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TETRAHEDRON: *ASYMMETRY*

# A new and highly stereoselective synthesis of polyhydroxyindolizidines from 4-octulose derivatives

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**Abstract**

(1*S*,2*S*,6*R*,7*R*,8*R*,8a*R*)-1,2,6,7,8-Pentahydroxyindolizidine **12** and (1*R*,6*R*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (1,6-diepicastanospermine, **24**) have been stereoselectively synthesized from the important key intermediates 1,4-dideoxy-1,4-imino-D-*erythro*-L-*altro*-octitol **7** and 1,2,4-trideoxy-1,4-imino-D-*glycero*-D-*talo*-octitol **20** in three steps. Compounds **7** and **20** were readily obtained from 2,3:4,5:6,7-tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose **1** and 2-deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranose **13** in four steps, respectively. 

## 1. Introduction

The indolizidine bicyclic system is extensively found in nature, since a large proportion of alkaloids incorporate this moiety. Polyhydroxyindolizidines[1] are important inhibitors of glycosidases, enzymes that are essential in the biosynthetic processing of polysaccharides and glycoproteins and thus, could be considered as potential chemotherapeutic agents against viral infections, cancer, malaria and diabetes.[2] Given that the activity as glycosidase inhibitors of such compounds can not be reliably predicted, the synthesis of their natural and unnatural analogues is of great importance for structure–activity relationship studies.[3]

We report herein highly stereoselective syntheses of 1,2,6,7,8-pentahydroxy **12** and 1,6,7,8-tetrahydroxy indolizidine (1,6-diepicastanospermine, **24**). To the best of our knowledge, only a few syntheses of these kinds of compound can be found in the literature. Thus, Vogel et al.[4] have described several pentahydroxyindolizidines, stereoisomers of **12** derived from their so-called 'naked sugars',[5] whereas Fleet et al.[6] used octonolactone derivatives as chiral starting materials. Alternatively, **24** has been synthesized by Fleet et al.[7] from L-gulonolactone, by Burgess et al.[8] from D-arabinose, and finally by Leeper et al.[9] from malic acid.

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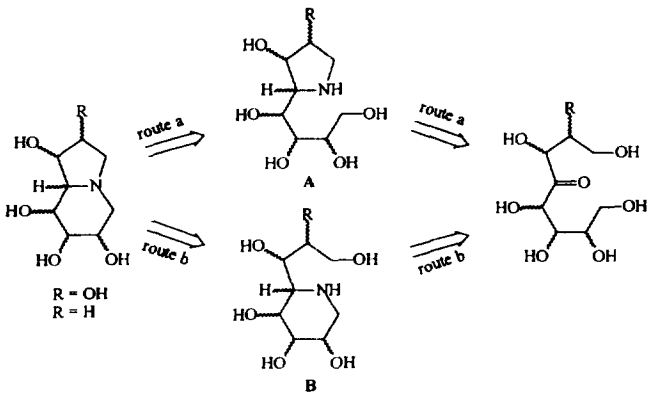
Recently, our group reported on the highly stereoselective synthesis of some derivatives of 4-octulose[10,11] and 2-deoxy-4-octulose[11,12] using common hexuloses (D-fructose and L-sorbose) as chiral starting materials. Moreover, the retrosynthetic analysis shown in Scheme 1, clearly demonstrated that a 4-octulose, due to the diversity of its funtional groups, could be considered as an excellent intermediate for the stereoselective synthesis of the above-mentioned polyhydroxyindolizidines, since those groups can be easily transformed into the appropriate ones for building up the indolizidine skeleton. Two possible synthetic routes are outlined in Scheme 1 which involve construction of either a polyhydroxylated branched-chain pyrrolidine (**A**) (route a) or piperidine (**B**) (route b) intermediates that are subsequently cyclized to the bicyclic indolizidine system. In the present case, and according to the starting 4-octulose derivatives, route a was chosen.



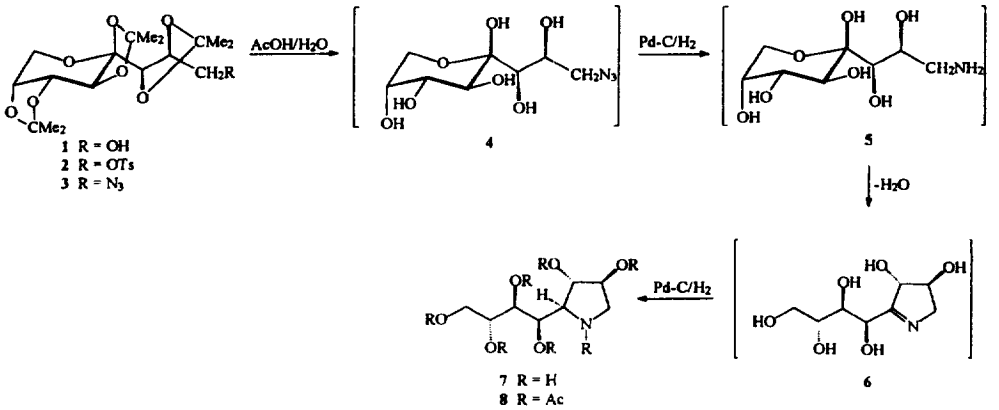

Scheme 1.

## 2. Results and discussion

Reaction of 2,3:4,5:6,7-tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose[10] **1** with *p*-toluenesulfonyl chloride in dry pyridine gave the corresponding 1-*O*-*p*-toluenesulfonyl derivative **2** that was transformed into 1-azido-1-deoxy-2,3:4,5:6,7-tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose **3** by displacement of the sulfonate group with sodium azide. Deacetonation of **3** in an acid medium afforded the corresponding 1-azido-1-deoxy-D-*glycero*-D-*galacto*-4-octulose **4** as a mixture of anomers ($^{13}$C-NMR evidence). Treatment of **4** with Pd–C/$H_2$ gave only one product, that was identified as 1,4-dideoxy-1,4-imino-D-*erythro*-L-*altro*-octitol **7**. Formation of **7** must take place by an $N_3 \rightarrow NH_2$ reduction to produce the corresponding 1-amino-1-deoxy-4-octulose **5** (not isolated), followed by a nucleophilic attack of the amino group at C-1 to the carbonyl group at C-4 giving the cyclic pyrrolinic intermediate **6** that was subsequently hydrogenated to **7** (see below, Scheme 2).

The structure of **7**, and hence the stereochemistry of the newly formed stereogenic centre (C-4), was determined on the basis of its analytical and spectroscopic data as well as those of its peracetylated derivative **8**. Thus, $^{1}$H, $^{13}$C and 2D COSY-45, $^{13}$C–$^{1}$H homo and heteronuclear shift correlation spectra were in agreement with the proposed structures for **7** and **8**.

Attempts at **7**→**12** cyclisation by applying either the Appel[13] ($CCl_4$/$Ph_3P$/$Et_3N$) or Bernotas[14] (DEAD/$Ph_3P$) procedures for the synthesis of azacycles failed. When $I_2$/$Ph_3P$/imidazole[15] and then DABCO was used, cyclisation did not occur, instead, and after acetylation of the resulting reaction mixture, a compound tentatively identified as *N*-acetyl-2,3,5,7,8-penta-*O*-acetyl-1,4-dideoxy-1,4-imino-D-*erythro*-L-*altro*-octitol **9** was obtained. These results were in accordance to those found by other




Scheme 2.

authors[16] where no cyclisation took place when a fully deprotected 1,4-dideoxy-1,4-iminooctitol was used.

The target molecule **12** could finally be prepared in three steps from **7** by selective protection at the pyrrolidine nitrogen as *N*-benzyloxycarbonyl derivative **10**, which was not characterized but chemoselectively transformed into *N*-benzyloxycarbonyl-1,4-dideoxy-1,4-imino-8-*O*-mesitylenesulphonyl-D-*erythro*-L-*altro*-octitol **11**, in order to change the OH at C-8 into a good leaving group. Hydrogenation of **11** promoted the deprotection at the N and the subsequent cyclisation to (1*S*,2*S*,6*R*,7*R*,8*R*,8a*R*)-1,2,6,7,8-pentahydroxyindolizidine **12** through an intramolecular nucleophilic attack at C-8. The structure of **12** was established on the basis of its $^{1}H$, $^{13}C$ and 2D COSY-45, $^{13}C$–$^{1}H$ homo and heteronuclear shift correlation spectra (500 MHz, see Fig. 1). The spectral data were consistent with the conformer shown in Scheme 3, in which the piperidine ring adopts a chair conformation and the substituents at N-4 and C-7,8,8a are in equatorial positions. The coupling constants $J_{7,8}=J_{8,8a}=9.4$ Hz and $J_{1,8a}=6$ Hz, confirm the *trans* relationship between H-8 and H-8a. Furthermore, strong NOEs between H-7 and H-8a, between H-5α and H-8a and finally beween H-3α and H-8a were also in agreement with our proposal. The calculated[17] and experimental coupling constant values (see Table 1) were in good accord. These results also confirm the configuration at C-4 in compound **7** and therefore in **8**.

Following the same protocol to that described above, compound **13**[12] was treated with *p*-toluenesulfonyl chloride in pyridine to afford not only the corresponding 1-*O*-*p*-toluenesulfonyl derivative **15** but the 1-chloro-1,2-dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranose **14**, presumably formed by nucleophilic substitution of the *p*-toluenesulfonyloxy group at C-1 in **15** by the present chloride ion. In order to avoid the formation of **14**, compound **13** was alternately treated with $I_2/Ph_3P$/imidazole[15] in anhydrous dichloromethane to give 1,2-dideoxy-1-iodo-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranose **16** in 85% yield. Treatment of compounds **14**, **15** and **16**, separately, with sodium azide in dry DMF afforded the related 1-azido-1,2-dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranose **17** in quantitative yield, in all cases.

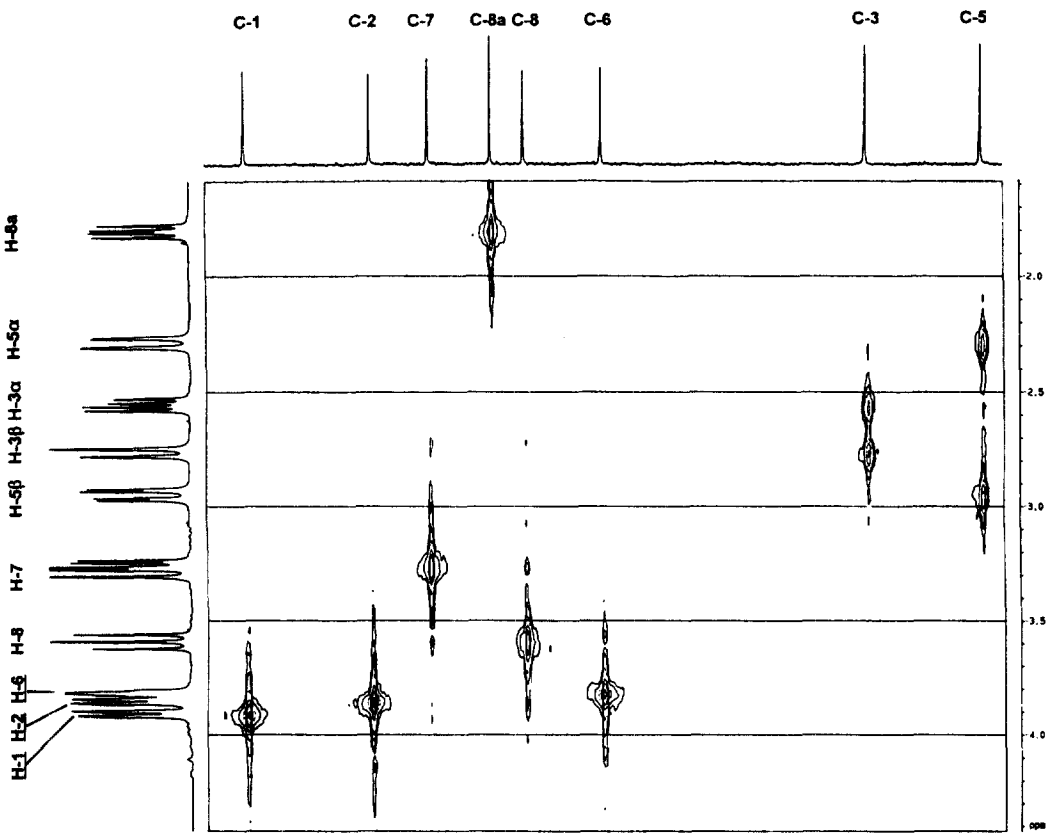
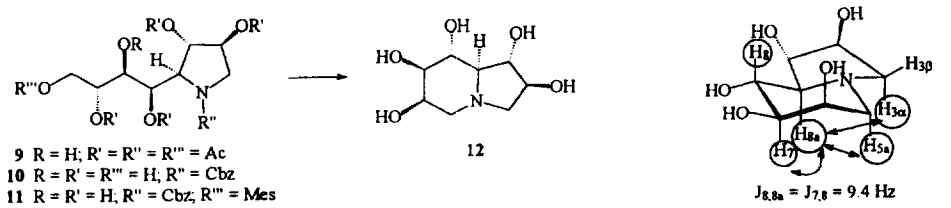
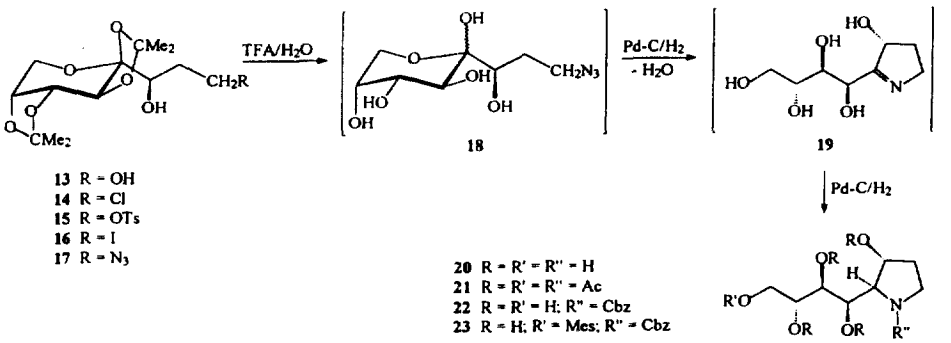



Fig. 1.




Scheme 3.




Deacetonation of **17** in an acid medium gave the free 1-azido-1,2-dideoxy-D-*manno*-4-octulose **18** as a mixture of the four possible anomers ($^{13}$C-NMR evidence), where those resonance signals for

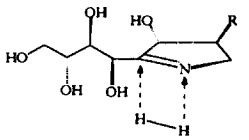
Table 1
Calculated and experimental coupling constant values (Hz) for indolizidines **12** and **24**

| Compound | | $J_{1,2\beta}$ | $J_{1,2\alpha}$ | $J_{1,8a}$ | $J_{2\alpha,3\alpha}$ | $J_{2\alpha,3\beta}$ | $J_{2\beta,3\alpha}$ | $J_{2\beta,3\beta}$ | $J_{5\alpha,6}$ | $J_{5\beta,6}$ | $J_{6,7}$ | $J_{7,8}$ | $J_{8,8a}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **12** | Calculated | --- | 3.7 | 9.5 | 7.6 | 2.1 | --- | --- | 2.1 | 3.1 | 3.1 | 8.6 | 10.3 |
| | Experimental | --- | ≈0* | 6.0 | 5.3* | ≈0* | --- | --- | 1.2 | 2.8 | 3.4 | 9.4 | 9.4 |
| **24** | Calculated | 9.6 | 5.4 | 8.9 | 10.8 | 1.4 | 7.8 | 10.6 | 2.1 | 3.2 | 3.0 | 8.7 | 10.3 |
| | Experimental | 9.7 | 3.7 | 6.7 | 8.3 | 1.7 | 9.5 | 9.5 | 1.4 | 2.7 | 3.6 | 9.5 | 9.5 |

*Refers to $J_{1,2}$, $J_{2,3\alpha}$ and $J_{2,3\beta}$

the β-furanose (δ 102.5 ppm) and β-pyranose (δ 98.0 ppm) anomeric carbon atoms were of higher intensity in agreement with data previously reported[18] for analogous hexuloses and 3-heptuloses. As in the case of compound **4**, hydrogenation of **18** afforded 1,2,4-trideoxy-1,4-imino-D-*glycero*-D-*talo*-octitol **20** characterized as its peracetylated derivative **21**.

The high stereoselectivity found in the hydrogenation of the 1-pyrroline intermediates **6** and **19** was crucial for the final chirality of the bicyclic system and was also in accordance with that previously reported by other authors,[19] where the hydrogen molecule approached the same face occupied by the substituent at C-3 (see Scheme 4).




**6** R = OH
**19** R = H

Scheme 4.

Compound **20** was transformed into *N*-benzyloxycarbonyl-1,2,4-trideoxy-1,4-imino-8-*O*-mesitylenesulphonyl-D-*glycero*-D-*talo*-octitol **23**. Subsequent reaction of **23** with Pd–C/$H_2$ caused the hydrogenolysis of the Cbz group at the pyrrolidine nitrogen and the subsequent nucleophilic attack of N at the carbon bearing the mesitylenesulfonyloxy group (C-8) to afford the bicyclic system of (1*R*,6*R*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (1,6-diepicastanospermine, **24**).

The structure of **24** was established on the basis of its $^1H$, $^{13}C$ and 2D $^{13}C$–$^1H$ heteronuclear shift correlation spectra (see Fig. 2). Their spectral data were consistent, as in the case of compound **12**, with the configuration and conformation shown in Scheme 5 (see Table 1).

## 3. Experimental

### 3.1. General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The $^1H$ and $^{13}C$ NMR spectra were recorded with Bruker AMX-300, AM-300, ARX-400, and AMX-500 spectrometers for solutions in $CDCl_3$ (internal reference $Me_4Si$). IR spectra were recorded with a Perkin–Elmer 782 instrument and

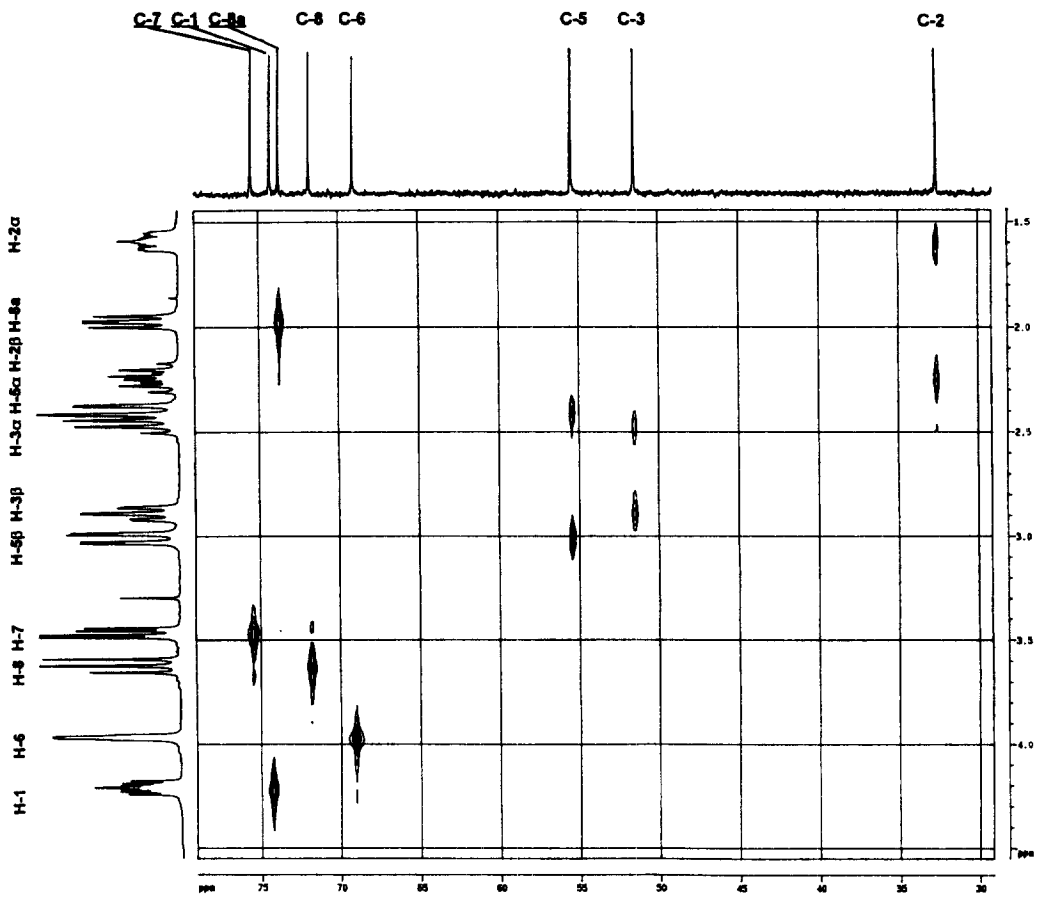
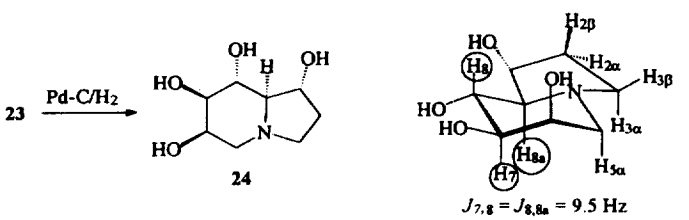



Fig. 2.




Scheme 5.

mass spectra with a Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1 dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 $F_{254}$ aluminium sheets and detection by charring with $H_2SO_4$ (*A*), phosphomolybdic acid (*B*), and ninhydrin (*C*). Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds, for which elemental analyses were not obtained, were shown to be homogeneous by chromatography and characterized by NMR and HRMS.

### 3.2. 2,3:4,5:6,7-Tri-O-isopropylidene-1-O-p-toluenesulfonyl-β-D-glycero-D-galacto-oct-4-ulo-4,8-pyranose 2

To an ice–water cooled and stirred solution of 2,3:4,5:6,7-tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose (**1**,[10] 5 g, 13.9 mmol) in dry pyridine (25 mL), *p*-toluenesulfonyl chloride (3 g, 15.73 mmol) was added portionwise and the mixture kept at room temperature for 20 h. TLC (ether:hexane=2:1) then revealed (*A*) the presence of a faster-running compound. The mixture was poured into ice–water and after 2 h extracted with ether (3×50 mL). The extracts were washed with aqueous 10% hydrochloric acid, water, saturated $NaHCO_3$ solution, water and then concentrated to a residue that crystallized on standing. Recrystallization from ether–hexane gave pure **2** (6.5 g, 91%): m.p.: 100–101°C; $[\alpha]_D^{25}$ −28.5 (c 1); $\nu_{max}^{KBr}$ 1600, 1387, 1381, 1372, and 1364 ($CMe_2$), and 663 $cm^{-1}$ (aromatic). NMR data: $^1H$, δ 7.78 and 7.31 (2 d, 4H, J=8.3 Hz, Me*Ph*), 4.58 (dd, 1H, $J_{5,6}$=2.7, $J_{6,7}$=7.8 Hz, H-6), 4.39 (d, 1H, H-5), 4.38 (dd, 1H, $J_{1,2}$=2, $J_{1,1'}$=10.5 Hz, H-1), 4.34 (ddd, 1H, H-2), 4.19 (bdd, 1H, H-7), 4.09 (dd, 1H, $J_{1',2}$=4.9 Hz, H-1′), 3.95 (d, 1H, $J_{2,3}$=8.3 Hz, H-3), 3.81 (dd, 1H, $J_{7,8ax}$=1.9, $J_{8ax,8eq}$=12.9 Hz, H-8*ax*), 3.62 (bd, 1H, H-8*eq*), 2.43 (s, 3H, *Me*Ph), 1.50, 1.44, 1.38, 1.34, 1.33, and 1.32 (6 s, 18H, 3 $CMe_2$); $^{13}C$, δ 144.6, 133.2, 129.7, and 128.2 (Me*Ph*), 110.3, 109.3, and 109.2 (3 *C*$Me_2$), 102.4 (C-4), 77.3, 76.5, 75.2, 70.9, 70.2 (C-2,3,5,6,7), 70.0 (C-1), 61.5 (C-8), 27.2, 26.8, 26.6, 26.0, 25.7, and 24.3 (3 C*Me*$_2$), and 21.7 (*Me*Ph). Mass spectrum (c.i. $CH_4$): *m/z* 515 (16.6%, $M^+$+1), 499 (16.1, $M^+$+1−$CH_4$), 457 (17.8, $M^+$+1−$Me_2CO$), 439 (6.3, $M^+$+1−$CH_4$–AcOH), 399 (10.8, $M^+$+1−2$Me_2CO$), 381 (7, $M^+$+1−$CH_4$–AcOH–$Me_2CO$), 229 (13.6), 227 (19.1), and 59 (100, $Me_2COH^+$). Anal. calcd for $C_{24}H_{34}O_{10}S$: C, 56.02; H, 6.66; S, 6.23. Found: C, 56.41; H, 6.60; S, 6.01.

### 3.3. 1-Azido-1-deoxy-2,3:4,5:6,7-tri-O-isopropylidene-β-D-glycero-D-galacto-oct-4-ulo-4,8-pyranose 3

To a stirred solution of **2** (6.5 g, 12.63 mmol) in dry DMF (5 mL), $NaN_3$ (2.5 g, 31 mmol) was added and the mixture heated at 80°C for 15 h. TLC (ether) revealed (*A*) the presence of a new compound of higher mobility. The reaction mixture was concentrated, diluted with water and extracted with ether (4×50 mL). The combined extracts were washed with brine, water then concentrated to a residue that was chromatographed (ether:hexane=1:3) to afford crystalline **3** (4 g, 82%): m.p.: 85–86°C; $[\alpha]_D^{25}$ −64 (c 1.1); $\nu_{max}^{KBr}$ 2108 ($N_3$), 1387, 1378, and 1368 $cm^{-1}$ ($CMe_2$). NMR data: $^1H$, δ 4.59 (dd, 1H, $J_{5,6}$=2.7, $J_{6,7}$=7.9 Hz, H-6), 4.42 (d, 1H, H-5), 4.38 (ddd, 1H, H-2), 4.20 (bdd, 1H, H-7), 3.39 (d, 1H, $J_{2,3}$=8.3 Hz, H-3), 3.85 (dd, 1H, $J_{7,8ax}$=1.9, $J_{8ax,8eq}$=12.9 Hz, H-8*ax*), 3.73 (dd, 1H, $J_{1,2}$=2.4, $J_{1,1'}$=13.1 Hz, H-1), 3.67 (bd, 1H, H-8*eq*), 3.31 (dd, 1H, $J_{1',2}$=5.0 Hz, H-1′), 1.53, 1.47, 1.46, 1.41, 1.40, 1.33 (6 s, 18H, 3 $CMe_2$); $^{13}C$, δ 110.1, 109.3, and 109.2 (3 *C*$Me_2$), 102.6 (C-4), 77.5, 76.6, 71.1, 70.9, 70.2 (C-2,3,5,6,7), 61.5 (C-8), 52.7 (C-1), 27.4, 26.8, 26.7, 25.9, 25.7, and 24.3 (3 C*Me*$_2$). Mass spectrum (c.i. $CH_4$): *m/z* 386 (1.75%, $M^+$+1), 384 (1.16, $M^+$−1), 370 (23, $M^+$+1−$CH_4$), 358 (68.6, $M^+$+1−$N_2$), 300 (39.9, $M^+$+1−$N_2$–$Me_2CO$), 229 (16.0), 227 (7.0), and 59 (100, $Me_2COH^+$). Anal. calcd for $C_{17}H_{27}N_3O_7$: C, 52.98; H, 7.06; N, 10.90. Found: C, 53.05; H, 7.24; N, 10.65.

### 3.4. 1,4-Dideoxy-1,4-imino-D-erythro-L-altro-octitol 7

A stirred suspension of **3** (4.0 g, 10.4 mmol) in aqueous 70% acetic acid (30 mL) was heated at 100°C for 22 h. During this time, the original suspension became a clear solution. TLC (chloroform:methanol=5:2) showed (*A*) one main product of lower mobility. The mixture was concentrated and the remaining acetic acid removed by repeated codistillation with water. The residue was dissolved in water and the decolorized solution (activated charcoal) was then concentrated. Column chromatography

(chloroform:methanol=10:1) of the residue gave 1-azido-1-deoxy-D-*glycero*-D-*galacto*-4-octulose (**4**, 2.3 g, 84%) as a syrup that was not characterized but hydrogenated in water (100 mL) with 10% Pd–C (460 mg) for 20 h, at which time TLC (chloroform:methanol=5:2) revealed (*B*) the absence of **4** and the presence of a non-mobile compound. The catalyst was filtered off, washed with water and the combined filtrate and washings concentrated to a thick syrup. Addition of methanol caused crystallization to afford **7** (1.7 g, 88%): m.p.: 172°C (dec.); $[\alpha]_D^{27}$+1.5 (c 1.1, water). NMR data (DMSO-$d_6$–$D_2O$): $^1$H, δ 3.82–3.80 (m, 2H, H-2,3), 3.61 (d, 1H, $J_{4,5}$=6.5 Hz, H-5), 3.56 (dd, 1H, $J_{7,8}$=3.2, $J_{8,8'}$=11 Hz, H-8), 3.47 (ddd, 1H, H-7), 3.42 (d, 1H, $J_{6,7}$=8.4 Hz, H-6), 3.35 (dd, 1H, $J_{7,8'}$=5.9, H-8′), 2.88 (dd, 1H, $J_{1,2}$=5.0, $J_{1,1'}$=11.5 Hz, H-1), 2.83 (dd, 1H, $J_{3,4}$=4.9 Hz, H-4), and 2.55 (dd, 1H, $J_{1',2}$=3.5 Hz, H-1′); $^{13}$C, δ 79.5 (C-3), 77.9 (C-2), 71.7 (C-6), 71.6 (C-7), 69.9 (C-5), 67.6 (C-4), 63.9 (C-8), and 51.9 (C-1). Anal. calcd for $C_8H_{17}NO_6$; C, 43.04; H, 7.68; N, 6.27. Found: C, 43.26; H, 7.39; N, 6.43.

Conventional acetylation of **7** (100 mg, 0.45 mmol) in dry pyridine (5 mL) with acetic anhydride (2 mL) and a catalytic amount of DMAP gave, after work-up and column chromatography (ether:acetone=10:1), the corresponding *N*-acetyl-2,3,5,6,7,8-hexa-*O*-acetyl derivative **8** (175 mg, 75%) as a syrup; $[\alpha]_D^{25}$ +44 (c 1.5); $\nu_{max}^{KBr}$ 1756 and 1749 (MeCOO), and 1660 cm$^{-1}$ (MeCON). NMR data: $^1$H, δ 5.59 (dd, 1H, $J_{4,5}$=5.3, $J_{5,6}$=3.3 Hz, H-5), 5.32 (dd, 1H, $J_{6,7}$=7.2 Hz, H-6), 5.31 (bd, 1H, H-3), 5.15 (m, 1H, H-2), 5.13 (ddd, 1H, H-7), 4.45 (bd, 1H, H-4), 4.29 (dd, 1H, $J_{7,8}$=3.1, $J_{8,8'}$=12.4 Hz, H-8), 4.06 (dd, 1H, $J_{7,8'}$=6.3 Hz, H-8′), 4.05 (dd, 1H, $J_{1,2}$=7.3, $J_{1,1'}$=12.1 Hz, H-1), 3.36 (dd, 1H, $J_{1',2}$=3.7 Hz, H-1′), 2.12, 2.11, 2.08, 2.04, 2.03, 2.02, and 2.01 (7 s, 21H, 7 Ac); $^{13}$C, δ 170.7, 170.5, 170.2, 170.0, 169.9, and 169.6 (7 Me*C*O), 76.4 (C-2,6), 69.6 (C-3), 68.9 (C-7), 68.8 (C-5), 62.6 (C-4), 62.0 (C-8), 52.5 (C-1), 22.4, 21.0, 20.9, 20.8, and 20.7 (7 *Me*CO). Mass spectrum (LSIMS): *m/z* 540.16914 ($M^+$+Na). For $C_{22}H_{31}NO_{13}Na$ 540.16931 (deviation 0.3 ppm).

### 3.5. *Attempted cyclisation of 7→12*

To a stirred solution of iodine (254 mg, 1 mmol) in dry pyridine (8.5 mL), triphenylphosphine (263 mg, 1 mmol) and imidazole (150 mg, 2 mmol) were added at room temperature. Then, compound **7** (223 mg, 1 mmol) was added and after 5 min TLC (methanol with a few drops of triethylamine) revealed (*B*) the presence of a faster-running compound. DABCO (223 mg, 2 mmol) was then added and after 1 h acetic anhydride (1 mL) was added and the reaction mixture left at room temperature overnight. Conventional work-up and column chromatography (ether:acetone=5:1) afforded crystalline *N*-acetyl-2,3,5,7,8-penta-*O*-acetyl-1,4-dideoxy-1,4-imino-D-*erythro*-L-*altro*-octitol (**9**, 120 mg, 25%): m.p.: 217–218°C; $[\alpha]_D^{27}$ +11, $[\alpha]_{405}^{27}$ +26.5 (c 1.1); $\nu_{max}^{KBr}$ 3278 (OH), 1748, 1744, and 1740 ($MeCO_2$), and 1633 cm$^{-1}$ (MeCON). NMR data: $^1$H, δ 5.55 (bs, 1H, OH), 5.22 (d, 1H, H-2), 5.18 (d, 1H, $J_{4,5}$=10.8 Hz, H-5), 5.09 (s, 1H, H-3), 4.98 (ddd, 1H, H-7), 4.49 (dd, 1H, $J_{7,8}$=2.2, $J_{8,8'}$=12.1 Hz, H-8), 4.32 (d, 1H, H-4), 4.26 (dd, 1H, $J_{7,8'}$=5.2 Hz, H-8′), 4.01 (dd, 1H, $J_{1,2}$=5.8, $J_{1,1'}$=12.2 Hz, H-1), 3.71 (d, 1H, H-1′), 3.70 (d, 1H, $J_{6,7}$=9.7 Hz, H-6), 2.20, 2.16, 2.12, 2.05, 2.04, and 1.99 (6 s, 18H, 6 Ac); $^{13}$C, δ 173.5, 171.0, 169.7, 169.6, and 168.7 (6 Me*C*O), 75.2 (C-3), 74.7 (C-2), 69.2 (C-7), 69.0 (C-5), 66.9 (C-6), 63.5 (C-8), 62.7 (C-4), 53.3 (C-1), 22.9, 21.0, 20.9, and 20.8 (6 *Me*CO). Anal. calcd for $C_{20}H_{29}NO_{12}$: C, 50.52; H, 6.16; N, 2.95. Found: C, 50.90; H, 6.61; N, 3.02.

### 3.6. N-*Benzyloxycarbonyl-1,4-dideoxy-1,4-imino-8*-O-*mesitylenesulphonyl*-D-erythro-L-altro-*octitol* **11**

To an ice–water cooled and stirred solution of **7** (400 mg, 1.8 mmol) in water (5 mL) containing sodium hydrogen carbonate (400 mg), benzyl chloroformate (800 μL, 5.6 mmol) was added dropwise. After 6 h TLC (isopropanol:methanol:ammonia=6:2:1) revealed (*B*) the presence of a faster-running compound.

The mixture was acidified (pH 4–5) with aqueous 1 N hydrochloric acid and then extracted with ether. The aqueous phase was concentrated and the residue dissolved in ethanol, filtered and the filtrate was concentrated. Column chromatography (isopropanol:methanol:ammonia=6:2:1) of the residue gave *N*-benzyloxycarbonyl-1,4-dideoxy-1,4-imino-D-*erythro*-L-*altro*-octitol (**10**, 525 mg, 81.6%) which was not characterized but dissolved in dry pyridine (10 mL). The cooled (ice–water) and stirred solution was treated with DMAP (50 mg) and mesitylenesulphonyl chloride (710 mg, 3.25 mmol) portionwise and the mixture left at room temperature for 15 h. TLC (isopropanol:methanol:ammonia=6:2:1) then revealed (*B*) the absence of **10** and the presence of a faster-running compound. The reaction mixture was concentrated and chromatographed (chloroform:methanol=15:1) to afford crystalline **11** (550 mg, 69.4%): m.p.: 58–61°C; $[\alpha]_D^{25}$ +4, $[\alpha]_{405}^{25}$ +15 (c 0.7); $\nu_{max}^{KBr}$ 3397 (OH) and 1675 $cm^{-1}$ (NCbz). NMR data: $^1H$ (*inter alia*), δ 7.40–7.20 (m, 7H, Mes and *Ph*$CH_2$), 5.16 and 5.10 (2 d, 2H, J=12.2 Hz, PhC$H_2$), 2.62 and 2.30 (2 s, 9H, Mes); $^{13}C$, δ 158.9 (CO), 144.9, 141.3, 137.9, 132.8, 129.6, 129.2, and 128.9 (Mes and *Ph*$CH_2$), 78.3 (C-3), 76.6 (C-2), 73.1 (Ph*C*$H_2$), 71.2, 69.6, 69.3, and 69.2 (C-4,5,6,7), 68.6 (C-8), 54.9 (C-1), 22.8 and 21.1 (Mes).

### 3.7. (1S,2S,6R,7R,8R,8aR)-1,2,6,7,8-Pentahydroxyindolizidine 12

A solution of **11** (450 mg, 0.83 mmol) in dry methanol (50 mL) containing sodium acetate (690 mg) and 10% Pd–C (210 mg) was hydrogenated at 75 psi for 7 h. TLC (isopropanol:methanol:ammonia=2:1:1) then revealed (*C*) that **11** had disappeared and that a slower-running product was present. The catalyst was filtered off, washed with methanol and the combined filtrate and washings concentrated to a residue that was chromatographed (isopropanol:methanol:ammonia=2:1:1) to afford **12** (120 mg, 70%) as a thick syrup, $[\alpha]_D^{27}$ −26, $[\alpha]_{405}^{28}$ −78 (c 0.5, methanol). NMR data (500 MHz, MeOH-$d_4$): $^1H$, δ 3.91 (bd, 1H, H-1), 3.85 (bd, 1H, H-2), 3.82 (m, 1H, H-6), 3.59 (t, 1H, $J_{7,8}=J_{8,8a}=9.4$ Hz, H-8), 3.26 (dd, 1H, $J_{6,7}=3.4$ Hz, H-7), 2.95 (dd, 1H, $J_{5\beta,6}=2.8$, $J_{5\alpha,5\beta}=11.9$ Hz, H-5β), 2.76 (bd, 1H, $J_{3\alpha,3\beta}=10$ Hz, H-3β), 2.55 (dd, 1H, $J_{2,3\alpha}=5.3$ Hz, H-3α), 2.28 (dd, 1H, $J_{5\alpha,6}=1.2$ Hz, H-5α) and 1.80 (dd, 1H, $J_{1,8a}=6$ Hz, H-8a); $^{13}C$, δ 84.4 (C-1), 79.6 (C-2), 77.4 (C-7), 75.1 (C-8a), 73.8 (C-8), 70.9 (C-6), 60.8 (C-3), and 56.4 (C-5). Mass spectrum (LSIMS): *m/z* 206.10236 ($M^+$+1). For $C_8H_{16}NO_5$ 206.10285 (deviation 2.4 ppm).

### 3.8. 1-Chloro-1,2-dideoxy-4,5:6,7-di-O-isopropylidene-β-D-manno-oct-4-ulo-4,8-pyranose 14 and 2-deoxy-4,5:6,7-di-O-isopropylidene-1-O-p-toluenesulfonyl-β-D-manno-oct-4-ulo-4,8-pyranose 15

To an ice–water cooled and stirred solution of 2-deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranose (**13**,[12] 2.9 g, 9.5 mmol) in dry pyridine (20 mL), *p*-toluenesulfonyl chloride (2.35 g, 12.3 mmol) was added portionwise and the mixture kept at room temperature for 2 days. TLC (ether:hexane=2:1) then revealed (*A*) the presence of two faster-running compounds. The mixture was poured into ice–water and after 2 h extracted with ether (3×50 mL). The extracts were washed with aqueous 10% hydrochloric acid, water, saturated $NaHCO_3$ solution and water, and then concentrated to a residue that was chromatographed (ether:hexane=1:2→1:1) to afford first syrupy 1-chloro-1,2-dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranose (**14**, 760 mg, 25%): $[\alpha]_{405}^{25}$ +1.2 (c 1); $\nu_{max}^{film}$ 3493 (OH), 1384 and 1373 $cm^{-1}$ ($CMe_2$). NMR data: $^1H$, δ 4.59 (dd, 1H, $J_{5,6}=2.6$, $J_{6,7}=7.8$ Hz, H-6), 4.43 (d, 1H, H-5), 4.22 (bdd, 1H, H-7), 3.89 (dd, 1H, $J_{7,8ax}=1.9$, $J_{8ax,8eq}=13.0$ Hz, H-8*ax*), 3.88 (dd, 1H, $J_{2,3}=2.6$, $J_{2',3}=9.9$ Hz, H-3), 3.76 (d, 1H, H-8*eq*), 3.74–3.70 (m, 2H, H-1,1′), 2.36 (dddd, 1H, $J_{2,2'}=14.8$ Hz, H-2), 1.88 (bddd, 2H, H-2′,OH-3), 1.53, 1.46, 1.40, and 1.32 (4 s, 12H, 2 $CMe_2$); $^{13}C$, δ 109.2 and 108.7 (2 *C*$Me_2$), 104.2 (C-4), 70.8, 70.5, and 70.3 (C-3,5,6,7), 61.5 (C-8), 42.2 (C-1), 34.1 (C-

2), 26.7, 25.8, and 24.1 (2 C*Me*$_2$). Eluted second was syrupy **15** (1.2 g, 28%), $[\alpha]_D^{25}$ −5, $[\alpha]_{405}^{25}$ −10 (c 1); $\nu_{max}^{film}$ 3525 (OH) and 1600 cm$^{-1}$ (aromatic). NMR data: $^1$H, δ 7.75 and 7.30 (2 d, 4H, J=8.3 Hz, Me*Ph*), 4.59 (dd, 1H, $J_{5,6}$=2.6, $J_{6,7}$=7.9 Hz, H-6), 4.39 (d, 1H, H-5), 4.29 (dt, 1H, $J_{1,1'}$=$J_{1,2}$=9.7, $J_{1,2'}$=4.9 Hz, H-1), 4.20 (bd, 1H, H-7), 4.16 (ddd, 1H, $J_{1',2}$=6, $J_{1',2'}$=4.5 Hz, H-1′), 3.87 (dd, 1H, $J_{7,8ax}$=1.8, $J_{8ax,8eq}$=13.0 Hz, H-8*ax*), 3.74 (m, 1H, H-3), 3.71 (bd, 1H, H-8*eq*), 2.43 (s, 3H, *Me*Ph), 2.29 (dddd, 1H, $J_{2,3}$=2.5, $J_{2,2'}$=15.2 Hz, H-2), 2.05 (d, 1H, $J_{HO,3}$=8.6 Hz, HO-3), 1.73 (ddt, 1H, $J_{2',3}$=9.6 Hz, H-2′), 1.50, 1.41, 1.37, and 1.31 (4 s, 12H, 3 C*Me*$_2$); $^{13}$C, δ 144.7, 133.2, 129.9, and 128.0 (Me*Ph*), 109.1 and 108.7 (2 *C*Me$_2$), 104.0 (C-4), 70.8, 70.3, and 69.7 (C-3,5,6,7), 68.0 (C-1), 61.4 (C-8), 30.7 (C-2), 26.7, 25.8, 25.7, and 24.0 (2 C*Me*$_2$), and 21.7 (*Me*Ph). Mass spectrum (LSIMS): *m/z* 459.16869 ($M^+$+1). For $C_{21}H_{31}O_9S$ 459.16888 (deviation 0.4 ppm).

### 3.9. *1,2-Dideoxy-1-iodo-4,5:6,7-di-*O*-isopropylidene-β-*D-manno-*oct-4-ulo-4,8-pyranose* **16**

To a stirred solution of **13** (3.22 g, 10.6 mmol) in anhydrous dichloromethane (15 mL) a solution of iodine (2.96 g, 11.6 mmol), triphenylphosphine (3.05 g, 11.6 mmol), and imidazole (1.58 g, 23.2 mmol) in the same solvent (40 mL), was added at room temperature. After 4 h TLC (ether:hexane=3:2) then revealed (UV) the presence of a faster-running compound. The mixture was filtered and concentrated. Column chromatography (ether:hexane=1:4) gave syrupy **16** (3.74 g, 85%): $[\alpha]_D^{25}$ +8 (c 0.6); $\nu_{max}^{film}$ 3486 (OH), 1384 and 1373 cm$^{-1}$ (CMe$_2$). NMR data: $^1$H, δ 4.62 (dd, 1H, $J_{5,6}$=2.6, $J_{6,7}$=7.9 Hz, H-6), 4.45 (d, 1H, H-5), 4.25 (dd, 1H, H-7), 3.92 (dd, 1H, $J_{7,8ax}$=1.8, $J_{8ax,8eq}$=13.0 Hz, H-8*ax*), 3.79 (bd, 2H, H-3,8*eq*), 3.42 (ddd, 1H, $J_{1,2}$=7.3, $J_{1,2'}$=4.3, $J_{1,1'}$=9.6 Hz, H-1), 3.33 (dt, 1H, $J_{1',2}$=9,7, $J_{1',2'}$=6.4 Hz, H-1′), 2.45 (dddd, 1H, $J_{2,3}$=2.5, $J_{2,2'}$=14.9 Hz, H-2), 1.93 (m, 2H, H-2′,OH-3), 1.55, 1.52, 1.43, and 1.36 (4 s, 12H, 2 CMe$_2$); $^{13}$C, δ 109.1 and 108.6 (2 *C*Me$_2$), 104.1 (C-4), 73.2, 70.8, 70.5, and 70.2 (C-3,5,6,7), 61.4 (C-8), 34.9 (C-2), 26.7, 26.0, 25.8, and 24.0 (2 C*Me*$_2$), and 3.7 (C-1). Mass spectrum (LSIMS): *m/z* 437.04239 ($M^+$+Na). For $C_{14}H_{23}O_6NaI$ 437.04371 (deviation 3.0 ppm).

### 3.10. *1-Azido-1,2-dideoxy-4,5:6,7-di-*O*-isopropylidene-β-*D-manno-*oct-4-ulo-4,8-pyranose* **17**

To a stirred solution of **16** (3.51 g, 8.47 mmol) in dry DMF (20 mL) sodium azide (1.38 g, 21.2 mmol) was added and the mixture heated at 60°C for 15 h. TLC (ether:hexane=3:2) then revealed (UV) the absence of **16** and the presence (*A*) of a new compound. The reaction mixture was concentrated, diluted with water and extracted with ether (4×50 mL). The combined extracts were washed with brine and water then concentrated to a residue that was chromatographed (ether:hexane=1:3) to afford syrupy **17** (2.65 g, quantitative); $[\alpha]_D^{25}$ +2, $[\alpha]_{405}^{25}$ +6 (c 1.2); $\nu_{max}^{film}$ 3496 (OH), 2099 ($N_3$), 1384 and 1374 cm$^{-1}$ (CMe$_2$). NMR data: $^1$H, δ 4.62 (dd, 1H, $J_{5,6}$=2.6, $J_{6,7}$=7.9 Hz, H-6), 4.46 (d, 1H, H-5), 4.25 (dd, 1H, H-7), 3.92 (dd, 1H, $J_{7,8ax}$=1.9, $J_{8ax,8eq}$=13.0 Hz, H-8*ax*), 3.78 (m, 2H, H-3,8*eq*), 3.53 (dd, 2H, H-1,1), 2.21 (ddt, 1H, $J_{1,2}$=8, $J_{2,3}$=2.7, $J_{2,2'}$=14.5 Hz, H-2), 2.02 (bs, 1H, HO-3), 1.73 (ddt, 1H, $J_{1,2'}$=5.6, $J_{2',3}$=9.8 Hz, H-2′), 1.56, 1.48, 1.44, and 1.35 (4 s, 12H, 2 CMe$_2$); $^{13}$C, δ 109.1 and 108.7 (2 *C*Me$_2$), 104.2 (C-4), 71.1, 70.8, 70.4, and 70.3 (C-3,5,6,7), 61.4 (C-8), 48.8 (C-1), 30.4 (C-2), 26.7, 25.8, and 24.0 (2 C*Me*$_2$). Mass spectrum (LSIMS): *m/z* 330.16621 ($M^+$+1). For $C_{14}H_{24}N_3O_6$ 330.16651 (deviation 0.9 ppm).

Compound **17** was also obtained in quantitative yield from **14** and **15** by treatment with sodium azide in DMF, respectively.

### 3.11. N-*Acetyl-3,5,6,7,8-penta*-O-*acetyl-1,2,4-trideoxy-1,4-imino*-D-glycero-D-talo-*octitol* **21**

A stirred suspension of **17** (2.44 g, 7.41 mmol) in aqueous 40% acetic acid (30 mL) was heated at 100°C for 18 h. During this time, the original suspension became a clear solution. TLC (chloroform:methanol=4:1) showed (*A*) a main product of lower mobility. The mixture was concentrated and the remaining acetic acid removed by repeated codistillation with water. The residue was dissolved in water and the decolorized solution (activated charcoal) was then concentrated. Column chromatography (chloroform:methanol=9:1) of the residue gave 1-azido-1,2-dideoxy-D-*manno*-4-octulose (**18**, 1.52 g, 82.5%) as a syrup that was shown to be a mixture of anomers, mainly the β-furanose and β-pyranose forms ($^{13}$C-NMR evidence). Compound **18** (1.36 g, 5.46 mmol) was hydrogenated in water (40 mL) with 10% Pd–C (220 mg) for 16 h, at which time TLC (isopropanol:methanol:ammonia=2:1:1) revealed (*B*) the absence of **18** and the presence of a slightly mobile compound. The catalyst was filtered off, washed with water and the combined filtrate and washings concentrated to syrupy compound **20**. Conventional acetylation of **20** (36 mg, 0.19 mmol) in dry pyridine (0.5 mL) with acetic anhydride (0.5 mL) gave, after work-up and column chromatography (ether:acetone=5:1), the peracetylated derivative of **20** (**21**) that crystallized on standing: m.p.: 89–91°C; $[\alpha]_D^{25}$ +48 (c 2.3); $\nu_{max}^{KBr}$ 1757, 1745 and 1739 (MeCOO), and 1658 cm$^{-1}$ (MeCON). NMR data: $^1$H, δ 5.58 (m, 1H, H-5), 5.44 (dd, 1H, $J_{5,6}$=3.6, $J_{6,7}$=8.2 Hz, H-6), 5.40 (bd, 1H, H-3), 5.09 (ddd, 1H, H-7), 4.27 (bs, 1H, H-4), 4.21 (dd, 1H, $J_{7,8}$=2.8, $J_{8,8'}$=12.5 Hz, H-8), 4.10 (dd, 1H, $J_{7,8'}$=5.4 Hz, H-8′), 3.50–3.41 (m, 2H, H-1,1′), 2.18–1.96 (2 m, 2H, H-2,2′), 2.04, 2.03, 2.01, 2.00, and 1.99 (5 s, 18H, 6 Ac); $^{13}$C, 170.7, 170.5, 170.1, 170.0, 169.8, and 169.7 (6 Me*C*O), 73.7 (C-3), 70.1 (C-6), 69.1 (C-5), 68.6 (C-7), 64.3 (C-4), 61.7 (C-8), 45.4 (C-1), 31.8 (C-2), 22.5, 21.0, 20.8, and 20.7 (6 *Me*CO). Anal. calcd for $C_{20}H_{29}NO_{11}$: C, 52.28; H, 6.36; N, 3.05. Found: C, 52.47; H, 6.94; N, 3.21.

### 3.12. N-*Benzyloxycarbonyl-1,2,4-trideoxy-1,4-imino-8*-O-*mesitylenesulphonyl*-D-glycero-D-talo-*octitol* **23**

To an ice–water cooled and stirred solution of compound **20** (865 mg, 4.17 mmol) in water (15 mL) and ethanol (5 mL) containing sodium hydrogen carbonate (760 mg), benzyl chloroformate (1.29 mL, 9 mmol) was added dropwise. After 9 h TLC (isopropanol:methanol:ammonia=2:1:1) revealed (*B*) the presence of a faster-running compound. The mixture was acidified (pH 4–5) with aqueous 1 N hydrochloric acid and then extracted with ether. The aqueous phase was concentrated and the residue dissolved in ethanol, filtered and the filtrate was concentrated. Column chromatography (isopropanol:methanol:ammonia=6:2:1) of the residue gave *N*-benzyloxycarbonyl-1,2,4-trideoxy-1,4-imino-D-*glycero*-D-*talo*-octitol (**22**, 1.21 g, 85%) which was not characterized but dissolved in dry pyridine (20 mL). The cooled (ice–water) and stirred solution was treated with DMAP (50 mg) and mesitylenesulphonyl chloride (1.36 g, 6.22 mmol) portionwise and the mixture left at room temperature for 17 h. TLC (chloroform:methanol=7:1) then revealed (*B*) the absence of **22** and the presence of a faster-running compound. The reaction mixture was concentrated and chromatographed (chloroform→chloroform:methanol=30:1) to afford crystalline **23** (1.77 g, 81%): m.p.: 82–84°C; $[\alpha]_D^{25}$ +7, $[\alpha]_{405}^{25}$ +14(c 1); $\nu_{max}^{KBr}$ 3407 (OH) and 1672 cm$^{-1}$ (NCbz). NMR data: $^1$H (*inter alia*), δ 7.37–7.27 and 6.97 (m and s, 7H, Mes and *Ph*$CH_2$), 5.14 and 5.10 (2 d, 2H, J=12.3 Hz, PhC*H*$_2$), 4.58 (d, 1H, J=3 Hz), 4.29 (d, 1H, J=8.9 Hz), 4.04–3.9 (m, 2H), 3.80 (d, 1H, J=10.3 Hz), 3.68 (dt, 1H, J=10.6, J=7.3 Hz), 3.59 (vbs, 1H, 4 HO), 3.52–3.36 (m, 2 H), 2.62 and 2.31 (2 s, 9H, Mes), 2.08 (m, 1H, H-2), and 1.94 (dd, 1H, J=7, $J_{2,2'}$=13.5 Hz, H-2′); $^{13}$C, δ 159.1 (CO), 144.9, 141.3, 137.9, 132.8, 129.6, 129.2, and 128.9 (Mes and *Ph*$CH_2$), 73.6, 70.7, 70.5, and 69.2 (C-3,5,6,7), 73.0 (Ph$CH_2$), 68.6 (C-8), 49.9 (C-4), 45.9 (C-

1), 32.2 (C-2), 22.9 and 21.1 (Mes). Mass spectrum (LSIMS): *m/z* 524.19447 ($M^+$+1). For $C_{25}H_{34}NO_9S$ 524.19543 (deviation 1.8 ppm).

### *3.13. (1R,6R,7R,8R,8aR)-1,6,7,8-Tetrahydroxyindolizidine (1,6-diepicastanospermine)* **24**

A solution of **23** (1.77 g, 3.3 mmol) in dry methanol (50 mL) containing sodium acetate (2.69 g) and 10% Pd–C (1.25 g) was hydrogenated at 75 psi for 20 h. TLC (isopropanol:methanol:ammonia=2:1:1) revealed (*C*) that **23** had disappeared and that a slower-running product was present. The catalyst was filtered off, washed with methanol and the combined filtrate and washings concentrated to a residue that was chromatographed (isopropanol:methanol:ammonia=16:4:1→5:2:0.5) to afford **24** (230 mg, 36%) as a thick syrup, $[\alpha]_D^{25}$ −79, $[\alpha]_{577}^{25}$ −85, $[\alpha]_{546}^{25}$ −96, $[\alpha]_{435}^{25}$ −158, (c 0.8, methanol) [lit.[7] $[\alpha]_D^{24}$ −72, $[\alpha]_{578}^{24}$ −75, $[\alpha]_{546}^{25}$ −85, $[\alpha]_{436}^{25}$ −140 (c 0.7, methanol)]. NMR data (500 MHz, $D_2O$; for other coupling constants see Table 1): $^1$H, δ 4.15 (ddd, 1H, H-1), 3.90 (m, H-6), 3.56 (t, 1H, H-8), 3.41 (dd, 1H, H-7), 2.95 (dd, 1H, $J_{5\alpha,5\beta}$=12.6 Hz, H-5β), 2.83 (dt, 1H, $J_{3\alpha,3\beta}$=10 Hz, H-3β), 2.40 (q, 1H, H-3α), 2.34 (dd, 1H, H-5α), 2.18 (dq, 1H, $J_{2\alpha,2\beta}$=13.7 Hz, H-2β), 1.91 (dd, 1H, H-8a) and 1.53 (m, 1H, H-2α); $^{13}$C, δ 75.4 (C-7), 74.2 (C-1), 73.6 (C-8a), 71.7 (C-8), 69.0 (C-6), 55.3 (C-5), 51.4 (C-3), and 32.5 (C-2). Mass spectrum (LSIMS): *m/z* 212.09035 ($M^+$+Na). For $C_8H_{15}NO_4Na$ 212.08988 (deviation −2.2 ppm).

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