substituent is kept perpendicular to the C=N bond. We believe that the C–O bond will adopt this position; in fact it is known that nucleophilic attack seeks the LUMO of the nitrone which may be stabilized through mixing of the π^* C=N orbital with the lowest energy σ^* orbital of a substituent, generally associated with the most electronegative substituent.[13] Amongst the two transition states, the TS **A** offers the more favorable Burgi–Dunitz trajectory for the incoming nucleophile[14] thus favoring the formation of D-*gluco* isomer in a major amount and this effect is magnified in the presence of TMSOTf.

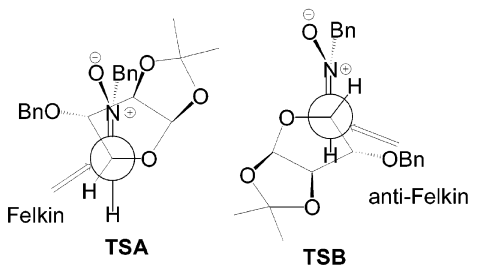


Figure 2.

2.4. Synthesis of 3a and 3b

The utility of **5a** and **5b** were demonstrated in the formation of the corresponding quinolizidine alkaloids **3a** and **3b**. As shown in Scheme 1, the N–O bond reductive cleavage of *N*-benzylhydroxylamine **5a** with zinc in acetic acid–water (85:15) at 70 °C for 1 h afforded the *N*-benzylamino sugar **6a** in good yield. The amino functionality in **6a** was protected with benzyloxycarbonyl chloride in the presence of sodium bicarbonate in aq. ethanol to afford *N*-Cbz protected compound **7a** in 95% yield.[15] Ozonolysis of **7a** at −40 °C in dry CH_2Cl_2 for 2 h afforded aldehyde **8a** in 80% yield. Wittig reaction of aldehyde **8a** with Ph_3-P=CHCOOEt in methanol gave a geometric mixture of α,β-unsaturated-δ-amino esters in 92% yield which was directly subjected to hydrogenation followed by treatment with sodium acetate in methanol to afford six membered δ-lactam **9a** in 70% yield. In the subsequent steps, reduction of the lactam functionality in **9a** with LAH in THF and N-protection with benzyl chloroformate gave **10a** in 78% yield. Finally, compound **10a** was reacted with TFA–H_2O and the hemiacetal thus obtained was subjected to hydrogenation to give (1*R*,2*R*,3*S*,9a*R*)-octahydro-2*H*-quinolizine-1,2,3-triol **3a**. The same reaction sequence was repeated for the *N*-hydroxylamine **5b** (Scheme 1). The corresponding C5-epimeric compounds **6b**, **7b**, **8b** and **9b** were isolated and characterized by spectral and analytical data. Comparison of the IR and ^{1}H NMR spectra of C5-epimeric compounds **9a** and **9b** led to an interesting observation. In the IR spectrum, compound **9a** (D-*gluco*) showed the amide carbonyl stretching frequency at 1658 cm^{-1} while; in compound **9b** (L-*ido*) amide stretching frequency was appeared at 1624 cm^{-1}. The decrease in IR carbonyl frequency in **9b** could be attributed to the intramolecular hydrogen bonding between C3–OH and amide carbonyl oxygen as shown in Figure 3. This observation is substantiated by the fact that, in the ^{1}H NMR spectra, the observed $J_{4,5}$ is found to be larger in D-*gluco* isomer **9a** (9.3 Hz) than the corresponding C5 epimeric L-*ido* isomer **9b** (4.8 Hz). This finding is opposite to that reported ($J_{4,5}$ in L-*ido*>D-*gluco*)[11] and could be attributed to the possible six membered intramolecular hydrogen bonding in **9a** and **9b** between NH and C3 oxygen by rotation about the C4–C5 bond (Fig. 3). In this situation, the molecule is held in such a way that, for the hydrogen bonded D-*gluco* isomer **9a**, the dihedral angle between H4 and H5 is ~180° and that for L-*ido* isomer **9b** is ~45° thus resulting in the observed coupling constants.

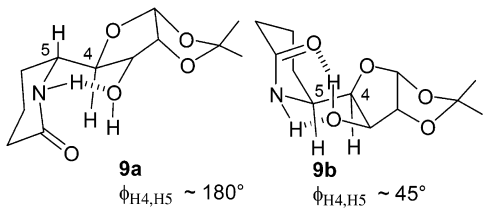


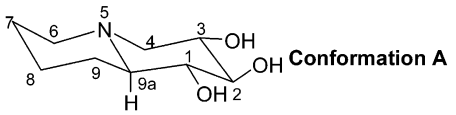
Figure 3.

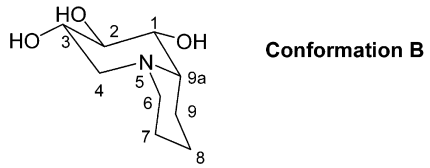
In the next step, reduction of the lactam functionality in **9b** with LAH in THF followed by the *N*-Cbz protection afforded **10b**.[16] Compound **10b** was reacted with TFA–H_2O and the hemiacetal thus obtained was subjected for hydrogenation to give (1*R*,2*R*,3*S*,9a*S*)-octahydro-2*H*-quinolizine-1,2,3-triol **3b**.

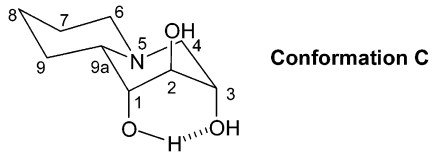
2.5. Conformational assignment of 3a and 3b

Azasugars can exist in different conformations. For example, nojirimycin exists in $^4C_1$ conformation and the castanospermine and 1-deoxy-castanospermine are present

in $^{8}C_{5}$ conformation while; we have reported that the 1-deoxy-8a-*epi*-castanospermine is present in $^{5}C_{8}$ conformation.[8h] The quinolizidine alkaloids **3a** and **3b** have the framework of aza-decalin system wherein one can expect *trans* or *cis* ring fusion. In order to know the conformations, we studied the ^{1}H NMR spectra of **3a** and **3b** and the coupling constant information was obtained by decoupling experiments. In the ^{1}H NMR spectra of **3a** the doublet of triplet ($J_{3,4e}$=4.4 Hz and $J_{3,4a}$=$J_{3,2}$=9.5 Hz), corresponding to H3 proton, indicated the axial orientation of this proton. The triplet ($J_{2,3}$=$J_{2,1}$=9.5 Hz), corresponding to H2, requires *trans*-diaxial relationship with H3 and H1. As the *trans* aza-decalin is conformationally rigid chair-chair system, the conformation **A** was assigned to **3a**. Since the ^{1}H NMR spectrum of **3b** is very different from **3a** it was thought that **3b** could exist in different conformation. Thus, for **3b** we considered two conformations—one with *cis* ring fusion and equatorially oriented OH substituents (conformation **B**) and the other *trans* ring fusion with axially oriented OH substituents (conformation **C**). The initial geometry in the precursor **10b** ensures that in the product **3b** the substituents at C1, C2 and C2, C3 should be *trans*. The ^{1}H NMR of **3b** showed the low coupling constant values ($J_{1,2}$=$J_{2,3}$~3 Hz) between the H1-H2 and H2-H3. This indicated the equatorial orientation of these protons at C1/C2/C3. This fact is supported by the noticeable downfield shift of H1/H2/H3 as compared to the respective protons in **3a**. Based on this observation, we assigned the preferred *trans* ring fused conformation **C**, with axial orientation of the OH substituents, for compound **3b**.[17]







In conclusion, we have demonstrated that the 1,3-addition reaction of allylmagnesium bromide to sugar derived nitrone **4** can be stereocontrolled in favor of D-*gluco* isomer by the use of TMSOTf. The two diastereomeric γ-alkenylamines thus obtained were successfully utilized in the synthesis of trihydroxy quinolizidine alkaloids **3a** and **3b**.

3. Experimental

3.1. General

Melting points were recorded with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded with FTIR spectrophotometer as a thin film or in nujol mull and are expressed in cm^{-1}. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ as a solvent unless otherwise noted. NMR Chemical shifts are reported in δ (ppm) downfield from TMS. Elemental analyses were carried out with an elemental analyzer. Optical rotations were measured with a polarimeter using sodium light (D line 589.3 nm) at 25 °C. TLC was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with 100–200 mesh silica gel. The reactions were carried out in oven-dried glassware under dry N_2. Allylmagnesium bromide was prepared from Mg and allyl bromide in dry ether prior to use. *N*-Benzylhydroxylamine hydrochloride, LAH, Cbz-Cl was purchased from Aldrich and/or Fluka. Methanol, diethyl ether, dichloromethane, THF were purified and dried before use. Petroleum ether (PE) is a distillation fraction between 40–60 °C. After work up, organic layer was washed with water, brine and dried over anhydrous sodium sulfate and evaporated at reduced pressure. Sugar nitrone **4** was prepared from 1,2-*O*-benzyl-α-D-*xylo*-pento-dialdose in 78% yield as reported earlier.[4a] ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) of compounds **7a**, **7b** and **8a**, **8b** showed doubling of signals and therefore not stated in the experimental.[15]

3.1.1. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-5-(*N*-benzyl-*N*-hydroxyamino)-α-D-*gluco*-7-eno-octo-1,4-furanose (5a) and 3-*O*-benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetra-deoxy-5-(*N*-benzyl-*N*-hydroxyamino)-β-L-*ido*-7-eno-octo-1,4-furanose (5b). To a stirred solution of nitrone **4** (1 g, 2.61 mmol) in THF under nitrogen atmosphere, at −10 °C, was added dropwise TMSOTf (0.47 mL, 2.61 mmol). After stirring for 10 min. the mixture was cooled to −78 °C and allylmagnesium bromide (1 M in diethylether, 1.4 mL, 6.52 mmol) was added dropwise with stirring at −78 °C for 2 h. Quenching was performed with 2 M HCl (2 mL), with stirring at room temperature for 30 min. The reaction mixture was neutralized with saturated solution of $NaHCO_3$ and was extracted with diethyl ether (3×15 mL). The ethereal layer on work up afforded a thick oil. Column chromatograph using (2% EtOAc/Pet. Ether) gave **5a** (0.890 g, 80%) as thick liquid; [Found: C, 70.51; H, 7.30. $C_{25}H_{31}NO_5$ requires C, 70.57; H, 7.34%]; R_f (30% EtOAc/Hexane) 0.52; $[\alpha]_D$ −30.0 (*c* 2.40, $CHCl_3$); ν_{max}(neat) 3510–3160 (br), 1639 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (3H, s, *Me*), 1.44 (3H, s, *Me*), 2.49–2.69 (2H, m, *H*6), 3.41 (1H, ddd, *J*=8.3, 7.8, 4.8 Hz, *H*5), 3.76 (1H, d, *J*=13.6 Hz, CH_2Ph), 3.94 (1H, d, *J*=13.6 Hz, CH_2Ph), 4.01 (1H, d, *J*=3.0 Hz, *H*3), 4.37 (1H, dd, *J*=8.3, 3.0 Hz, *H*4), 4.40–4.45 (1H, bs, exchanges with D_2O, O*H*), 4.50 (1H, d, *J*=11.7 Hz, CH_2Ph), 4.54 (1H, d, *J*=3.9 Hz, *H*2), 4.63 (1H, d, *J*=11.7 Hz, CH_2Ph), 4.98 (1H, dd, *J*=11.1, 1.6 Hz, =CH_2), 5.10 (1H, dd, *J*=17.0, 1.6 Hz, =CH_2), 5.87 (1H, d, *J*=3.9 Hz, *H*1), 5.92–6.10 (1H, m, =C*H*), 7.12–7.28 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.2, 26.7, 31.4, 60.8, 63.4, 72.0, 79.6, 81.9, 82.5, 104.5, 111.3, 115.6, 127.1, 127.5, 127.6, 128.2, 128.4, 129.1, 137.6, 137.7, 138.3. Further elution with (5% EtOAc/Pet. Ether) afforded **5b** (0.145, 13%) as a thick liquid; [Found: C, 70.29; H, 7.59. $C_{25}H_{31}NO_5$ requires C, 70.57; H, 7.34%]; R_f (30% EtOAc/Hexane) 0.44; $[\alpha]_D$ −48.0 (*c* 0.25, $CHCl_3$); ν_{max}(neat) 3530–3150 (br), 1639 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.27 (3H, s, *Me*), 1.46 (3H, s, *Me*),

1.91–2.09 (1H, m, *H*6$_a$), 2.21–2.35 (1H, m, *H*6$_b$), 3.38 (1H, ddd, *J*=9.5, 8.1, 4.3 Hz, *H*5), 3.84 (1H, d, *J*=3.0 Hz, *H*3), 3.92 (1H, d, *J*=13.9 Hz, C*H*$_2$Ph), 4.09 (1H, d, *J*=13.9 Hz, C*H*$_2$Ph), 4.39 (1H, d, *J*=11.6 Hz, C*H*$_2$Ph), 4.44 (1H, dd, *J*=9.5, 3.0 Hz, *H*4), 4.57 (1H, d, *J*=3.8 Hz, *H*2), 4.61 (1H, d, *J*=11.6 Hz, C*H*$_2$Ph), 4.84–4.92 (2H, m, =C*H*$_2$), 4.93–4.96 (1H, bs, exchanges with D_2O, O*H*), 5.83–6.05 (1H, m, =C*H*), 5.93 (1H, d, *J*=3.8 Hz, *H*1), 7.10–7.38 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.5, 26.8, 34.3, 49.4, 57.3, 72.0, 81.3, 81.9, 83.5, 104.9, 111.3, 115.0, 126.2, 127.4, 127.5, 127.7, 128.2, 128.4, 137.9, 138.2, 141.5.

3.1.2. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-5-*N*-(benzylamino)-α-D-*gluco*-7-eno-octo1,4-furanose (6a). Zinc dust (0.275 g, 4.23 mmol) was added to a solution of copper(II) acetate (0.015 g) in glacial acetic acid (1 mL) under nitrogen and the mixture was stirred at 25 °C for 15 min until the color disappeared. *N*-Benzylhydroxylamine **5a** (0.30 g, 0.70 mmol) in glacial acetic acid (0.7 ml) and water (0.3 mL) was successively added; the reaction mixture was heated at 70 °C for 1 h and cooled to room temperature. The sodium salt of EDTA (0.1 g) was added to the mixture and stirred for 10 min and then made alkaline to pH 10 by addition of 3 M NaOH. The resulting solution was extracted with chloroform (3×15 mL) and the combined organic layer was evaporated to give an oil. Purification by column chromatography (15% EtOAc/Pet. Ether) gave **6a** (0.22 g, 76%) as a thick liquid; [Found: C, 73.26; H, 7.58. $C_{25}H_{31}NO_4$ requires C, 73.32; H, 7.63]; R_f 0.19 (50% EtOAc/Hexane); $[\alpha]_D$ −31.0 (*c* 1.55, $CHCl_3$); ν_{max}(neat) 3640–3310 (br), 1588 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (3H, s, *Me*), 1.47 (3H, s, *Me*), 1.59–1.62 (1H, bs, exchanges with D_2O, O*H*), 2.31–2.42 (1H, m, *H*6$_a$), 2.51–2.61 (1H, m, *H*6$_b$), 3.20 (1H, ddd, *J*=9.3, 6.0, 4.0 Hz, *H*5), 3.68 (1H, d, *J*=12.7 Hz, C*H*$_2$Ph), 3.85 (1H, d, *J*=12.7 Hz, C*H*$_2$Ph), 3.99 (1H, dd, *J*=9.3, 3.1 Hz, *H*4), 4.09 (1H, d, *J*=3.1 Hz, *H*3), 4.53 (1H, d, *J*=11.5 Hz, C*H*$_2$Ph), 4.60 (1H, d, *J*=3.8 Hz, *H*2), 4.68 (1H, d, *J*=11.5 Hz, C*H*$_2$Ph), 5.10–5.20 (2H, m, =C*H*$_2$), 5.71–6.00 (1H, m, =C*H*), 5.92 (1H, d, *J*=3.8 Hz, *H*1), 7.18–7.38 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.3, 26.8, 34.8, 51.5, 54.0, 71.9, 81.7, 81.8, 81.9, 104.7, 111.4, 118.1, 126.8, 127.7, 127.8, 128.1, 128.3, 128.4, 134.5, 137.5, 140.7.

3.1.3. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-5-*N*-(benzylamino)-β-L-*ido*-7-eno-octo-1,4-furanose (6b). The reaction of *N*-benzylhydroxylamine **5b** (0.30 g, 0.70 mmol) with Zn/Cu couple under the same reaction conditions reported for **6a**, gave *N*-benzylamine **6b** (0.23 g, 80%) as a thick liquid; [Found: C, 73.22; H, 7.51. $C_{25}H_{31}NO_4$ requires C, 73.32; H, 7.63%]; R_f (50% EtOAc/Hexane) 0.11; $[\alpha]_D$ −60.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat) 3620–3260 (br), 1638.6 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (3H, s, *Me*), 1.49 (3H, s, *Me*), 1.80–1.97 (1H, bs, exchanges with D_2O, O*H*), 2.01–2.14 (1H, m, *H*6$_a$), 2.20–2.32 (1H, m, *H*6$_b$), 3.19 (1H, ddd, *J*=10.0, 9.3, 5.1 Hz, *H*5), 3.83 (2H, ABq, *J*=12.3 Hz, C*H*$_2$Ph), 3.89 (1H, d, *J*=3.0 Hz, *H*3), 4.08 (1H, dd, *J*=9.3, 3.0 Hz, *H*4), 4.44 (1H, d, *J*=11.7 Hz, C*H*$_2$Ph), 4.64 (1H, d, *J*=3.9 Hz, *H*2), 4.86 (1H, d, *J*=11.7 Hz, C*H*$_2$Ph), 4.93–5.08 (2H, m, =C*H*$_2$), 5.81–5.98 (1H, m, =C*H*), 5.93 (1H, d, *J*=3.9 Hz, *H*1), 7.19–7.39 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.4, 26.7, 34.8, 51.7, 55.3, 71.4, 81.3, 81.7, 82.6, 104.5, 111.4, 116.7, 126.6, 127.8, 127.9, 128.1, 128.2, 128.3, 135.1, 136.9, 140.5.

3.1.4. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-α-D-*gluco*-7-eno-octo-1,4-furanose (7a). To a stirred solution of *N*-benzylamine **6a** (0.622 g, 1.52 mmol) in methanol (5 mL) was added benzyloxycarbonyl chloride (0.322 g, 2.28 mmol) and sodium bicarbonate (0.253 g, 3.00 mmol) and the reaction mixture was stirred at room temperature for 2 h. The methanol was evaporated under reduced pressure and water (10 mL) was added and extracted with chloroform (20 mL×3). Usual work up gave an oil which on purification by column chromatography (5% EtOAc/Pet. Ether) gave **7a** (0.610 g, 73%) as a thick liquid; [Found: C, 73.11; H, 7.09. $C_{33}H_{37}NO_6$ requires C, 72.91; H, 6.86%]; R_f (30% EtOAc/Hexane) 0.72; $[\alpha]_D$ −43.8 (*c* 3.75, $CHCl_3$); ν_{max}(neat) 1695, 1601 cm^{-1}.

3.1.5. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-β-L-*ido*-7-eno-octo-1,4-furanose (7b). The reaction of **6b** (1.5 g, 3.66 mmol) with benzyloxycarbonyl chloride (0.775 g, 5.50 mmol) and sodium bicarbonate (0.610 g, 7.26 mmol) was performed under the same conditions as reported for **7a**. Column chromatography (5% EtOAc/Pet. Ether) afforded **7b** (1.5 g, 79%) as a thick liquid; [Found: C, 72.98; H, 7.13. $C_{33}H_{37}NO_6$ requires C, 72.91; H, 6.86%]; R_f (30% EtOAc/Hexane) 0.59; $[\alpha]_D$ −8.1 (*c* 1.85, $CHCl_3$); ν_{max}(neat) 1697, 1598 cm^{-1}.

3.1.6. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-α-D-*gluco*-heptodialdo-1,4-furanose (8a). Ozone was bubbled through a solution of **7a** (0.3 g, 0.55 mmol) in dichloromethane (10 mL) at −40 °C until a blue color persisted. The reaction mixture was purged with O_2 until the blue color disappeared Dimethyl sulfide (1 mL, 5.5 mmol) was added and the reaction mixture was allow to attain room temperature and stirred for 2 h. The solvent was evaporated under reduced pressure to give a crude product that was purified by column chromatography (10% EtOAc/Pet. Ether) to give aldehyde **8a** (0.275 g, 91%) as a thick liquid; [Found: C, 70.31; H, 6.38. $C_{32}H_{35}NO_7$ requires C, 70.44; H, 6.47%]; R_f (30% EtOAc/Hexane) 0.65; $[\alpha]_D$ −28.7 (*c* 3.35, $CHCl_3$); ν_{max}(neat) 2731, 1722.3, 1697.2 cm^{-1}.

3.1.7. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-β-L-*ido*-heptodialdo-1,4-furanose (8b). The reaction of **7b** (1.0 g, 1.84 mmol)) with ozone in dichloromethane at −40 °C was performed under the same conditions as reported for **8a**. Column chromatography (10% EtOAc/Pet. Ether) afforded **8b** (0.900 g, 89%) as a thick liquid; [Found: C, 70.29; H, 6.32. $C_{32}H_{35}NO_7$ requires C, 70.44; H, 6.47%]; R_f (30% EtOAc/Hexane) 0.61; $[\alpha]_D$ −23.0 (*c* 2.0, $CHCl_3$); ν_{max}(neat) 2722, 1726, 1697 cm^{-1}.

3.1.8. 1,2-*O*-Isopropylidene-5,6,7,8-tetra-deoxy-5,9-imino-α-D-*gluco*-nona-1,4-furan-9-ulose (9a). To a solution of aldehyde **8a** (1 g, 1.83 mmol) in methanol (5 mL), Wittig reagent, triphenylethoxycarbonylmethylene phosphorane (0.957 g, 2.75 mmol) was added and reaction mixture was stirred for 2.5 h at room temperature. The methanol was evaporated the thick liquid obtained which on usual work up gave an oil. The crude product was directly

subjected to hydrogenation with 10% Pd/C (0.200 g) in methanol (10 mL) at 80 psi for 12 h. The solution was filtered through Celite and washed with methanol. To the filtrate anhydrous sodium acetate (0.265 g, 3.18 mmol) was added and refluxed for 6 h. The pH of the solution was adjusted to eight by addition of 1 M NaOH. Methanol was removed and the solution was extracted with chloroform (3×15 mL). The combined chloroform layer was dried and evaporated to give gummy solid, which was purified by column chromatography (2% MeOH/$CHCl_3$) to give **9a** (0.321 g, 68%) as a white solid; melting point 166–168 °C; [Found: C, 55.94; H, 7.29. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44%]; R_f (10% MeOH/$CHCl_3$) 0.61; $[\alpha]_D$ −24.0 (*c* 2.0, $CHCl_3$); ν_{max}(neat) 3330–2880, 1658 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, *Me*), 1.50 (3H, s, *Me*), 1.62–2.08 (4H, m, *H*6, *H*7), 2.19–2.36 (2H, m, *H*8), 3.64–3.76 (1H, m, *H*5), 3.95 (1H, dd, *J*=9.3, 2.4 Hz, *H*4), 4.27 (1H, d, *J*=2.4 Hz, *H*3), 4.55 (1H, d, *J*=3.6 Hz, *H*2), 4.78–5.11 (1H, bs, exchanges with D_2O, O*H*), 5.91 (1H, d, *J*=3.6 Hz, *H*1), 8.05–8.22 (1H, bs, exchanges with D_2O, N*H*); δ_C (75 MHz, $CDCl_3$) 17.8, 24.5, 26.1, 26.9, 31.2, 50.3, 73.4, 82.1, 85.5, 104.8, 111.3, 174.4.

3.1.9. 1,2-*O*-Isopropylidene-5,6,7,8-tetra-deoxy-5,9-imino-β-L-*ido*-nona-1,4-furan-9-ulose (9b). The reaction of **8b** (0.91 g, 1.67 mmol) with Wittig reagent triphenylethoxycarbonylmethylene phosphorane (0.871 g, 2.50 mmol) and followed by hydrogenation with 10% Pd/C (0.180 g) and sodium acetate (0.242 g, 2.96 mmol) was performed under the same conditions as reported for **9a**. Column chromatography (4% MeOH/$CHCl_3$) afforded **9b** (0.330 g, 70%) as a white solid; melting point 156–157 °C; [Found: C, 55.91; H, 7.25. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44%]; R_f (10% $CHCl_3$/MeOH) 0.58; $[\alpha]_D$ −11.5 (*c* 2.25, $CHCl_3$); ν_{max}(neat) 3330– 2880, 1624,cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, s, *Me*), 1.49 (3H, s, *Me*), 1.59–1.81 (2H, m, *H*6), 1.82 (2H, m, *H*7), 2.21–2.49 (2H, m, *H*8), 3.65–3.80 (1H, m, *H*5), 3.95 (1H, dd, *J*=4.8, 2.7 Hz, *H*4), 4.22 (1H, d, *J*=2.7 Hz, *H*3), 4.51 (1H, d, *J*=3.6 Hz, *H*2), 5.01–5.21 (1H, bs, exchanges with D_2O, O*H*), 5.95 (1H, d, *J*=3.6 Hz, *H*1), 7.10–7.22 (1H, bs, exchanges with D_2O, N*H*); δ_C (75 MHz, $CDCl_3$) 19.8, 25.9, 26.2, 26.8, 30.9, 52.6, 75.7, 81.3, 85.2, 104.6, 111.5, 173.16.

3.1.10. 1,2-*O*-Isopropylidine-5,6,7,8,9-penta-deoxy-5,9-(*N*-benzoxycarbonyl-imino)-α-D-*gluco*-nona-1,4-furanose (10a). To an ice cooled suspension of LAH (0.223 g, 6.03 mmol) in dry THF (10 mL) was added a solution of **9a** (0.310 g, 1.20 mmol) in dry THF (15 mL) over a period of 10 min. The mixture was allowed to attain the room temperature and stirred for 2 h. Ethyl acetate (10 mL) was added at 0 °C and stirred for 10 min. The reaction was quenched by slow addition of saturated aq. solution of NH_4Cl (2 mL), filtered and residue rinsed with ethyl acetate (5 mL). The usual work up afforded a thick oil that was dissolved in ethanol/water (2 mL, 1/1). The solution was cooled to 0 °C and sodium bicarbonate (0.299 g, 2.41 mmol), benzyloxycarbonyl chloride (0.304 g, 1.80 mmol) was added successively. The mixture was stirred at 25 °C for 2 h. Ethanol was evaporated at reduced pressure and the residue was extracted with chloroform (3×15 mL). The usual work up afforded a thick liquid, that was purified by column chromatography (15% EtOAc/Pet. Ether) to give **10a** (0.365 g, 80%) as a thick liquid; [Found: C, 63.51; H, 7.09. $C_{20}H_{27}NO_6$ requires C, 64.63; H, 7.21%]; R_f (60% EtOAc/Hexane) 0.76; $[\alpha]_D$ −43.0 (*c* 2.0, $CHCl_3$); ν_{max}(neat) 3475, 1674 cm^{-1}; δ_H (300 MHz, $CDCl_3$+D_2O) 1.31 (3H, s, *Me*), 1.48 (3H, s, *Me*), 1.88–2.02 (4H, m, *H*6, *H*7), 2.20–2.35 (2H, m, *H*8), 3.38–3.48 (2H, m, *H*9), 3.79 (1H, dd, *J*=9.9, 1.8 Hz, *H*4), 4.02 (1H, d, *J*=1.8 Hz, *H*3), 4.08–4.19 (1H, m, *H*5), 4.58 (1H, d, *J*=3.6 Hz, *H*2), 5.12 (2H, ABq, *J*=12.0 Hz, CH_2Ph), 5.88 (1H, d, *J*=3.6 Hz, *H*1), 7.22–7.41 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.9, 25.1, 25.3, 26.2, 27.0, 41.1, 48.5, 67.8, 73.6, 76.6, 84.5, 104.8, 111.3, 127.8, 128.4, 128.5, 135.9, 156.9.

3.1.11. 1,2-*O*-Isopropylidine-5,6,7,8,9-penta-deoxy-5,9-(*N*-benzoxycarbonyl-imino)-β-L-*ido*-nona-1,4-furanose (10b). The reaction of **9b** (0.342 g, 1.33 mmol) with LAH (0.250 g, 6.65 mmol) followd by reaction with sodium bicarbonate (0.223 g, 2.66 mmol) and benzyloxycarbonyl chloride (0.340 g, 1.99 mmol) under the same conditions as reported for **10a** and column chromatography (15% EtOAc/Pet. Ether) afforded **10b** (0.350 g, 69%) as a thick liquid; [Found: C, 63.86; H, 7.45. $C_{20}H_{27}NO_6$ requires C, 64.63; H, 7.21%]; R_f (60% EtOAc/ Hexane) 0.68; $[\alpha]_D$ −72.3 (*c* 1.55, $CHCl_3$); ν_{max}(neat) 3110–3620, 1674 cm^{-1}; δ_H (300 MHz, $CDCl_3$+D_2O) 1.32 (3H, s, *Me*), 1.51 (3H, s, *Me*), 1.60–1.80 (2H, m, *H*6), 1.81–1.98 (2H, m, *H*7), 2.01–2.22 (2H, m, *H*8), 3.41–3.60 (2H, m, *H*9), 3.98 (1H, dd, *J*=3.0, 1.8 Hz, *H*4), 4.13 (1H, d, *J*=1.8 Hz, *H*3), 4.28–4.35 (1H, m, *H*5), 4.47 (1H, d, *J*=3.6 Hz, *H*2), 5.13 (2H, ABq, *J*=12.3 Hz, CH_2Ph), 5.87 (1H, d, *J*=3.6 Hz, *H*1), 7.21–7.41 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 19.6, 25.2, 26.1, 26.2, 26.8, 40.0, 48.9, 66.9, 74.6, 77.6, 85.4, 104.1, 111.1, 127.3, 127.5, 128.2, 136.8, 156.2.

3.1.12. (1*R*,2*R*,3*S*,9a*R*)-Octahydro-2*H*-quinolizine-1,2,3-triol (3a). A solution of **10a** (0.100 g, 0.26 mmol) in TFA–H_2O (2 mL, 3/2) was stirred at 25 °C for 2 h. Trifluroacetic acid was co-evaporated with benzene to furnish a thick liquid, which was directly used in the next reaction. To a solution of above product in methanol (5 mL) was added 10% Pd/C (0.01 g) and solution was hydrogenated at 80 psi for 16 h. The solution was filtered through Celite and washed with methanol and the filtrate concentrated to get a sticky solid which was purified by column chromatography (5% MeOH/$CHCl_3$) to give **3a** (0.042 g, 85%) as a thick liquid; [Found: C, 51.51; H, 10.99. $C_9H_{17}NO_3 3H_2O$ requires C, 51.65; H, 11.08%]; R_f (30% chloroform/methanol) 0.29; $[\alpha]_D$ −36.0 (*c* 0.2, MeOH); ν_{max}(neat) 3676–3250 cm^{-1}; δ_H (300 MHz, D_2O) 1.24–1.53 (2H, m, *H*7), 1.55–1.72 (1H, m, *H*9), 1.79–1.98 (3H, m, *H*8, *H*9), 2.26 (1H, brd, *J*=13.2 Hz, $H6_a$), 2.60–2.86 (3H, m, *H*4, $H6_b$), 3.22–3.36 (2H, m, *H*1, *H*9a), 3.41 (1H, t, *J*=9.5 Hz, *H*2), 3.69 (1H, dt, *J*=9.5, 4.5 Hz, *H*3); δ_C (75 MHz, D_2O) 21.6, 23.4, 26.9, 55.3, 56.8, 65.0, 67.0, 72.7, 76.5.

3.1.13. (1*R*,2*R*,3*S*,9a*S*)-Octahydro-2*H*-quinolizine-1,2,3-triol (3b). The reaction of **10b** (0.13 g, 0.34 mmol) with TFA–H_2O (3 mL, 3/2) followed by hydrogenation with 10% Pd/C (0.02 g) as reported for **3a**. Column chromatography (10% MeOH/$CHCl_3$) afforded **3b** (0.058 g, 91%) as a thick liquid; [Found: C, 51.95; H, 10.30. $C_9H_{17}NO_3.2H_2O$ requires C, 52.15; H, 10.21%]; R_f (30% chloroform/methanol) 0.25; $[\alpha]_D$ −80.0 (*c* 0.1, MeOH); ν_{max}(neat)

3640–3180 cm^{-1}; δ_H (300 MHz, D_2O) 1.42–1.80 (6H, m, *H*7, *H*8, *H*9), 2.79–2.91 (1H, m, $H6_a$), 3.15–3.38 (4H, m, *H*4, $H6_b$, *H*9a), 3.65 (1H, bs, W_H 6 Hz, *H*3), 3.87 (2H, bs, W_H 6 Hz, *H*2, *H*1); δ_C (75 MHz, D_2O) 21.7, 22.9, 25.7, 55.7, 61.6, 66.4, 67.2, 70.2 (strong).

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References and notes

1. For reviews see: (a) Padwa, A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 123. (b) Tufariello, J. J. In *1,3-Dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Chapter 9, p 83. (c) In *1,3-Dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Chapter 9, p 277. (d) Balasubramanian, N. *Org. Prep. Proced.* **1985**, *17*, 23. (e) Torssell, K. B. G. Nitrile oxides, nitrones and nitronates. *Organic synthesis*; VCH: New York, 1988. (f) Wade, P. A. Intramolecular 1,3-dipolar cycloadditions. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 1111. (g) Fisera, L.; Al-Timari, U. A. R.; Ertl, P. *Cycloadditions in carbohydrate chemistry*. *ACS Monograph*; American Chemical Society: Washington, 1992; p 158. (h) Frederickson, M. *Tetrahedron* **1997**, *53*, 403. (i) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (j) Merino, P.; Tejero, T. *Molecules* **1999**, *4*, 169. (k) Osborn, H.; Gemmell, N.; Harwood, L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419.
2. Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, *6*, 695, and references cited therein.
3. (a) Merino, P.; Castello, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Teterahedron* **1998**, *54*, 12301. (b) Merino, P.; Franco, S.; Gascon, J. M.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1867. (c) Merino, P.; Anoro, S.; Franco, S.; Gascon, J. M.; Martin, V.; Merchan, F. L.; Revuelta, J.; Tunon, V.; Tejero, T. *Synth. Commun.* **2000**, 2989. (d) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759.
4. (a) Dhavale, D.; Desai, V.; Sindkhedkar, M.; Mali, R.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, 1475. (b) Saha, N.; Desai, V.; Dhavale, D. *Tetrahedron* **2001**, 39.
5. (a) Hughes, A. B.; Rudge, A. *J. Nat. Prod. Rep.* **1994**, *11*, 135. (b) Sears, P.; Wong, C. *J. Chem. Soc., Chem, Commun.* **1998**, 1161. (c) Butters, T. D.; Van den Brock, L. A. G. M.; Fleet, G. W. J.; Krulle, T. M.; Wormold, M. R.; Dwek, R. A.; Platt, F. M. *Tetrahedron: Asymmetry* **2000**, *11*, 113. (d) Elbein, A. D.; Molyneux, R. J. *Alkoloids: chemical and biological prespectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1, p 1. (e) Howard, A. S.; Micheal, J. P. *Alkoliods (N.Y.)* **1986**, *28*, 183. (f) Micheal, J. P. *Nat. Prod. Rep.* **1990**, 485. (g) Asano, N.; Nash, R.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (h) Elbein, A. D.; Molyneux, R. J. Alkaloid glycosidase inhibitors. *Comprehensive natural products chemistry*; Barton, D., Nakanishi, K., Meth-cohn, O., Eds.; Elsevier: Oxford, 1999; Vol. 3, p 129. (i) Sears, P.; Wong, C.-H. *Chem. Commun.* **1998**, 1161. (j) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. (k) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (l) Kaushal, G. P.; Elbein, A. D. *Meth. Enzymol.* **1994**, *230*, 316. (m) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182. (n) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (o) Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1171. (p) Asano, N. *Curr. Top. Med. Chem.* **2003**, *3*, 471. (q) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515. (r) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J. *Phytochemistry* **2001**, *56*, 265. (s) Michael, J. P. *Nat. Prod. Rep.* **2002**, *18*, 719.
6. Jones, T.; Gorman, J.; Snelling, R.; Delabie, J.; Blum, M.; Garraffo, H.; Jain, P.; Daly, J.; Spande, T. *J. Chem. Ecol.* **1999**, *25*, 1179.
7. (a) Michael, J. *Nat. Prod. Rep.* **1999**, *16*, 675. (b) Michael, J. *Nat. Prod. Rep.* **2000**, *17*, 579. (c) Gradnig, G.; Berger, A.; Stutz, A. *Tetrahedron Lett.* **1991**, *32*, 4889. (d) Liu, P.; Rogers, R.; Kang, M.; Sankara, P. *Tetrahedron Lett.* **1991**, *32*, 5853. (e) Herczegh, P.; Kovacs, I.; Szilagyi, L.; Sztaricskai, F. *Tetrahedron* **1995**, *51*, 2969. (f) Carretero, J.; Arrayas, R.; Gracia, I. *Tetrahedron Lett.* **1997**, *38*, 8537. (g) Overkleeft, H.; Bruggeman, P.; Pandit, U. *Tetrahedron Lett.* **1998**, *39*, 3869. (h) Pearson, W.; Hembre, E. *J. Org. Chem.* **1996**, *61*, 5537. (i) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5492. (j) Gebarowski, P.; Sas, W. *Chem. Commun.* **2001**, 915. (k) Pandit, U. K.; Overkleeft, H.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, 959.
8. (a) Dhavale, D.; Saha, N.; Desai, V. *J. Org. Chem.* **1997**, *62*, 7482. (b) Dhavale, D.; Saha, N.; Desai, V. *J. Org. Chem.* **1999**, *64*, 1715. (c) Dhavale, D.; Saha, N.; Desai, V. *J. Chem. Soc., Chem. Commun.* **1999**, 1719. (d) Patil, N.; Tilekar, J.; Dhavale, D. *Tetrahedron Lett.* **2001**, *42*, 747. (e) Dhavale, D.; Patil, N.; John, S.; Sabharwal, S. *Bioorg. Med. Chem.* **2002**, *10*, 2155. (f) Dhavale, D.; Saha, N.; Desai, V.; Tilekar, J. *Arkivoc* **2002**, *VII*, 91. (g) Patil, N.; Tilekar, J.; Jadhav, H.; Dhavale, D. *Tetrahedron* **2003**, *59*, 1873. (h) Patil, N.; Tilekar, J.; Dhavale, D. *J. Org. Chem.* **2001**, *66*, 1065.
9. Pandit, U. K. et al. claimes the synthesis of **3b**, no spectral and analytical data is given for the compound **3b**, See Ref. 7g.
10. (a) Dondoni, A.; Franco, S.; Merchan, F.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5475. (b) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem. Eur. J.* **1995**, *1*, 505. (c) Merchan, F.; Merino, P.; Rojo, I.; Tejero, T.; Dondoni, A. *Tetrahedron: Asymmetry* **1996**, *7*, 667. (d) Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059. (e) Trombini, C.; Dhavale, D. *Heterocycles* **1992**, *34*, 2253. (f) Trombini, C.; Dhavale, D. *J. Chem. Soc. Chem. Commun.* **1992**, 1268. (g) Camiletti, C.; Dhavale, D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3157. (h) Camiletti, C.; Dhavale, D.; Donati, F.; Trombini, C. *Tetrahedron Lett.* **1995**, *36*, 7239.
11. Cornia, M.; Casiraghi, G. *Tetrhedron* **1989**, *45*, 2869.
12. (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrhedron Lett.* **1968**, 2199. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrhedron Lett.* **1968**, 2205. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
13. 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.
14. Burgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065.
15. The ^1H and ^{13}C NMR spectra of compounds **7a**, **8a**, and **7b**, **8b**, in which a *N*-Cbz group is present, showed doubling of

signals. This was due to isomerisation by restricted rotation around C=N, see: In *Applications of NMR spectroscopy in organic chemistry*; Jackman, L. M., Sternhell, S., Eds.; Pergamon: Elmsford, NY, 1978; p 361. An analogous observation was also noticed by us and others see Ref. 8h.

16. Here also we have observed an analogues observation as in case of **9a** and **9b**. The ^{1}H NMR data of **10a** and **10b** showed coupling constant between H4 and H5 as 9.9 and 3.0 Hz, respectively, (for **9a** and **9b** $J_{4,5}$ is 9.3 and 4.8 Hz). Similar findings we have reported earlier see Ref. 8h.
17. Although, the OH substituents are equatorial in the conformation **B**, the butane–gauche interactions destabilize this conformation while; in the conformation **C** the butane–guache interactions are minimum and in addition the intramolecular hydrogen bonding in the six membered transition state stabilize the conformation **C** for **3b**. The counting of butane–guache interactions in the decalin systems reveal three such interactions in the cis isomer and none in the *trans*. Therefore, the calculated difference in heats of formation between the decalins is 2.7 kcal/mol, the *trans* isomer being the more stable. See: In *Stereochemistry of organic compounds*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1994; p 777.