An Efficient Synthesis of Trihydroxy Quinolizidine Alkaloids Using Ring-Closing Metathesis

Dilip D. Dhavale,*[a] Santosh M. Jachak,[a] Navnath P. Karche,[a] Claudio Trombini[b]

[a] Department of Chemistry, Garware Research Centre, University of Pune, Pune 411 007, India
E-mail: ddd@chem.unipune.ernet.in

[b] Dipartimento di Chimica 'G. Ciamician', via Selmi-2, 40126-Bologna, Italy

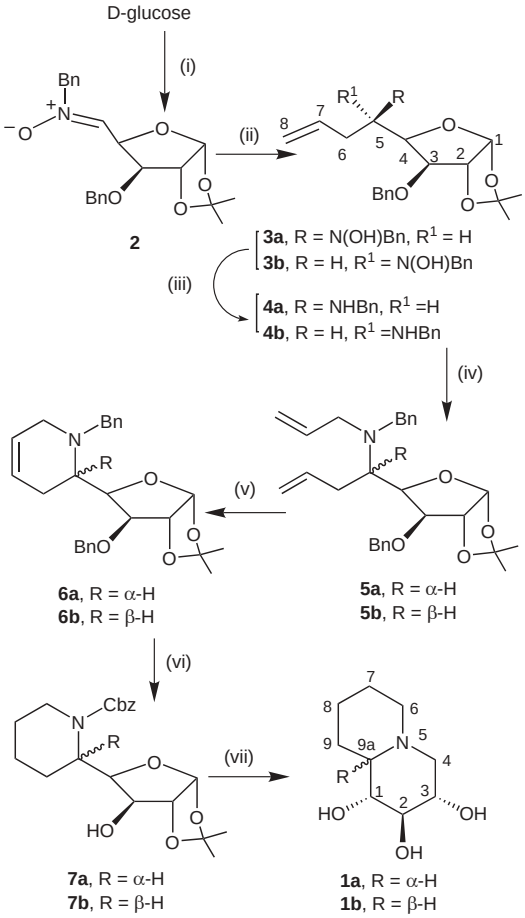
Received 24 December 2003

Abstract: The sequential C- and N-allylation of D-glucose-derived nitrone **2** provides the required diene functionality with nitrogen linker that was used in ring-closing metathesis pathway in the synthesis of quinolizidine alkaloids **1a** and **1b**.

Key words: alkaloids, azasugars, carbohydrates, glycosidase, metathesis

The ring-closing metathesis (RCM) of diene-substrate containing nitrogen functionality has found wide applicability in the synthesis of nitrogen heterocycles, alkaloids, peptides and peptidomimetics.[1] The utility of this approach with sugar substrates wherein the presence of a hydroxylated carbon framework and feasibility to manipulate the functional groups into the required diene-functionality, containing a nitrogen atom, give an easy access towards the synthesis of a variety of aza-sugars.[2] This class of compounds, especially the polyhydroxylated indolizidine and quinolizidine alkaloids are promising glycosidase inhibitors with potential antibacterial, antiviral, antimetastatic, and antidiabetes activity.[3] Most naturally occurring quinolizidine alkaloids[4] are devoid of polyhydroxylated functionalities and in the search for structure-activity relationship, the hydroxylated unnatural analogues are interesting targets for obtaining the better understanding of mechanisms of action and in design of even more potent inhibitors. As a part of our continuing efforts in the synthesis of aza-sugars,[5] we have developed a new methodology for the synthesis of trihydroxy quinolizidine alkaloids **1a** and **1b** using ring closing metathesis of D-glucose derived dienes with nitrogen linkage as a key step. A few reports are available for the synthesis of polyhydroxylated quinolizidine alkaloids.[2e,h,o,6] However, only a single report describes the synthesis of **1b** while the synthesis of **1a** has been reported so far.[2e]

Recently, we have described the preparation and reaction of D-glucose nitrone **2** in the synthesis of 6-deoxynojirimycin.[5a] Similarly, the reaction of nitrone **2** with allylmagnesium bromide in the presence of TMSOTf (1 equiv) at –78 °C in dry THF afforded a mixture of D-*gluco*- and L-*ido*-diastereomers **3a** and **3b** in the ratio of 86:14 (Scheme 1). The absolute configuration at the newly



Scheme 1 *Reagents and conditions*: (i) See Ref. 5a; (ii) allylmagnesium bromide (2.5 equiv), TMSOTf (1.0 equiv), dry THF, –78 °C, 2 h, 93%; (iii) Zn (2.0 equiv), $Cu(OAc)_2$, HOAc, 70 °C, 1 h, 80%; (iv) allyl bromide (1.5 equiv), K_2CO_3, (5 equiv), dry DMF, 25 °C, 18 h, 71%; (v) Grubb's catalyst (5% mol), dry benzene, reflux, 18 h, 81%; (vi) a) H_2, 10% Pd/C, MeOH, 25 °C, 12 h; b) Cbz-Cl (1.5 equiv), $NaHCO_3$, aq EtOH, 0 °C to r.t., 2 h, 78%; (vii) a) TFA–H_2O (3:2), 0 °C to r.t., 2.5 h; b) H_2, 10% Pd/C, MeOH, 25 °C, 12 h, 85%.

generated C5 in **3a** and **3b** was established by comparing the ^{1}H NMR data.[7] The appreciable difference in R_f values allowed us to separate **3a** and **3b** by flash chromatography. Subsequently, the *N*-benzylhydroxylamine (**3a**) was treated with zinc in acetic acid–water and N–O bond reductive cleavage afforded the *N*-benzylamino sugar **4a** in good yield. The reaction of **4a** with allyl bromide, in the presence of potassium carbonate in dry DMF, afforded N-allylated product **5a**.

SYNLETT 2004, No. 9, pp 1549–1552
Advanced online publication: 01.07.2004
DOI: 10.1055/s-2004-829538; Art ID: G36303ST

The ruthenium-catalyzed ring-closing metathesis successfully converted **5a** into the desired dihydropiperidine **6a** in high yield.[8] The analytical and spectroscopic data was found to be in agreement with the proposed structure **6a**.[9] One-pot reduction of the double bond and removal of N- and O-benzyl groups in **6a**, by hydrogenation using 10% Pd/C, was followed by selective N-protection with benzyl chloroformate to afford **7a**. In the next step, compound **7a** reacted with TFA–water to give the corresponding hemiacetal that was subjected to hydrogenation to give (1*R*,2*R*,3*S*,9a*R*)-octahydro-2*H*-quinolizine-1,2,3-triol (**1a**) as a thick liquid.[8] The same reaction sequence was repeated for the *N*-benzylhydroxylamine (**3b**, Scheme 1). The corresponding C5-epimeric compounds **4b**, **5b**, **6b** and **7b** were isolated and characterized by spectral and analytical data.[9] Finally, compound **7b** reacted with TFA–water and the hemiacetal was subjected to hydrogenation to give (1*R*,2*R*,3*S*,9a*S*)-octahydro-2*H*-quinolizine-1,2,3-triol (**1b**) as a thick liquid.[8]

The ^{1}H NMR spectra of **1a** and **1b** were found to be completely different. Therefore, it was thought that **1a** and **1b** could exist in different conformations. For this, we did decoupling experiments and coupling constant values obtained are shown in Table 1. The initial geometry in the precursors **7a** and **7b** ensures, that in the product **1a** and **1b** the substituents at C-1, C-2 and C-2, C-3 should be *trans*. In the ^{1}H NMR spectra of **1a** the doublet of triplet ($J_{3,4e}$ = 4.4 and $J_{3,4a}$ = $J_{3,2}$ = 9.5 Hz), corresponding to H-3 proton, indicated the axial orientation of this proton. The triplet ($J_{2,3}$ = $J_{2,1}$ = 9.5 Hz), corresponding to H-2, requires *trans*-diaxial relationship with H-3 and H-1. This suggests the *trans*-fused rigid chair-chair conformation (**A**) with equatorial orientation of the OH substituents, for compound **1a** (Figure 1). The comparison of ^{1}H NMR spectra of **1a** and **1b** revealed the downfield shift of H-1/H-2/H-3 in **1b** as compared to the respective protons in **1a**. This is indicative of equatorial orientation of these protons in **1b** as against axial as noted for **1a**. In the case of **1b**, H-1 appeared as a broad singlet at δ = 3.65 ppm while H-2 and H-3 were found to be accidentally equivalent and showed a broad singlet at δ = 3.87 ppm. This indicates that $J_{1,2}$ and $J_{2,3}$ are relatively small (J_H = 6 Hz), and is consistent with the equatorial positions of these protons. The small value of $J_{1,9a}$, along with the axial orientation of C-1-OH, suggests that the C-9a substituent is equatorial. This is suggestive of a *trans*-fused conformation (**B**) with axial orientation of the OH substituents for compound **1b** (Figure 1).

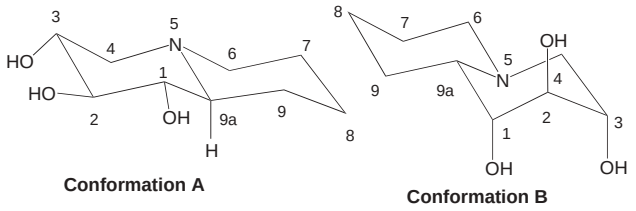


Figure 1

In conclusion, we have successfully synthesized the required diene from D-glucose and used ring-closing metathesis to obtained Δ^3-piperideine, which was used for the synthesis of trihydroxy quinolizidine alkaloids **1a** and **1b**. The easy availability of the chiral starting materials, mild reaction conditions and good yields make the route attractive and indicate that it could operate on a gram scale.

Acknowledgment

We are thankful to Department of Science and Technology, New Delhi, for financial support (SP/S1/G-32/2000). One of us (SMJ) is grateful to CSIR, New Delhi for a fellowship.

References

(1) For recent reviews, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036; *Angew. Chem.* **1997**, *109*, 2124. (b) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37. (c) Armstrong, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 317. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (e) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (f) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; *Angew. Chem.* **2000**, *112*, 3140. (g) Larry, Y. *Chem. Rev.* **2000**, *100*, 2963.

(2) For the application of the ring-closing metathesis reaction to the synthesis of aza-sugars, see: (a) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621. (b) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547. (c) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61. (d) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359. (e) Overkleeft, H. S.; Bruggeman, P.; Pandit, U. K. *Tetrahedron Lett.* **1998**, *39*, 3869. (f) Lindstrom, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173. (g) Ovaa, H.; Stragies, R.; van der Marel, G. A.; van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501. (h) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971. (i) Subramanian, T.; Lin, C.-C. *Tetrahedron Lett.* **2001**, *42*, 4079. (j) Klitze, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605. (k) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org.*

Table 1 Comparison of ^{1}H NMR Spectra of **1a** and **1b**

	H-3	H-2	H-1	H-9a
1a	δ = 3.69 ppm (dt) $J_{2,3}$ = $J_{4a,3}$ = 9.5 Hz $J_{4e,3}$ = 4.5 Hz	δ = 3.41 ppm (t) $J_{1,2}$ = $J_{2,3}$ = 9.5 Hz	δ = 3.22–3.36 ppm (m)	δ = 3.22–3.36 ppm (m)
1b	δ = 3.87 ppm (br s) J_H = 6 Hz	δ = 3.87 (br s) J_H = 6 Hz	δ = 3.65 ppm (br s) J_H = 6 Hz	δ = 3.15–3.38 ppm (m)

Chem. **2002**, *67*, 4630. (l) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774. (m) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325. (n) Lee, H. K.; Chun, J. S.; Pak, C. S. *J. Org. Chem.* **2003**, *68*, 2471. (o) Verhelst, S. H. L.; Martinez, B. P.; Timmer, S. M.; Lodder, G.; Van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598.

(3) (a) Grandnig, G.; Berger, A.; Grassberger, V.; Stuetz, A. *Tetrahedron Lett.* **1991**, *32*, 4849. (b) Rassu, G.; Casiraghi, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Cornia, M.; Zanardi, F. *Tetrahedron* **1993**, *49*, 6627. (c) Herzegh, P.; Kovacs, I.; Szilagyi, L.; Sztaricskai, F.; Bericibar, A.; Riche, C.; Chiaroni, A.; Olesker, A.; Lukacs, G. *Tetrahedron* **1995**, *51*, 2969. (d) Carretero, J. C.; Arrayas, R. G.; De Garcia, I. S. *Tetrahedron Lett.* **1997**, *38*, 8537. (e) *Iminosugars as Glycosidase Inhibitors*; Stuetz, A. E., Ed.; Wiley-VCH: Weinheim, **1999**. (f) Schaller, C.; Vogel, P. *Synlett* **1999**, 1219.

(4) (a) Michael, J. *Nat. Prod. Rep.* **1999**, *16*, 675. (b) Michael, J. *Nat. Prod. Rep.* **2000**, *17*, 579. (c) Michael, J. *Nat. Prod. Rep.* **2003**, *20*, 458.

(5) (a) Dhavale, D.; Desai, V.; Sindkhedkar, M.; Mali, R.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, 1475. (b) Dhavale, D.; Saha, N.; Desai, V. *J. Org. Chem.* **1997**, *62*, 7482. (c) Dhavale, D.; Saha, N.; Desai, V. *J. Org. Chem.* **1999**, *64*, 1715. (d) Dhavale, D.; Saha, N.; Desai, V. *J. Chem. Soc., Chem. Commun.* **1999**, 1719. (e) Saha, N.; Desai, V.; Dhavale, D. *Tetrahedron* **2001**, 39. (f) Patil, N.; Tilekar, J.; Dhavale, D. *J. Org. Chem.* **2001**, *66*, 1065. (g) Patil, N.; Tilekar, J.; Dhavale, D. *Tetrahedron Lett.* **2001**, *42*, 747. (h) Dhavale, D.; Patil, N.; John, S.; Sabharwal, S. *Bioorg. Med. Chem.* **2002**, *10*, 2155. (i) Dhavale, D.; Saha, N.; Desai, V.; Tilekar, J. *Arkivoc* **2002**, 91. (j) Patil, N.; Tilekar, J.; Jadhav, H.; Dhavale, D. *Tetrahedron* **2003**, *59*, 1873.

(6) (a) Liu, P.; Rogers, R.; Kang, M.; Sankara, P. *Tetrahedron Lett.* **1991**, *32*, 5853. (b) Pearson, W.; Hembre, E. *Tetrahedron Lett.* **1993**, 8221. (c) Herczegh, P.; Kovacs, I.; Szilagyi, L.; Sztaricskai, F. *Tetrahedron* **1995**, *51*, 2969. (d) Carretero, J.; Arrayas, R.; Gracia, I. *Tetrahedron Lett.* **1997**, *38*, 8537. (e) Pearson, W.; Hembre, E. *J. Org. Chem.* **1996**, *61*, 5537. (f) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5492. (g) Pandit, U. K.; Overkleeft, H.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, 959. (h) Schaller, C.; Vogel, P. *Helv. Chim. Acta* **2000**, 193. (i) Gebarowski, P.; Sas, W. *Chem. Commun.* **2001**, 915.

(7) (a) 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). In addition, the chemical shift of H-3 in L-*ido* isomer is upfield as compared to D-*gluco* isomer. The higher value of $J_{4,5}$ observed in the diastereomer **3b** (9.5 Hz) as compared to **3a** (8.3 Hz) indicated the L-*ido* configuration for **3b** and the D-*gluco* configuration for **3a**. This fact was further supported by comparison of the chemical shift of H-3 in both the isomers. In **3b** H-3 appeared upfield at δ = 3.84 ppm as compared to **3a** at δ = 4.01 ppm, further supporting the D-*gluco*- and L-*ido* configuration at C5 to **3a** and **3b**, respectively. Thus, the absolute configurations at C-5 in **3a** and **3b** were assigned as (5*R*) and (5*S*), respectively. (b) See: Cornia, M.; Casiraghi, G. *Tetrahedron* **1989**, *45*, 2869.

(8) **General Procedure for the Ring-Closing Metathesis**: To a solution of **5a**,**b** (0.180 g, 0.4 mmol) in dry benzene (15 mL) at 25 °C was added benzylidene-bis-tricyclohexyl-phosphine-dichlororuthenium (0.006 g, 5% mol) and the reaction mixture was refluxed under nitrogen for 18 h. Removal of solvent under vacuum afforded a thick oil that on purification by column chromatography using EtOAc–*n*-hexane (5:95) afforded corresponding Δ^3-piperidine **6a**,**b**. **General Procedure for the Reductive Aminocyclization**: A solution of **7a**,**7b** (0.100 g, 0.26 mmol) in TFA–H_2O (3:2, 2 mL) was stirred at 25 °C for 2 h. TFA was co-evaporated with benzene to furnish a thick liquid, which was directly used in the next reaction. To a solution of the above product in MeOH (5 mL) was added 10% Pd/C (0.01 g) and the solution was hydrogenated at 80 psi for 16 h. The solution was filtered through celite and the filtrate concentrated to get a sticky solid, which was purified by column chromatography (MeOH–$CHCl_3$ = 5:95) to give **1a**,**b**.

(9) All new compounds have been characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis. Selected procedures and data for **3-*O*-benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetra-deoxy-5-(*N*-benzyl-*N*-hydroxyamino)-α-D-*gluco*-7-eno-octo-1,4-furanose (3a)**: thick liquid; 80%; R_f = 0.52 (EtOAc–hexane = 3:7); $[\alpha]_D$ = –30.0 (*c* 2.40, $CHCl_3$). IR (neat): 3510–3160 (br), 1639 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 1.44 (s, 3 H), 2.49–2.69 (m, 2 H), 3.41 (ddd, *J* = 8.3, 7.8, 4.8 Hz, 1 H), 3.76 (d, *J* = 13.6 Hz, 1 H), 3.94 (d, *J* = 13.6 Hz, 1 H), 4.01 (d, *J* = 3.0 Hz, 1 H), 4.37 (dd, *J* = 8.3, 3.0 Hz, 1 H), 4.40–4.45 (br s, exchanges with D_2O, 1 H), 4.50 (d, *J* = 11.7 Hz, 1 H), 4.54 (d, *J* = 3.9 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.98 (dd, *J* = 11.1, 1.6 Hz, 1 H), 5.10 (dd, *J* = 17.0, 1.6 Hz, 1 H), 5.87 (d, *J* = 3.9 Hz, 1 H), 5.92–6.10 (m, 1 H), 7.12–7.28 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34. Found: C, 70.51; H, 7.30.
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 (3b): thick liquid; 13%; R_f = 0.44 (EtOAc–hexane = 3:7); $[\alpha]_D$ = –48.0 (*c* 0.25, $CHCl_3$). IR (neat): 3530–3150 (br), 1639 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 3 H), 1.46 (s, 3 H), 1.91–2.09 (m, 1 H), 2.21–2.35 (m, 1 H), 3.38 (ddd, *J* = 9.5, 8.1, 4.3 Hz, 1 H), 3.84 (d, *J* = 3.0 Hz, 1 H), 3.92 (d, *J* = 13.9 Hz, 1 H), 4.09 (d, *J* = 13.9 Hz, 1 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 4.44 (dd, *J* = 9.5, 3.0 Hz, 1 H), 4.57 (d, *J* = 3.8 Hz, 1 H), 4.61 (d, *J* = 11.6 Hz, 1 H), 4.84–4.92 (m, 2 H), 4.93–4.96 (br s, exchanges with D_2O, 1 H), 5.83–6.05 (m, 1 H), 5.93 (d, *J* = 3.8 Hz, 1 H), 7.10–7.38 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34. Found: C, 70.29; H, 7.59.
3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-propenylamino)-α-D-*gluco*-7-eno-octo-1,4-furanose (5a): thick liquid; 71%; R_f = 0.65 (EtOAc–hexane = 2:8); $[\alpha]_D$ = –36.4 (*c* 0.44, $CHCl_3$). IR (neat): 1639, 1605 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.46 (s, 3 H), 2.48 (br t, *J* = 7.2 Hz, 2 H), 3.12 (dd, *J* = 14.1, 6.6 Hz, 1 H), 3.22 (dd, *J* = 14.1, 6.3 Hz, 1 H), 3.34 (q, *J* = 7.2 Hz, 1 H), 3.73 (ABq, *J* = 14.4 Hz, 2 H), 3.95 (d, *J* = 3.0 Hz, 1 H), 4.22 (dd, *J* = 7.2, 3.0 Hz, 1 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 4.53 (d, *J* = 3.6 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.87–5.18 (m, 4 H), 5.63–5.80 (m, 1 H), 5.89 (d, *J* = 3.6 Hz, 1 H), 5.92–6.08 (m, 1 H), 7.16–7.22 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 26.8, 32.9, 54.5, 54.7, 57.3, 71.8, 79.9, 81.6, 82.7, 104.7, 111.4, 115.4, 116.6, 126.7, 127.6, 127.7, 128.1, 128.3, 128.5, 137.2, 137.6, 138.3, 140.5. Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85. Found: C, 74.65; H, 7.70.

3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-propenylamino)-β-L-*ido*-7-eno-octo-1,4-furanose (5b): thick liquid; 71%; R_f = 0.53 (EtOAc–hexane = 2:8). $[\alpha]_D$ = –38.2 (*c* 0.33, $CHCl_3$). IR (neat): 1641, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.59 (s, 3 H), 1.80–1.93 (m, 1 H), 2.11–2.23 (m, 1 H), 3.30–3.47 (m, 3 H), 3.81 (d, *J* = 3.0 Hz, 1 H), 3.83 (d, *J* = 14.1 Hz, 1 H), 3.94 (d, *J* = 14.1 Hz, 1 H), 4.30 (dd, *J* = 9.6, 3.0 Hz, 1 H), 4.45 (d, *J* = 11.7 Hz, 1 H), 4.64 (d, *J* = 3.9 Hz, 1 H), 4.70 (d, *J* = 11.7 Hz, 1 H), 4.90–5.24 (m, 4 H), 5.79–5.96 (m, 2 H), 6.02 (d, *J* = 3.9 Hz, 1 H), 7.20–7.46 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 26.8, 34.5, 53.3, 54.9, 56.8, 71.3, 81.1, 81.9, 82.4, 104.8, 111.2, 115.1, 115.9, 126.3, 127.5, 127.8, 127.9, 128.4, 128.9, 137.2, 137.3, 138.3, 141.3. Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85. Found: C, 74.75; H, 7.66.

1,2-*O*-Isopropylidine-5,6,7,8,9-penta-deoxy-5,9-(*N*-benzyl-imino)-α-D-*gluco*-7-eno-nona-1,4-furanose (6a): thick liquid; 81%; R_f = 0.50 (EtOAc–hexane = 2:8); $[\alpha]_D$ = –21.8 (*c* 0.55, $CHCl_3$). IR (neat): 1640, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.46 (s, 3 H), 2.32–2.48 (m, 2 H), 3.10–3.20 (m, 2 H), 3.51 (dt, *J* = 9.3, 5.7 Hz, 1 H), 3.70 (d, *J* = 13.8 Hz, 1 H), 3.85 (d, *J* = 13.8 Hz, 1 H), 4.11 (d, *J* = 2.7 Hz, 1 H), 4.35 (dd, *J* = 9.3, 2.7 Hz, 1 H), 4.62 (d, *J* = 3.9 Hz, 1 H), 4.75 (ABq, *J* = 11.7 Hz, 2 H), 5.56–5.64 (m, 1 H), 5.87–5.92 (m, 1 H), 5.95 (d, *J* = 3.9 Hz, 1 H), 7.20–7.38 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 26.2, 26.8, 47.2, 54.1, 55.3, 72.4, 79.6, 81.8, 82.4, 104.5, 111.4, 124.0, 125.3, 126.7, 127.6, 127.7, 128.2, 128.4, 128.5, 137.9, 139.9. Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41. Found: C, 73.99; H, 7.46.

1,2-*O*-Isopropylidine-5,6,7,8,9-penta-deoxy-5,9-(*N*-benzyl-imino)-β-L-*ido*-7-eno-nona-1,4-furanose (6b): thick liquid; 78%; R_f = 0.46 (EtOAc–hexane = 2:8); $[\alpha]_D$ = –19.4 (*c* 0.22, $CHCl_3$). IR (neat): 1650, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.52 (s, 3 H), 1.72–1.79 (m, 1 H), 2.29–2.43 (m, 1 H), 3.10–3.28 (m, 2 H), 3.53 (ddd, *J* = 9.6, 5.8, 3.8 Hz, 1 H), 3.82 (d, *J* = 3.0 Hz, 1 H), 3.87 (d, *J* = 13.8 Hz, 1 H), 4.01 (d, *J* = 13.8 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.54 (dd, *J* = 9.6, 3.0 Hz, 1 H), 4.64 (d, *J* = 3.9 Hz, 1 H), 4.73 (d, *J* = 11.7 Hz, 1 H), 5.60–5.74 (m, 2 H), 6.05 (d, *J* = 3.9 Hz, 1 H), 7.19–7.45 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3, 26.7, 26.8, 47.0, 54.4, 58.3, 71.5, 78.4, 81.1, 82.6, 105.1, 111.3, 123.6, 125.7, 126.5, 127.7, 127.9, 128.1, 128.4, 128.8, 137.2, 140.5. Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41. Found: C, 74.15; H, 7.32.

(1*R*,2*R*,3*S*,9a*R*)-octahydro-2*H*-quinolizine-1,2,3-triol (1a): thick liquid; 85%; R_f = 0.29 ($CHCl_3$–MeOH = 7:3); $[\alpha]_D$ = –36.0 (*c* 0.2, MeOH). IR (neat): 3676–3250 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 1.24–1.53 (m, 2 H), 1.55–1.72 (m, 1 H), 1.79–1.98 (m, 3 H), 2.26 (br d, *J* = 13.2 Hz, 1 H), 2.60–2.86 (m, 3 H), 3.22–3.36 (m, 2 H), 3.41 (t, *J* = 9.3 Hz, 1 H), 3.69 (dt, *J* = 9.3, 4.5 Hz, 1 H). ^{13}C NMR (75 MHz, D_2O): δ = 21.6, 23.4, 26.9, 55.3, 56.8, 65.0, 67.0, 72.7, 76.5. Anal. Calcd for $C_9H_{17}NO_3 \cdot 3H_2O$: C, 57.73; H, 9.15. Found: C, 57.61; H, 9.01.

(1*R*,2*R*,3*S*,9a*S*)-octahydro-2*H*-quinolizine-1,2,3-triol (1b): The reaction of **7b** (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 **1a**. Column chromatography (MeOH–$CHCl_3$ = 10:90) afforded **1b** as a thick liquid (0.058 g, 91%); R_f = 0.25 ($CHCl_3$–MeOH = 7:3); $[\alpha]_D$ = –80.0 (*c* 0.1, MeOH). IR (neat): 3640–3180 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 1.42–1.80 (m, 6 H), 2.79–2.91 (m, 1 H), 3.15–3.38 (m, 4 H), 3.65 (br s, J_H = 6 Hz, 1 H), 3.87 (br s, J_H = 6 Hz, 2 H). ^{13}C NMR (75 MHz, D_2O): δ = 21.7, 22.9, 25.7, 55.7, 61.6, 66.4, 67.2, 70.2 (strong). Anal. Calcd for $C_9H_{17}NO_3 \cdot 2H_2O$: C, 57.73; H, 9.15. Found: C, 57.58; H, 8.97.