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A short and highly stereoselective route to polyhydroxy-perhydroazaazulenes via a *C*-(D-*galacto*-pentopyranos-5-yl)isoxazolidine

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Abstract—A short and efficient route to enantiomerically pure hexahydroxy- and pentahydroxy-perhydroazaazulenes, ring-homologues of castanospermine, starting from the sole isoxazolidine derivative obtained in the 1,3-dipolar cycloaddition of a D-galactose-derived nitrone and methyl acrylate, is established. The procedure allows both backbone and stereochemical modulation of the products by choice of the starting monosaccharide. Structural assignment was based on crystallographic analysis of the starting isoxazolidine and NMR techniques. The products were tested for inhibitory activity against several glycosidases.

1. Introduction

Polyhydroxy-indolizidines are a group of natural and synthetic compounds belonging to the wider class of the iminosugars (azasugars). Many of them show interesting biological activities, such as glycosidase inhibitory properties, and therefore therapeutic applications, such as immunosuppressive, anti-malarial, anti-viral, anti-cancer, and anti-diabetic agents.[1–3] Extensive efforts have been reported to obtain compounds of this kind, castanospermine **1** being one of the most representative, and a natural member of the series.[2] Analogues of **1** have also been synthesized in order to study their biological properties. The topic has been extensively reviewed in the last few years.[4–7] Diverse synthetic routes start from monosaccharide derivatives,[8] taking advantage of the configurational variety of sugars and their ability to exert asymmetric induction in the formation of new stereogenic centers. A very useful type of reaction for the synthesis of higher-chain amino sugars is the 1,3-dipolar cycloaddition reaction of olefins with *C*-glycosyl nitrones, including cyclic nitrones, in which glycosyl-isoxazolidines are regio- and stereoselectively formed.[9,10] Opening the isoxazolidine ring of the cycloadducts affords diverse kinds of higher-chain sugars; thus, we have described[11] the synthesis of C_7 and C_8 aminodialdoses by opening the cycloadduct obtained from conveniently protected *C*-glycosyl nitrones and vinyl trimethylsilane.

The perhydroazaazulene system **2** is a higher-ring homologue of indolizidine. A possible general route to new potential glycosidase inhibitors derived from **2** starts from methyl acrylate **3** (as the dipolarophile) and hexose *N*-benzyl-nitrones (as the 1,3-dipoles). Compound **3** is known to add to nitrones with high regioselectivity, so that, with few exceptions, the sole (or at least the main) product is the 5-methoxycarbonyl regioisomer.[12,13] We have briefly reported[14,15] that the cycloaddition reaction of **3** with the nitrone **4**, derived from D-galactose, affords

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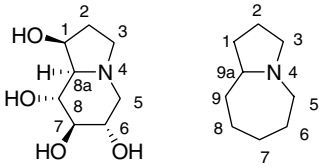
only one of the possible diastereomeric *N*-benzyl-3-(*O*-protected pentosyl)-5-methoxycarbonyl-isoxazolidines, whose hydrogenolysis, followed by reduction of the resulting lactam, leads to a 5-(O-protected pentosyl)-3-hydroxypyrrolidine. The chain of the sugar moiety in these compounds is long enough to undergo annellation in a subsequent step of the synthesis, giving rise to a seven-membered ring. This methodology might allow modulating both the ring size and the stereochemistry of the products. The synthetic versatility of this strategy is shown in Figure 1. Hence, the designed pathway would also allow the synthesis of polyhydroxy-indolizidines analogous to **1**, as well as their 5-hydroxy precursors.



We now report in detail the synthesis of two polyhydroxy-perhydroazaazulenes. To our knowledge, only one indolizidine homologue of this type has been synthesized.[16] We also include here a thorough configurational study of these molecules and their precursors, as well as the results of their biological evaluation. The first selected hexose nitrone was the O-protected D-galactose derivative **4**, which we have used for [3+2] cycloaddition reactions with other dipolarophiles.[10,11]

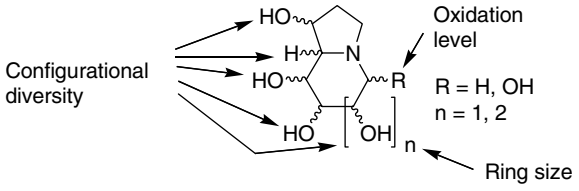
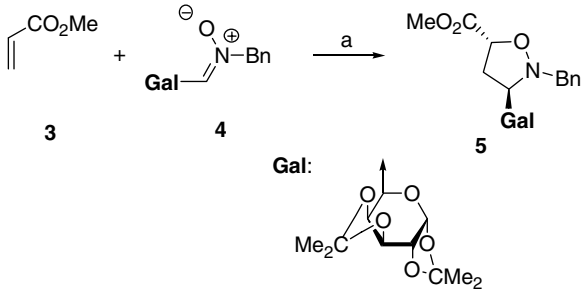


Figure 1. The synthetic versatility of the procedure, expressed on a general formula of the expected products.

2. Results

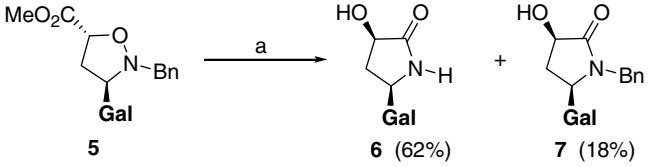
The reaction of **3** with the (*Z*)-*N*-benzyl-nitrone **4** (2:1 molar ratio) in toluene at 35 °C led with total regioselectivity to only one of the four possible diastereomeric cycloadducts—that coming from the *endo* attack of **3** to the *re* face of **4**—which was isolated as a crystalline compound **5** in 71% yield (Scheme 1). X-ray crystallographic analysis of **5** unambiguously showed, as discussed below, that it is the (2*R*) invertomer of the (3*R*,5*R*) configured diastereomer.[†]

[†] Compound **5** and the opening of its isoxazolidine ring under conditions different from those used by us have been described[17] after our first communication.[14]



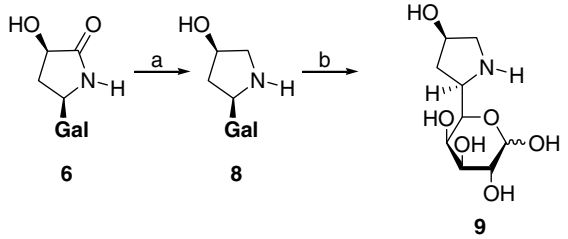
Scheme 1. Reagents and conditions: (a) Toluene, 35 °C, under Ar atmosphere (3 h), 71%.

Compound **5** was subjected to isoxazolidine-ring cleavage by treatment with hexacarbonylmolybdenum[18,19] to afford (3*R*,5*R*)-3-hydroxy-5-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)-2-oxopyrrolidine **6** and its *N*-benzyl derivative **7** in 62% and 18% yield, respectively, after column chromatography (Scheme 2). These nonopyranos-uronolactam derivatives should keep the (3*R*,5*R*) configuration coming from that of isoxazolidine C(5) and C(3) atoms, respectively. The (*R*) configuration assigned to C(5) for compounds **6** and **7** must be considered sure, since no epimerization of this center is to be expected. However, the C(3) of these compounds might have undergone epimerization. A correct assignment required the use of NMR techniques, as explained below.

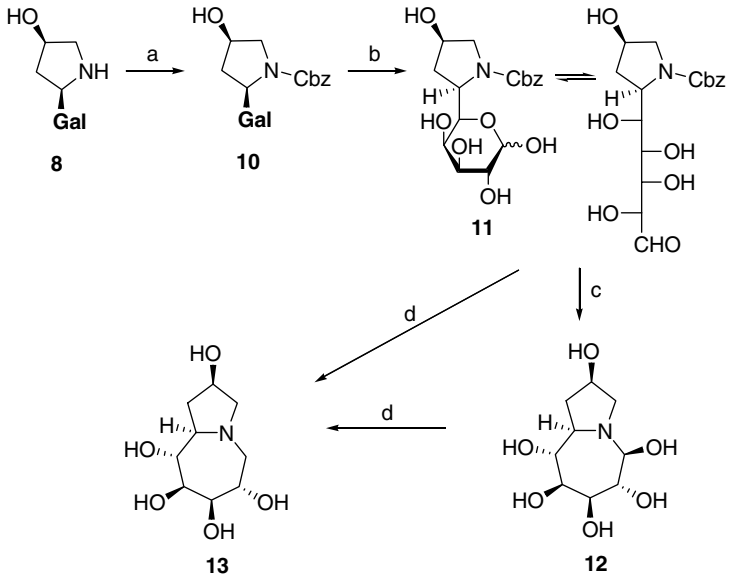


Scheme 2. Reagents and conditions: (a) $Mo(CO)_6$, $MeCN/H_2O$, reflux (7 h), yields: 62% for **6**; 18% for **7**.

As we have previously reported,[14,15] the major product **6** of the foregoing reaction was reduced with lithium aluminum hydride in ether to afford 96%, after column chromatography, of (2*R*,4*R*)-4-hydroxy-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)pyrrolidine **8**, whose treatment with trifluoroacetic acid (TFA), followed by cation-exchange chromatography, led to a product initially[14,15] formulated as the O-deprotected compound **9** (Scheme 3).



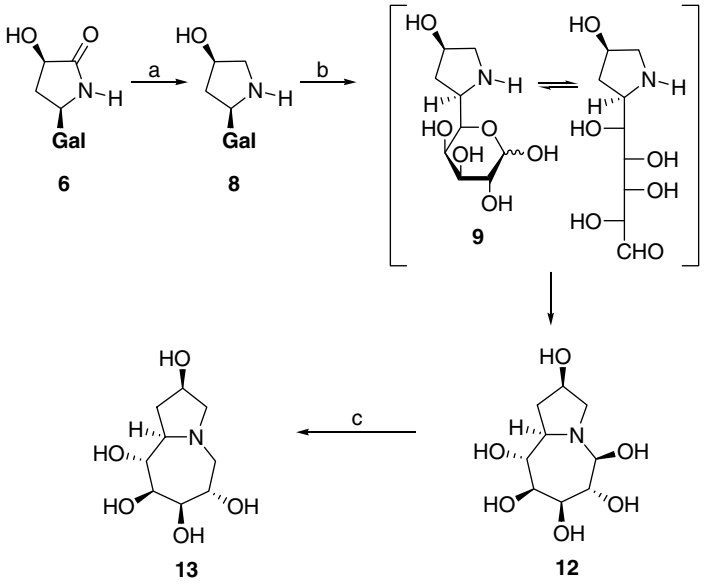
Scheme 3. Reagents and conditions: (a) $LiAlH_4$, ether, reflux (3 h), 96%; (b) 80% TFA, rt (24 h), 98%.



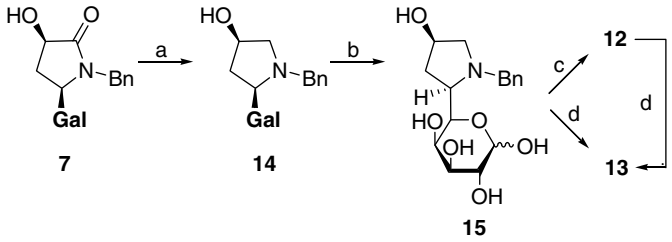
Scheme 4. Reagents and conditions: (a) CbzCl, $NaHCO_3$, 1:1 EtOH/H_2O, rt, 96%; (b) 80% TFA, rt (24 h), 95%; (c) H_2, 10% Pd/C, EtOH, rt (24 h), 99.5%; (d) H_2, 10% Pd/C, EtOH, HOAc, rt (2 h).

We aimed to complete our earlier route[15] to a castanospermine ring-homologue by selectively protecting the pyrrolidine N atom of compound **8** before trying to reduce the potential aldehyde group of the sugar moiety; the subsequent reduction and selective transformation of the expected primary alcohol into its *O*-tosyl derivative, followed by N-deprotection, should lead to the 5-deoxy annellated compound. Therefore, **8** was treated with benzyloxycarbonyl chloride (Scheme 4) to obtain **10** (96%), which was then O-deprotected by the action of 80% TFA at room temperature for 24 h, giving 95% of compound **11**, after column chromatography. When **11** was subjected to catalytic hydrogenation (Pd/C) using ethanol as the sole solvent, internal nucleophilic addition of the amine nitrogen to the aldehyde group took place to give the hexahydroxy-perhydroazaazulene derivative **12** in 99% yield, whereas in the presence of an additional amount of acetic acid, the hydrogenation gave (2*R*,6*S*,7*R*,8*S*,9*R*,9a*R*)-2,6,7,8,9-pentahydroxy-perhydroazaazulene **13**, isolated as a product containing 1 mol equiv of acetic acid, which could be totally removed by co-evaporation with ethanol–water to give pure **13** in high yield (99%). Hydrogenation of compound **12** under acid conditions also gave rise to **13**. This latter compound may be considered a castanospermine ring-homologue. The foregoing findings made unnecessary the planned aldehyde reduction and tosylation before deprotecting the pyrrolidine nitrogen.

When we started from **6** (Scheme 3), a thorough structural analysis of the product obtained in the hydrolysis of **8** with TFA, made us realize that its structure was not the one previously assigned **9**,[15] but **12**, isolated in high yield (98%) (Scheme 5). Compound **9** is very likely



Scheme 5. Reagents and conditions: (a) $LiAlH_4$, ether, reflux (3 h), 96%; (b) 80% TFA, rt (24 h), 98%; (c) H_2, 10% Pd/C, EtOH, HOAc, rt (7 h), 98%.



Scheme 6. Reagents and conditions: (a) $LiAlH_4$, ether, reflux (3 h), 99%; (b) 80% TFA, rt (15 h), 96%; (c) H_2, 10% Pd/C, EtOH, rt (24 h), 99%; (d) H_2, 10% Pd/C, EtOH, HOAc, rt (2 h), 99%.

an intermediate in equilibrium with the free aldehyde form of the sugar moiety, and the isolated product should arise from annellation of **9** by nucleophilic addition of the N atom to the carbonyl group. Here again, when **12** was subjected to Pd/C-catalyzed hydrogenation in the presence of acetic acid, **13** was isolated as a product containing acetic acid, which could be totally removed by co-evaporation with toluene–water or ethanol–water to give pure **13** in high yield (98%). Therefore, the route summarized in Scheme 5 is shown to be the shortest one toward compounds **12** and **13**.

In order to obtain additional amounts of the new compounds **12** and **13**, a route similar to that applied to the *N*-benzyloxycarbonyl-pyrrolidine derivative **10** was carried out with the *N*-benzyl lactam **7**. Its reduction with lithium aluminum hydride in ether (Scheme 6) afforded (2*R*,4*R*)-1-benzyl-4-hydroxy-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)pyrrolidine **14** in 99% yield after purification, whose treatment with TFA led to 96% of the O-deprotected compound **15**. Catalytic (Pd/C) hydrogenation of **15** in ethanol originated the hydrogenolysis of the *N*-benzyl bond, making possible the annellation to give the azabicyclic compound **12** in 99% yield. When acetic acid was added to the solvent for the hydrogenation of compound **15**, the castanospermine homologue **13** was again obtained in high yield after purification of the crude product by co-evaporation of the equimolar amount of acetic acid that it contained.

3. Discussion

The conditions used to open the isoxazolidine ring of **5** [$Mo(CO)_6$ as the reducing reagent in 16:1 acetonitrile/water at reflux] proved to be very suitable, since the major product was the N-deprotected lactam **6** (62%), a key intermediate in the shortest synthetic route (Scheme 5), while the *N*-benzyl derivative **7** was the minor product (18%). The (*R*) absolute configuration of C(5) for both compounds comes from that of C(3) in the isoxazolidine derivative **5**, and should not change under the reduction conditions. However, the stereogenic center C(3) of these pyrrolidin-2-ones could have undergone epimerization. A thorough structural study of **7** by NMR spectroscopic techniques allowed us to assign the (*R*)-configuration to C(3) of this compound. We carried out 1D-Double Pulse Field Gradient Spin Echo (DPFGSE)-NOE experiments, which showed C(3)H/C(5)H, C(3)H/C(*ortho*-arom.)H, and C(5)H/C(*ortho*-arom.)H contacts, in accordance with a 3,5-*cis* relationship. As expected, the hydroxyl proton did not show contact with the C(5)H. Furthermore, a long-range contact between the hydroxyl proton and the anomeric proton of the sugar moiety, as well as a C(5)H/C(4′)H contact, were observed, which allowed establishing the relative pyrrolidine/pyranose steric relationship. All that led us to conclude that our product is identical with the one obtained by reduction of **5** using another reagent.[17]

For the N-deprotected lactam **6**, the overlapping between some signals in its ^1H NMR spectrum prevented performing 1D NOESY experiments. These were possible, however, in the case of its reduction product **8**, for which C(3a)[‡]H/C(2)H and C(3a)H/C(4)H contacts were evidenced, but no C(2)H/C(4)H contact; furthermore, C(3b)H did not show any contact with either C(2)H or C(4)H. Therefore, the 2,4-*cis* relationship was also determined here, so that the (2*R*,4*R*) configuration was assigned for **8** and (3*R*,5*R*) for **6**.

A similar analysis of the NOESY spectra of the *N*-benzyloxycarbonyl-pyrrolidine derivative **10** was not possible since the H-2 and H-4 signals were too close to allow a fine observation of the cross peaks in the 2D-NOESY spectrum or to allow a suitable selection for 1D spectra. Selection of the H-3b signal evidenced a strong C(3b)H/C(2)H contact, and a weak C(3a)H/C(2)H contact; hence, the pro-(*S*) designation was attributed to C(3b)H, and the pro-(*R*) one to C(3a)H. However, the C(3a)H/C(4)H and C(3b)H/C(4)H contacts observed were of very similar magnitude, thus preventing any configurational assignment to C(4). The problem was solved by a semiquantitative analysis of the NOE data. Four 2D NOESY experiments at mixing times 100, 200, 300, and 400 ms were performed, and the integration volumes of the cross-peaks corresponding to the C(3a)H/C(2)H, C(3b)H/C(2)H, C(3a)H/C(4)H, and C(3b)H/C(4)H interactions were determined. The average value of the two cross-peaks observed for each interaction was used to obtain the NOE build-up curves. For every case, the range of mixing times used was checked as fitting into the lineal zone of the NOE build-up. Lineal regression analysis led to the slope for each interaction, and this value was used as a comparative estimation of the internuclear distances. The highest slope values corresponded to the C(3b)H/C(2)H and

[‡] For diastereotopic protons, that showing the highest δ value is named 'a'; the other one is named 'b'.

C(3b)H/C(4)H interactions, indicative of a 2,3b,4-*cis* relationship and, hence, the (4*R*) configuration.

Assignment of an annellated structure to compound **12** was based on the heteronuclear multiple bond correlation (HMBC) spectrum performed, where a C(5)/C(3b)H correlation peak was observed, in agreement with the presence of the new N–C(5) bond. The (*R*)-configuration was assigned to C(9a) on the basis of the high C(9a)H/C(9)H coupling constant value observed (10 Hz), corresponding to a 9,9a-*anti* disposition. Therefore, the configuration at this stereogenic center—C(3) in the starting isoxazolidine **5**—is maintained in every step of the synthesis, as expected. In addition, the diastereotopic C(1b) and C(1a) protons of **12** were designated pro-(*R*) and pro-(*S*), respectively, taking into account the C(9)H/C(1b)H contact observed in the 2D NOESY spectrum, and the absence of any C(9)H/C(1a)H contact. From that conclusion and the strong C(2)H/C(1a)H contact observed, we assigned the (*R*)-configuration to C(2). Analogously, from the contacts observed between C(2)H on the one hand, and C(3a)H or C(3b)H on the other, it was possible to assign the pro-(*S*) and pro-(*R*) designations to the diastereotopic C(3a)H and C(3b)H, respectively. Additionally, a C(9)H/C(3b)H contact was observed, corroborating the foregoing prochiral designations attributed to the C(3a) and C(3b) protons. This long-range contact, and that between C(9)H and C(1b)H commented on above, indicated the proximity of the respective pentagonal and heptagonal ring faces, in agreement with the (*R*)-configuration assigned to C(9a). Lastly, C(5)H/C(3a)H and C(5)H/C(3b)H contacts of similar intensities were also observed, preventing any configurational assignment for C(5); therefore, the C(5) configuration was tentatively assigned by applying the CS Chem3D Ultra® (CambridgeSoft) molecular modeling approach (force field MM2), to build the two energetically minimized structures of the (5*R*) and (5*S*) diastereomers. A study of the compatibility of each structure with the 2D NOESY data led us to conclude that all the theoretical (5*S*)-diastereomer interactions were in agreement with the contact set observed, whereas for the (5*R*)-diastereomer model, a C(5)H/C(3b)H contact stronger than the C(5)H/C(3a)H one, as well as another C(5)H/C(9)H contact, should have been observed.

The observation that the catalytic hydrogenation of **11** or **15** in the absence of any acid led to the 5-hydroxy derivative **12**, whilst in the presence of acetic acid the reaction proceeded up to the 5-deoxy product **13**, could be explained as shown in Scheme 7, that is, the protonation of **12** would generate an ammonium cation able to lose a water molecule, giving an iminium cation, hydrogenation of which, involving the loss of a proton, would lead to **13**.

3.1. X-ray structure analysis of crystalline compound 5

A perspective view of the molecule, showing the absolute configuration together with the atomic labeling scheme, is shown in Figure 2. The pyranose ring shows the anomeric effect [O5–C5 = 1.447(10) Å and O5–C1 = 1.395(12) Å]. The geometry observed for the pyranose, dioxolane, and isoxazolidine rings is shown in Table 1. The pyranose ring adopts an approximate twist-boat conformation. The two dioxolane rings show conformations intermediate between envelope (*E*) and twist (*T*), but one tends to the *E* conformation and the other to the *T*. The crystal cohesion is governed by van der Waals forces. The molecular pack to form a compact structure with a network of H-bonds is shown in Table 2, and the packing of the molecule, viewed down the *c*-axis, is shown in Figure 3, where hydrogen bonds are indicated by dashed lines.

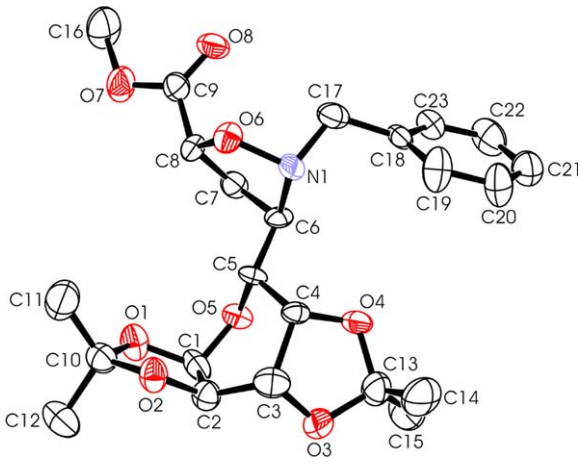
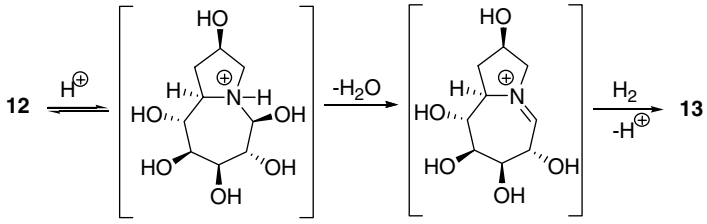


Figure 2. An ORTEP view of crystalline compound **5** showing the atomic numbering. The ellipsoids enclose 30% probability.

3.2. Glycosidase inhibitory essays

Compounds **12** and **13** were tested for inhibitory activity against a series of glycosidases (α-L-fucosidase, α-galactosidase, α-glucosidase, amyloglucosidase, β-glucosidase, α-mannosidase, β-mannosidase, β-xylosidase, α-*N*-acetylgalactosaminidase, and β-*N*-acetylgalactosaminidase) from diverse sources. For a 1 mM concentration, compound **12** showed 38% and 65% of inhibition against



Scheme 7. The action of acid on the catalytic hydrogenation of **11** or **15** through **12** up to **13**.

Table 1. Puckering coordinates, amplitudes and phase magnitudes, and asymmetry parameters for **5**

Ring	Q (Å)	φ(°)	θ (°)	ΔC_2	ΔC_s	Sequence
Pyranose	0.642(8)	−38.9(8)	78.8(8)	(C1) = 0.075	(O5–C5) = 0.056(4)	O5–C1–C2–C3–C4–C5
Dioxolane	0.231(9)	8(2)	—	(O1) = 0.061	—	O2–C10–O1–C1–C2
Dioxolane	0.261(9)	28(2)	—	(C4) = 0.028(3)	—	O3–C13–O4–C4–C3
Isoxazolidine	0.409(8)	70(1)	—	(C8) = 0.064(3)	—	O6–N1–C6–C7–C8

Table 2. Hydrogen bonding geometry

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A angle (°)
C17–H17B···O8^{i}	0.970(10)	2.580(7)	3.278(12)	129
C6–H6···O8^{ii}	0.980(8)	2.718(8)	3.427(12)	129
C1–H···O8^{iii}	0.980(11)	2.218(7)	3.163(13)	161
C19–H19···O2^{iv}	0.930(11)	2.460(6)	3.326(12)	154

Symmetry codes: (i) x, y, z; (ii) $-x+1$, $y+1/2$, $-z$; (iii) $-x+2$, $y-1/2$, $-z$; (iv) x, $y+1$, z.

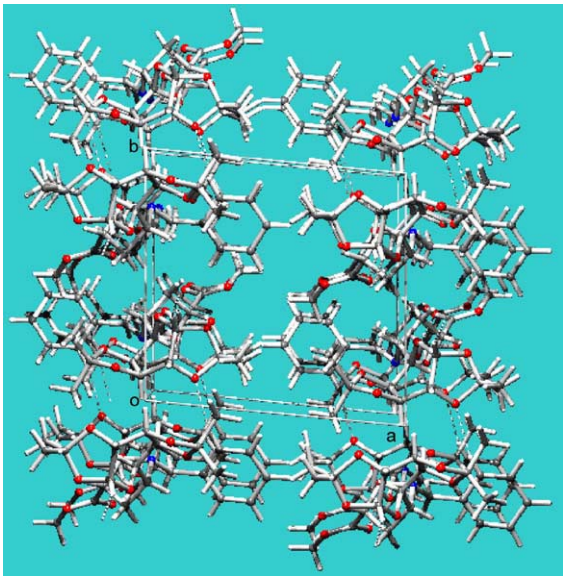


Figure 3. Packing of **5** viewed down the c-axis. Hydrogen bonds are indicated by dashed lines.

bovine liver β-galactosidase (EC 3.2.1.23) and *Rhizopus mold* amyloglucosidase, respectively, whilst compound **13** reached 36% and 62% against the same glycosidases, and 56% against *Aspergillus niger* amyloglucosidase.

4. Conclusion

In conclusion, we establish here a short, highly stereoselective route to ring-homologues of polyhydroxyindolizidines. When the synthesis started from a D-galactose-derived nitrone and methyl acrylate, the different steps of the synthesis took place in good to high yields. The synthetic procedure allows modulating both the backbone and the stereochemistry of the products by selection of the starting monosaccharide. Diverse polyols derived from the perhydroazaazulene heterocyclic system might be obtained by starting from other hexose nitrones, while from pentose derivatives, the products would be polyhydroxy-indolizidines. For the 5-deoxy product—a feature present in natural products such as castanospermine—catalytic hydrogenation of the 2-(glycos-5-yl)pyrrolidine intermediate is required to be performed in the presence of acetic acid, since the product of the reaction in the absence of acid is the 5-hydroxy compound, a hemiaminal. The new perhydroazaazulene derivatives were subjected to glycosidase inhibitory studies, and showed a rather low activity against bovine liver β-galactosidase (EC 3.2.1.23), *Rhizopus mold* amyloglucosidase, and *A. niger* amyloglucosidase.

5. Experimental

5.1. General

Hexane and ether were distilled from sodium prior to use. TLC was performed on silica gel plates (DC-Alufolien F_{254}, E. Merck, or Alugram Sil G/UV$_{254}$, Macherey-Nagel), and preparative TLC on Kieselgel 60 F_{254} DC-Platten 105715 HR; detection of compounds was accomplished with UV light (254 nm) and by charring with H_2SO_4 and phosphomolybdic reagent. Silica gel 60 (E. Merck, 230–400 mesh) was used for column chromatography. Solutions were concentrated under diminished pressure at <40 °C. Melting points were determined on a Gallenkamp MFB-595 apparatus and are uncorrected. A Perkin–Elmer 241 MC polarimeter was used for measurement of optical rotations. IR spectra (neat or on a KBr disc) were obtained on a FTIR Bomem Michelson MB-120 spectrophotometer. NMR experiments were recorded on a Bruker AMX-300 (or 500) or a Bruker Avance-300 (or 500) spectrometer; chemical shifts (δ) are given in ppm, using the residual protonated solvent signal as reference. Assignments were confirmed by selective homonuclear decoupling, homonuclear 2D COSY, NOESY (1D or 2D), 1D TOCSY, heteronuclear multiple (or single) quantum correlation (HMQC or HSQC), and heteronuclear multiple bond correlation (2D-HMBC) spectra. Selective inversion in 1D experiments were performed by using the Double Pulse Field Gradient Spin Echo (DPFGSE) module. For the NOESY experiments, the mixing times was 400 ms in all cases, except for compound **12**, for

which a set of mixing times of 100, 200, 300, and 400 ms was used. EI mass spectra (70 eV) were measured with a Kratos MS-80RFA instrument, with an ionizing current of 100 μA, an accelerating voltage of 4 kV, and a resolution of 10,000 (10% valley definition). Fast-atom bombardment mass spectrometry (FABMS) was performed on the same instrument; ions were produced by a beam of xenon atoms (6–7 keV) using a matrix consisting of *m*-nitrobenzyl alcohol or thioglycerol and NaI as salt. HRCIMS (150 eV) and HRLSIMS experiments were performed with a Micromass AutoSpecQ instrument with a resolution of 10,000 (5% valley definition).

5.2. Reaction of (*Z*)-*N*-benzyl-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-ylidene)amine *N*-oxide, 4 with methyl acrylate. Preparation of methyl (2*R*,3*R*,5*R*)-2-benzyl-3-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)isoxazolidine-5-carboxylate, 5

A solution of nitrone **4**[10] (0.400 g, 1.10 mmol) and methyl acrylate (207 μL, 0.198 g, 2.30 mmol) in toluene (3.6 mL) was stirred under argon atmosphere at 35 °C. Monitoring of the reaction (TLC, 3:1 hexane/ethyl acetate) indicated a complete conversion after 3 h. The solution was then concentrated to give a crude residue (0.437 g, 88%), which was crystallized (absolute ethanol) to afford pure **5** (0.350 g, 71%); mp 102–104 °C; crystallographic analysis evidenced its (2*R*,3*R*,5*R*) absolute configuration; R_f 0.48 (3:1 hexane/ethyl acetate); $[\alpha]_D^{25} = -44$ (*c* 1.0, CH_2Cl_2); {lit.[17] mp 117–119 °C; $[\alpha]_D^{25} = -82$ (*c* 0.40, $CHCl_3$)}; IR (KBr) ν_{max} 1753 (ester C=O), 1377 (CMe_2), 1209 and 1173 cm^{-1} (C–O–C); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.22 (m, 5H, Ph), 5.48 (d, 1H, $J_{1',2'} = 5.0$, H-1′), 4.51 (dd, 1H, $J_{2',3'} = 2.2$, $J_{3',4'} = 8.0$, H-3′), 4.48 (dd, 1H, $J_{4a,5} \approx J_{4b,5} = 8.4$, H-5), 4.42 (dd, 1H, $J_{4',5'} = 1.5$, H-4′), 4.23 (dd, 1H, H-2′), 4.23, 3.85 (each d, each 1H, $J_{gem} = 12.9$, CH_2Ph), 3.76 (s, 3H, MeOCO), 3.66 (m, 1H, H-3), 3.56 (dd, 1H, $J_{3,5'} = 9.9$, H-5′), 2.86 (ddd, 1H, $J_{4a,4b} = 12.3$, $J_{3,4a} = 1.7$, H-4a), 2.62 (ddd, 1H, $J_{3,4b} = 7.0$, H-4b), and 1.45, 1.29, 1.29, 1.27 (each s, each 3H, 2CMe_2); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.0 (*C*OOMe), 137.3 (*ipso*-C of Ph), 129.3, 128.0, 127.1 (Ph), 108.7, 108.4 (2*C*Me_2), 96.4 (C-1′), 77.0 (C-5), 70.8 (C-2′), 70.4, and 70.3 (C-3′/C-4′), 66.6 (C-5′), 63.8 (C-3), 61.5 (*C*H_2Ph), 52.2 (COO*Me*), 34.0 (C-4), 26.0, 25.6, 24.8, and 24.0 (2C*Me*$_2$); HRCIMS: *m*/*z* 450.2130 (calcd for $C_{23}H_{31}NO_8$+H: 450.2128). Anal. Calcd for $C_{23}H_{31}NO_8$: C, 61.46; H, 6.95; N, 3.12. Found: C, 61.38; H, 6.78; N, 3.25.

5.3. (3*R*,5*R*)-3-Hydroxy-5-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)-2-oxopyrrolidine, 6, and (3*R*,5*R*)-1-benzyl-3-hydroxy-5-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)-2-oxopyrrolidine, 7

To a solution of **5** (0.286 g, 0.63 mmol) in a mixture of acetonitrile (9.6 mL) and water (0.6 mL), hexacarbonylmolybdenum[18,19] (0.120 g) was added and the mixture was heated at reflux (85 °C). Monitoring of the reaction (TLC, 15:1 dichloromethane/methanol) indicated a complete conversion after 7 h. Silica gel (0.250 g) was then added and the suspension was stirred for 12 h, filtered through Celite, and the solid thoroughly washed with ethyl acetate. Evaporation of the solvent afforded a crude residue (0.300 g), which was subjected to column chromatography (40:1, 30:1, and 20:1 dichloromethane/methanol, successively); first eluted the *N*-benzyl-lactam **7** (0.049 g, 18%) and second the N-deprotected product **6** (0.128 g, 62%).

Compound **6** was an oil; R_f 0.46 (15:1 dichloromethane/methanol); $[\alpha]_D^{20} = -16$ (*c* 1.0, $CHCl_3$); {lit.[17] $[\alpha]_D^{25} = -29$ (*c* 0.65, $CHCl_3$)}; IR (KBr) ν_{max} 3262 (OH and NH), 1707 (amide C=O), 1379 (CMe_2), and 1067 cm^{-1} (C–OH); ^1H NMR (300 MHz, $CDCl_3$): δ 6.27 (br s, 1H, NH), 5.49 (d, 1H, $J_{1',2'} = 5.0$, H-1′), 4.61 (dd, 1H, $J_{2',3'} = 2.6$, $J_{3',4'} = 7.9$, H-3′), 4.31 (dd, 1H, H-2′), 4.24 (dd, 1H, $J_{4',5'} = 1.6$, H-4′), 4.24 (m, overlapped signal, H-3), 3.68 (dd, 1H, $J_{5,5'} = 2.3$, H-5′), 3.68 (m, overlapped signal, H-5), 3.34 (br m, 1H, HO), 2.62 (m, 1H, H-4a), 1.98 (m, 1H, H-4b), 1.49, 1.42, 1.32, and 1.30 (each s, each 3H, 2CMe_2); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 177.4 (*C*=O), 109.6, 108.8 (2*C*Me_2), 96.0 (C-1′), 70.7 (C-2′), 70.5 (C-3′), 70.5 (C-5′), 70.1 (C-4′), 69.1 (C-3), 51.1 (C-5), 33.5 (C-4), 29.5, 25.7, 24.8, and 24.3 (2C*Me*$_2$); HREIMS: *m*/*z* 329.1475 (calcd for $C_{15}H_{23}NO_7$: 329.1475).

Compound **7** was an amorphous material; R_f 0.60 (15:1 dichloromethane/methanol); $[\alpha]_D^{20} = -50$ (*c* 2.7, $CHCl_3$); {lit.[17] mp 124–126 °C; $[\alpha]_D^{25} = +47$ (*c* 0.40, $CHCl_3$)}; IR (KBr) ν_{max} 3316 (OH), 1686 (amide C=O), 1377 (CMe_2), 1069 (C–OH), and 899, 752, and 700 cm^{-1} (arom δC–H); ^1H NMR (300 MHz, $CDCl_3$): δ 7.65–7.12 (m, 5H, Ph), 5.55 (d, 1H, $J_{1',2'} = 5.2$, H-1′), 5.18, 3.96 (each d, each 1H, $J_{gem} = 15.1$, CH_2Ph), 4.55 (dd, 1H, $J_{2',3'} = 2.2$, $J_{3',4'} = 8.0$, H-3′), 4.29 (dd, 1H, H-2′), 4.27 (dd, 1H, $J_{3,4a} = 6.8$, $J_{3,4b} = 5.2$, H-3), 4.09 (dd, 1H, $J_{4',5'} = 1.9$, H-4′), 3.98 (dd, 1H, $J_{5,5'} = 3.4$, H-5′), 3.72 (br m, 1H, HO), 3.60 (ddd, 1H, $J_{4a,5} = 5.1$, $J_{4b,5} = 7.1$, H-5), 2.29 (m, 2H, 2H-4), 1.40, 1.30, 1.26, and 1.21 (each s, each 3H, 2CMe_2); 1D-DPFGSE-NOE contacts: H-3, H-5, *ortho*-H of Ph; H-5, H-4′, H-3, *ortho*-H of Ph; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.2 (*C*=O), 135.9 (*ipso*-C of Ph), 128.6, 127.6, 127.4 (Ph), 109.2, 108.4 (2*C*Me_2), 96.4 (C-1′), 71.3 (C-4′), 70.9 (C-3′), 70.2 (C-2′), 69.5 (C-3), 64.7 (C-5′), 55.3 (C-5), 43.8 (*C*H_2Ph), 30.0 (C-4), 25.9, 25.6, 24.5, and 23.9 (2C*Me*$_2$); HRCIMS: *m*/*z* 420.2008 (calcd for $C_{22}H_{29}NO_7$+H: 420.2022).

5.4. (2*R*,4*R*)-4-Hydroxy-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)pyrrolidine, 8

To a solution of **6** (0.27 g, 0.82 mmol) in ether (6.6 mL), cooled in an ice bath, a 1 M solution of lithium aluminum hydride in ether (2.45 mL; 2.45 mmol) was slowly added, and the mixture was then heated at reflux under stirring for 3 h. After destroying the excess of hydride by adding saturated aqueous sodium sulfate, the mixture was filtered through Celite, and the solid thoroughly washed with ethyl acetate and ether. The filtrate was concentrated and the residue was subjected to column chromatography (30:1 dichloromethane/methanol) to afford the reduced product **8** as an oil (0.248 g, 96%);

R_f 0.10 (15:1 dichloromethane/methanol); $[\alpha]_D^{20} = -30$ (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3183 (OH and NH), 1377 (CMe_2), and 1067 cm^{-1} (C–OH); ^1H NMR (300 MHz, $CDCl_3$): δ 5.51 (d, 1H, $J_{1',2'} = 5.0$, H-1′), 4.57 (dd, 1H, $J_{2',3'} = 2.4$, $J_{3',4'} = 8.0$, H-3′), 4.32 (dd, 1H, $J_{4',5'} = 1.8$, H-4′), 4.27 (dd, 1H, H-2′), 4.27 (m, overlapped signal, H-4), 3.70 (dd, 1H, $J_{2,5'} = 6.5$, H-5′), 3.34 (ddd, 1H, $J_{2,3a} = 9.2$, $J_{2,3b} = 5.4$, H-2), 2.95 (ddd, 1H, $J_{5a,5b} = 11.3$, $J_{4,5a} = 1.8$, $^4J_{3b,5a} = 1.8$, H-5a), 2.82 (dd, 1H, $J_{4,5b} = 4.1$, H-5b), ~2.5 (br s, 2H, NH and OH), 2.14 (ddd, 1H, $J_{3a,3b} = 14.6$, $J_{3a,4} = 5.8$, H-3a), 1.83 (dddd, 1H, $J_{3b,4} = 5.2$, H-3b), and 1.49, 1.41, 1.30, 1.29 (each s, each 3H, $2CMe_2$); 1D-DPFGSE-NOESY contacts: H-3a, H-2, H-4; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 109.0, 108.6 ($2CMe_2$), 96.3 (C-1′), 71.9 (C-4), 71.3 (C-4′), 70.6 (C-2′), 70.4 (C-3′), 70.2 (C-5′), 56.9 (C-2), 55.2 (C-5), 37.7 (C-3), 25.8, 25.7, 24.8, and 24.1 ($2CMe_2$); HRCIMS: *m*/*z* 316.1757 (calcd for $C_{15}H_{25}NO_6$+H: 316.1760).

5.5. (2*R*,4*R*)-1-Benzyloxycarbonyl-4-hydroxy-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)-pyrrolidine, 10

Sodium hydrogen carbonate (0.117 g, 1.39 mmol) and benzyl chlorocarbonate (126.56 μL, 0.896 mmol) were added to a solution of **8** (0.258 g, 0.818 mmol) in 1:1 ethanol/H_2O (5.3 mL). The mixture was left to cool down to room temperature, then poured into saturated aqueous sodium hydrogen carbonate (17 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (40:1 dichloromethane/methanol) to afford **10** as an amorphous white material (0.352 g, 96%); R_f 0.50 (30:1 dichloromethane/methanol); $[\alpha]_D^{24} = +4.5$ (*c* 3.1, CH_2Cl_2); IR (KBr) ν_{max} 3180 (OH and NH), 1416 (C–O), 1370 (CMe_2), and 1069 cm^{-1} (C–OH); ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.29 (m, 5H, Ph), 5.59 (d, 1H, $J_{1',2'} = 5.0$, H-1′), 5.18, 5.10 (each d, each 1H, $J_{gem} = 12.5$, CH_2Ph), 4.62 (dd, 1H, $J_{2',3'} = 2.5$, $J_{3',4'} = 8.0$, H-3′), 4.49 (s, 1H, $J_{2,5'} \approx J_{4',5'} \approx 0$, H-5′), 4.38 (d, 1H, H-4′), 4.33 (dd, 1H, H-2′), 4.28 (m, 1H, H-4), 4.20 (d, 1H, $J_{2,3a} \approx 0$, $J_{2,3b} = 10.5$, H-2), 3.57 (d, 1H, $J_{5a,5b} = 12.0$, $J_{4,5a} \approx 0$, H-5a), 3.49 (dd, 1H, $J_{4,5b} = 4.0$, H-5b), 2.56 (d, 1H, $J_{3a,3b} = 15.5$, $J_{3a,4} \approx 0$, H-3a), 2.22 (ddd, $J_{3b,4} = 5.5$, H-3b), and 1.49, 1.39, 1.36, 1.31 (each s, each 3H, $2CMe_2$); NOE contacts (1D-NOESY): H-3b, H-2; 2D-NOESY (four experiments at 100, 200, 300, and 400 ms; see Section 3): Higher slope values: H-3b/H-2, H-3b/H-4; ^{13}C NMR (124.5 MHz, $CDCl_3$): δ 155.4 (*C*=O), 136.9 (*ipso*-C of Ph), 128.6–127.0 (Ph), 109.5 ($2CMe_2$), 96.4 (C-1′), 72.3 (C-4′), 71.6 (C-3′), 70.8 (C-2′), 70.3 (C-4), 66.9 (C-5′), 66.7 (CH_2Ph), 59.2 (C-2), 56.4 (C-5), 34.4 (C-3), and 25.8 and 24.1 ($2CMe_2$); HRFABMS: *m*/*z* 472.2127 (calcd for $C_{23}H_{32}NO_8$+Na: 472.2125).

5.6. (2*R*,4*R*)-1-Benzyloxycarbonyl-4-hydroxy-2-(D-*galacto*-pentos-5-yl)pyrrolidine, 11

Compound **10** (0.534 g, 1.30 mmol) was treated with 80% trifluoroacetic acid (40 mL) and the mixture was kept at room temperature, monitoring the reaction by TLC (15:1 dichloromethane/methanol). After 24 h, all the starting material had been transformed, and the mixture was concentrated. The residue was subjected to column chromatography (15:1 dichloromethane/methanol) to obtain **11** as a colorless oil (0.454 g, 95%); R_f 0.25 (8:1 dichloromethane/methanol); IR (KBr) ν_{max} 3362 (OH), 1746 (carbamate C=O), 1684 (arom), 1454 and 1430 (C–O), and 1016 cm^{-1} (C–OH); HRFABMS: *m*/*z* 392.1321 (calcd for $C_{17}H_{23}NO_8$+Na: 392.1326).

5.7. Catalytic hydrogenation of (2*R*,4*R*)-1-benzyloxycarbonyl-4-hydroxy-2-(D-*galacto*-pentos-5-yl)pyrrolidine, 11, in neutral medium. Synthesis of (2*R*,5*S*,6*R*,7*S*,8*S*,9*R*,9a*R*)-2,5,6,7,8,9-hexahydroxy-perhydroazaazulene, 12

To a solution of compound **11** (0.252 g, 0.683 mmol) in ethanol (23.5 mL), 10% Pd/C catalyst (39.25 mg) was added. The mixture was shaken at room temperature under hydrogen for 24 h, and then filtered through Celite, which was washed with ethyl acetate and methanol. The combined filtrate and washings were concentrated and the residue was subjected to column chromatography (5:1 → 4:1 gradient, dichloromethane/methanol) to give **12** (0.160 g, 99.5%); white, amorphous material; R_f 0.33 (3:1 dichloromethane/methanol); $[\alpha]_D^{20} = +58.9$ (*c* 0.45, MeOH); IR (KBr) ν_{max} 3396 (OH), 1094 (C–O), and 1017 cm^{-1} (C–N); ^1H NMR (500 MHz, CD_3OD): δ 4.76 (d, 1H, $J_{5,6} = 6.0$, H-5), 4.42 (dddd, 1H, $J_{1,2} = 8.5$, $J_{1',2} = 4.5$, $J_{2,3} \approx J_{2,3'} \approx 6.5$, H-2), 4.12 (d, 1H, $J_{6,7} = 2.5$, $J_{7,8} \approx 0$, H-7), 4.10 (dd, 1H, H-6), 3.87 (d, 1H, $J_{8,9} = 4.5$, H-8), 3.77 (dd, 1H, $J_{9,9a} = 10.0$, H-9), 3.18 (dd, 1H, $J_{3,3'} = 9.5$, H-3), 3.06 (dd, 1H, H-3′), 3.00 (ddd, 1H, $J_{1,9a} = 8.0$, $J_{1',9a} = 2.0$, H-9a), 2.33 (ddd, 1H, $J_{1,1'} = 14.0$, H-1), and 1.75 (ddd, 1H, H-1′); HMBC experiments: H-3b, C-5; NOE contacts (2D-NOESY): H-9, H-1b; H-9a, H-1a; H-2, H-1a; H-3b, H-9; H-3a, H-2; ^{13}C NMR (125.7 MHz, CD_3OD): δ 88.8 (C-5), 85.4 (C-8), 80.1 (C-7), 76.2 (C-6), 70.2 (C-2), 67.4 (C-9), 57.9 (C-9a), 56.7 (C-3), and 37.9 (C-1); HRFABMS: *m*/*z* 258.0953 (calcd for $C_9H_{17}NO_6$+Na: 258.0954), 236.1116 (calcd for $C_9H_{17}NO_6$+H: 236.1134).

5.8. Catalytic hydrogenation of (2*R*,4*R*)-1-benzyloxycarbonyl-4-hydroxy-2-(D-*galacto*-pentos-5-yl)pyrrolidine, 11, in the presence of acetic acid. Synthesis of (2*R*,6*S*,7*R*,8*S*,9*R*,9a*R*)-2,6,7,8,9-pentahydroxy-perhydroazaazulene hydroacetate, 13·HOAc, and (2*R*,6*S*,7*R*,8*S*,9*R*,9a*R*)-2,6,7,8,9-pentahydroxy-perhydroazaazulene, 13

To a solution of compound **11** (0.050 g, 0.136 mmol) in ethanol (5 mL), acetic acid (three drops, ≈0.025 g, 0.42 mmol) and 10% Pd/C catalyst (15 mg) were added. The mixture was shaken at room temperature under hydrogen for 2 h and then filtered through Celite, which was washed with methanol. The combined filtrate and washings were concentrated, and the residue was repeatedly dissolved in ethanol and water, and concentrated. The residue was purified by column chromatography (5:1 dichloromethane/methanol) to afford **13·HOAc** (29 mg, 99.5%); R_f 0.25 (3:1 dichloromethane/metha-

nol); $[\alpha]_D^{20} = -1.4$ (*c* 0.5, MeOH); IR (KBr) ν_{max} 3390 (OH), 1094 (C–O), and 1018 cm^{-1} (C–N); ^1H NMR (300 MHz, CD_3OD): δ 4.41 (m, 1H, H-2), 4.19 (ddd, 1H, $J_{6,7} = 6.6$, $J_{5,6} = 5.7$, $J_{5',6} = 6.0$, H-6), 4.04 (dd, 1H, $J_{7,8} = 1.2$, H-7), 3.90 (dd, 1H, $J_{8,9} = 7.2$, H-8), 3.82 (dd, 1H, $J_{9,9a} = 9.3$, H-9), 3.70 and 2.94 (each dd, each 1H, $J_{5,5'} = 13.2$, H-5 and H-5′), 3.38 (d, 1H, $J_{3,3'} = 11.4$, H-3), 3.32 (m, 1H, H-9a), 3.15 (dd, 1H, $J_{2,3'} = 3.9$, H-3′), 2.55 (ddd, 1H, $J_{1,1'} = 14.4$, $J_{1,2} = 5.4$, $J_{1,9a} = 9.6$, H-1), 2.12 (ddd, 1H, $J_{1',2} = 2.7$, $J_{1',9a} = 5.4$, H-1′), and 1.99 (s, 3H, OCOCH_3); ^{13}C NMR (75.4 MHz, CD_3OD): δ 178,5 (C=O), 78.1 (C-8), 77.6 (C-7), 76.7 (C-9), 72.1 (C-2), 71.2 (C-9a), 70.7 (C-6), 68.0 (C-3), 61.4 (C-5), 42.6 (C-1), and 23.7 (OCO*C*H_3); HRFABMS: *m*/*z* 220.1181 (calcd for $C_9H_{17}NO_5$+H: 220.1184). The acetic acid of the remainder **13**·**HOAc** was several times co-evaporated with ethanol and water, and the residue was purified by column chromatography (5:1 dichloromethane/methanol) to give pure **13**; R_f 0.37 (3:1 dichloromethane/methanol); $[\alpha]_D^{20} = +6.1$ (*c* 1.55, MeOH); IR (KBr) ν_{max} 3380 (OH), 1092 (C–O), and 1024 cm^{-1} (C–N); ^1H NMR (300 MHz, CD_3OD): δ 4.29 (m, 1H, H-2), 4.09 (ddd, 1H, $J_{6,7} = J_{5,6} = 6.9$, $J_{5',6} = 7.2$, H-6), 3.87 (d, 1H, $J_{7,8} \approx 0$, H-7), 3.83 (d, 1H, $J_{8,9} = 6.6$, H-8), 3.70 (dd, 1H, $J_{9,9a} = 9.0$, H-9), 3.43 (dd, 1H, $J_{5,5'} = 13.2$, H-5), 3.12 (br d, 1H, $J_{3,3'} = 10.2$, $J_{2,3} \approx 0$, H-3), 2.76 (dd, 1H, $J_{2,3'} = 3.6$, H-3′), 2.71 (overlapped m, 1H, $J_{1,9a} = 5.1$, H-9a), 2.53 (overlapped dd, 1H, H-5′), 2.50 (overlapped ddd, 1H, H-1), and 1.92 (m, 1H, H-1′); ^{13}C NMR (75.4 MHz, CD_3OD): δ 77.0 (C-8), 76.7 (C-7 and C-9), 70.7 (C-2), 69.8 (C-6 and C-9a), 65.5 (C-3), 60.4 (C-5), and 41.5 (C-1); HRFABMS: *m*/*z* 220.1183 (calcd for $C_9H_{17}NO_5$+H: 220.1184).

5.9. (2*R*,5*S*,6*R*,7*S*,8*S*,9*R*,9a*R*)-2,5,6,7,8,9-Hexahydroxyperhydroazaazulene, 12

An 80% solution of trifluoroacetic acid (20 mL) was added to compound **8** (0.200 g, 0.63 mmol) and the mixture was kept at room temperature, monitoring the reaction by TLC (15:1 dichloromethane/methanol). After 24 h, all the starting material had been transformed, and the mixture was applied to a Dowex 50W × 8 (H^+) resin column, then eluting with methanol (150 mL), water (150 mL), and 10% aqueous ammonia. The fractions eluted by ammonia were concentrated to afford pure **12** as an oil (0.148 g, 98%); R_f 0.51 (8:4:1 dichloromethane/methanol/10% aqueous ammonia); NMR and MS data, respectively, identical with those of compound obtained from **11** (Section 5.7).

5.10. (2*R*,6*S*,7*R*,8*S*,9*R*,9a*R*)-2,6,7,8,9-Pentahydroxyperhydroazaazulene, 13

To a solution of compound **12** (0.068 g, 0.289 mmol) in ethanol (10 mL), glacial acetic acid (five drops, ≈0.042 g, 0.70 mmol) and 10% Pd/C catalyst (0.020 g) were added. The mixture was shaken at room temperature under hydrogen for 7 h (TLC monitoring, 3:1 dichloromethane/methanol) and then filtered through Celite, which was washed several times with ethanol and methanol. The combined filtrate and washings were concentrated, and the acetic acid was co-evaporated with ethanol and water to afford **13** (0.062 g, 98%), which showed NMR and MS data, respectively, identical with those of compound obtained from **11** (Section 5.8).

5.11. Reduction of (3*R*,5*R*)-1-benzyl-3-hydroxy-5-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)-2-oxopyrrolidine, 7, with lithium aluminum hydride. Synthesis of (2*R*,4*R*)-1-benzyl-4-hydroxy-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)pyrrolidine, 14

Lithium aluminum hydride (1 M ethereal solution, 1.58 mL, 1.58 mmol) was added to a cold (ice bath) solution of **7** (0.182 g, 0.434 mmol) in ether (3.5 mL), and the mixture was heated to reflux under stirring until no longer progress of the reaction was observed (3 h, TLC, 15:1 dichloromethane/methanol). Then, saturated aqueous sodium sulfate (554 μL) was added to eliminate the excess of reductive reagent. The mixture was filtered through Celite, and this successively washed with ethyl acetate and ether. The combined filtrate and washings were concentrated to obtain **14** (0.176 g, 99%); R_f 0.34 (15:1 dichloromethane/methanol); $[\alpha]_D^{20} = -29.7$ (*c* 0.3, CH_2Cl_2); IR (KBr) ν_{max} 1092 (C–OH) and 1032 cm^{-1} (C–N); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.24 (m, 5H, Ph), 5.65 (d, 1H, $J_{1',2'} = 4.8$, H-1′), 4.64 (dd, 1H, $J_{2',3'} = 2.4$, $J_{3',4'} = 8.1$, H-3′), 4.34 (overlapped dd, 1H, H-2′ or H-4′), 4.33 (overlapped dd, 1H, H-4′ or H-2′), 4.18, 3.47 (each d, each 1H, $J_{gem} = 13.5$, CH_2Ph), 4.13 (m, overlapped signal, H-4), 3.93 (dd, 1H, $J_{2,5'} = 3.0$, $J_{4',5'} = 1.8$, H-5′), 3.02 (ddd, 1H, $J_{2,3a} = 3.0$, $J_{2,3b} = 10.2$, H-2), 2.95 (br s, 1H, OH), 2.89 (dd, 1H, $J_{5a,5b} = 9.9$, $J_{4,5a} = 2.1$, H-5a), 2.32 (dd, 1H, $J_{4,5b} = 3.3$, H-5b), 2.28 (ddd, 1H, $J_{3a,3b} = 12.9$, $J_{3a,4} = 2.4$, H-3a), 2.13 (m, 1H, H-3b), and 1.49,1.36, (each s, each 6H, 2CMe_2); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 140.0 (*ipso*-C of Ph), 128.6–126.9 (Ph), 109.1, 108.6 (2*C*Me_2), 96.7 (C-1′), 72.2 (C-4′), 70.8 (C-2′), 71.1 (C-3′), 71.1 (C-4), 68.1 (C-5′), 62.5 (C-2), 61.3 (C-5), 58.6 (*C*H_2Ph), 35.6 (C-3), and 26.2, 25.8, 25.0, and 24.1 (2C*Me*$_2$); HRCIMS: *m*/*z* 406.2219 (calcd for $C_{22}H_{32}NO_6$+H: 406.2229).

5.12. O-Deprotection of (2*R*,4*R*)-1-benzyl-4-hydroxy-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)pyrrolidine, 14. Synthesis of (2*R*,4*R*)-1-benzyl-4-hydroxy-2-(D-*galacto*-pentos-5-yl)pyrrolidine, 15

An 80% solution of trifluoroacetic acid (5 mL) was dropwise added to 0.080 g (0.197 mmol) of compound **14**, and the mixture was stirred at room temperature until the starting material was totally consumed (15 h, TLC). The solution was concentrated under diminished pressure, and the residue was dissolved in dichloromethane and washed with aqueous 10% sodium hydrogen carbonate until pH ~7.5. After drying (Na_2SO_4), the solvent was evaporated at reduced pressure to afford **15** as an oil (0.061 g, 96%); R_f 0.40 (3:1 dichloromethane/methanol); HRFABMS: *m*/*z* 348.1423 (calcd for $C_{16}H_{23}NO_6$+Na: 348.1449). This product was used for other transformations without more purification.

5.13. N-Deprotection of (2*R*,4*R*)-1-benzyl-4-hydroxy-2-(D-*galacto*-pentos-5-yl)pyrrolidine, 15. Synthesis of (2*R*,5*S*,6*R*,7*S*,8*S*,9*R*,9a*R*)-2,5,6,7,8,9-hexahydroxy-perhydroazaazulene, 12

To a solution of **15** (0.180 g, 0.553 mmol) in abs ethanol (20 mL), 10% Pd/C catalyst (0.020 g) was added, and the mixture was shaken under hydrogen atmosphere for 24 h. The suspension was filtered through a plug of Celite, and the solids were washed with methanol. The combined filtrate and washings were concentrated at reduced pressure to give **12** (0.129 g, 99%), which showed NMR and MS data, respectively, identical with those of the compound obtained from **8** (Section 5.5).

5.14. Preparation of compound 13 by catalytic hydrogenation of 15 in the presence of acetic acid

To a solution of compound **15** (0.080 g, 0.246 mmol) in abs ethanol (10 mL), 10% Pd/C catalyst and acetic acid (three drops, ≈0.025 g, 0.42 mmol) were added, and the mixture was shaken under hydrogen atmosphere for 2 h. After filtration through a plug of Celite and washing of the solids with methanol, the combined filtrate and washings were concentrated, and the acetic acid was co-evaporated with ethanol and water, to afford **13** (0.0535 g, 99%), which showed NMR and MS data, respectively, identical with those of the product obtained from **12** (Section 5.6) or from **11** (Section 5.10).

5.15. Crystallographic analysis of compound 5[§]

Crystals of the compound appear as colorless prisms with well shaped faces. Specimen size $0.10 \times 0.20 \times 0.40$ mm crystallizes in the monoclinic system, space group $P2_1$; unit-cell dimensions, $a = 11.042(10)$, $b = 9.458(10)$, $c = 11.384(10)$ Å, $\beta = 95.62(6)°$; unit-cell volume, V, 1183(2) Å^3; formula units per unit cell, $Z = 2$; calculated density, $D_x = 1.26$ Mg m^{-3}; measured density $D_m = 1.25$ Mg m^{-3}; $F(000)$ value, 480; absorption coefficient, μ, 0.952 cm^{-1}; temperature, T, 293 K. Unit-cell parameters and crystal orientation matrix were determined on a CAD4 Enraf-Nonius four-circle automated, graphite-monochromated, diffractometer from the least-squares treatment of the setting angles of 25 independent reflections. Intensity data were collected at room temperature in the $\omega/2\theta$ scan mode, using Mo Kα radiation, ($\lambda = 0.071069$ Å) up to $\theta = 30°$; range of h, k, and l, $-15 < h < 15$, $-13 < k < 0$, $-15 < l < 0$. Three standard reflections were measured every hour to monitor crystal stability and were re-centered after every hundred measured reflections to monitor crystal orientation. No significant intensity changes were observed. Number of measured reflections, 3633; number of significant reflections, 935; criterion for significance, $I > 2\sigma(I_0)$; final R, 0.07: final $\omega R(F^2)$, 0.16, goodness-of-feet S, 0.88. Corrections were made for Lorentz-polarization effects, but not for extinction and absorption. This effect was not taken into account because the crystal absorption with Mo radiation was practically negligible. The structure was solved by direct methods using SIR2002[20] and refined with SHELX97.[21] All geometric calculations were performed using PARST97.[22]

[§] Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Centre as supplementary publication number CCDC 271098. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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