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Synthesis of (+)-1-*epi*-castanospermine from L-sorbose

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ABSTRACT

Diastereoselective synthesis of 1-*epi*-castanospermine (**2**) from L-sorbose is described. The successful approach involved the use of 8-azido-2,8-dideoxy-α-L-*gulo*-oct-4-ulo-4,7-furanosononitrile intermediate (**17**). This compound was easily made in five steps from 3-*O*-benzoyl-2-deoxy-4,5:6,8-di-*O*-isopropylidene-α-L-*gulo*-oct-4-ulo-4,7-furanosononitrile (**7**) previously synthesized from L-sorbose. Catalytic hydrogenation of the azido intermediate **17** with Pd–C afforded with total stereocontrol one of the two possible piperidine diastereomers. Acid-catalyzed internal reductive deamination of the nitrile derivative completed the total synthesis of (1*R*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine [(+)-1-*epi*-castanospermine, **2**].

1. Introduction

Polyhydroxyindolizidines are a widespread variety of alkaloids well known for their glycosidase inhibitory activity.[1] One of the most representative examples is castanospermine (**1**), first isolated[2] from the seeds of the Australian legume *Castanospermum australe*. This and other closely related compounds (Fig. 1), as is the case of 1-*epi*-castanospermine (**2**), have been extensively studied as potential therapeutic agents against diabetes,[3] cancer[4] and viral infections such as HIV.[5]

For these reasons, many synthetic methodologies[6] have been explored in order to set up chemical libraries of these and related isomers for biological and structure–activity studies.

Particularly, in the case of 1-*epi*-castanospermine (**2**), several syntheses[7] have been published to date, many of them based on sugar chemistry. As part of our previous work, we reported[8] on the synthesis of several polyhydroxyindolizidines based on 4-octulose intermediates readily available from commercial sugars. Retrosynthetic analysis of 1-*epi*-castanospermine (**2**) (see Scheme 1) shows that this molecule can be synthesized by appropriate chain extension and functional group modification of a partially protected aldehyde **6**, obtained in two steps from L-sorbose.

According to the synthetic strategy, the presence of a masked amino group at C-8 in intermediate **5** makes this compound a good substrate for a one-step double cyclization synthesis of **2**, after removal of the suitable protecting groups. Hence, in this work we want to communicate the stereoselective synthesis of (+)-1-*epi*-castanospermine by means of the key intermediate **5**, readily obtained from commercially and cheap L-sorbose.

2. Results and discussion

The previously described[9] 3-*O*-benzoyl-4-octulosononitrile **7**, obtained from L-sorbose in four steps, was initially deacetonated with 50% aqueous AcOH to afford diol **8**, a candidate of choice for the introduction at C-8 of the masked amino group. With this aim, regioselective tosylation of the primary alcohol gave **9** in good yield (see Scheme 2). Regrettably, attempt to introduce the azido moiety with LiN_3 was unsuccessful, leading only to substrate decomposition.

Based on this negative result a different approach was tried. Diol **8** was transformed into mono-iodo derivative **10** under Garegg's conditions (^{13}C NMR evidence); unfortunately, nucleophilic displacement on **10** using LiN_3 yielded an inseparable mixture of the substitution (**11**) and elimination (**12**) products (see Scheme 3).

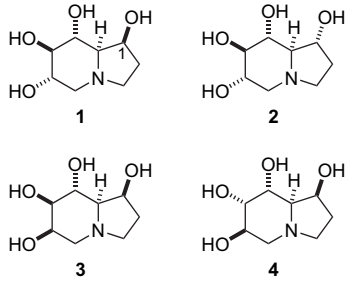

Figure 1. Structure of natural (+)-castanospermine (**1**) and some of its isomers: 1-*epi*-castanospermine (**2**), 6-*epi*-castanospermine (**3**) and 6,7-di-*epi*-castanospermine (**4**).

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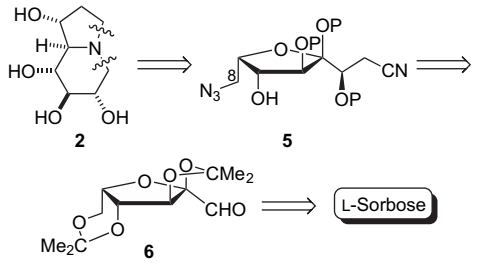
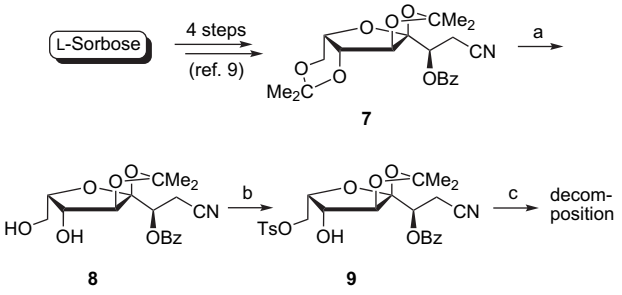
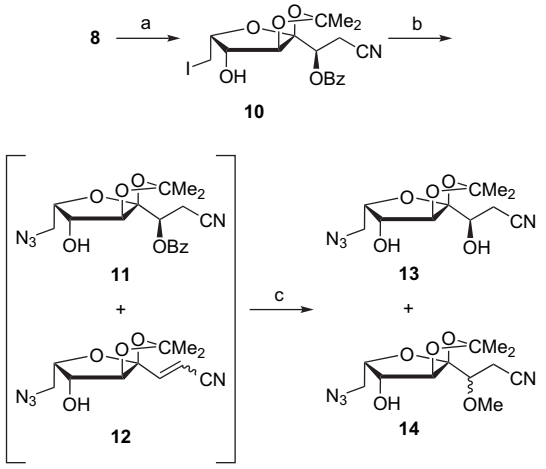


Scheme 1. Retrosynthetic analysis of 1-*epi*-castanospermine (**2**).



Scheme 2. Synthesis of tosylate **9** from nitrile **7**. Reagents and conditions: (a) 50% aqueous AcOH, 50 °C, 92%; (b) TsCl–TEA–DMAP (cat.)–CH_2Cl_2, rt, 91%; (c) LiN_3–anhyd DMF, 60 °C.

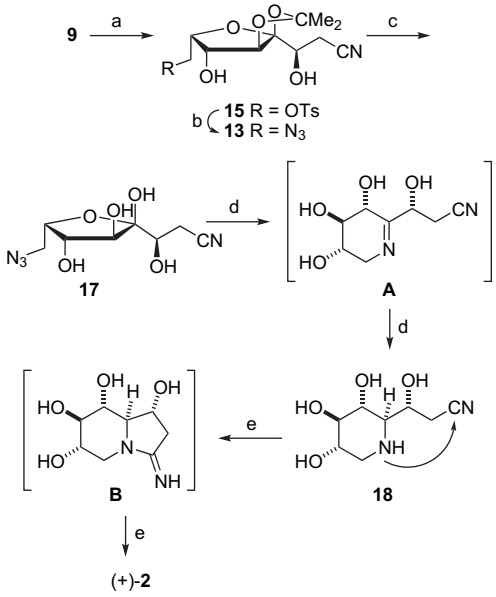


Scheme 3. Unsuccessful route to azide **13**. Reagents and conditions: (a) I_2–Ph_3P–imidazole, $PhCH_3$, 100 °C, 85%; (b) LiN_3–anhyd DMF, 60 °C; (c) MeONa–MeOH, rt.

Subsequent Zemplen's debenzoylation of this mixture afforded the desired **13** together with compound **14**, resulting from the Michael addition of MeOH to the α,β-unsaturated nitrile **12**. Compounds **13** and **14** could be finally separated by column chromatography and **13** was fully characterized.

Due to the low yield obtained in the synthesis of **13**, an alternative route was sought where OH at C-3 is unprotected (see Scheme 4). Thus, tosylate **9** was debenzoylated under Zemplen conditions to afford diol **15** without production of elimination by-products. Satisfactorily, reaction of LiN_3 with **15** afforded **13** in quantitative yield. Deacetonation of **13** with 50% aqueous TFA afforded the totally deprotected 8-azido-2,8-dideoxy-α-L-*gulo*-oct-4-ulo-4,7-furanosononitrile (**17**).

Compound **17** was subjected to catalytic hydrogenation (H_2–Pd–C–MeOH) to afford, after 18 h, a single compound that showed lower R_f by TLC, presumably the piperidine intermediate **18**. Subsequent acid-catalyzed (AcOH–AcONa–H_2O, pH=3.9) internal nucleophilic addition of the piperidine nitrogen to the protonated



Scheme 4. Synthesis of (+)-1-*epi*-castanospermine (**2**). Reagents and conditions: (a) MeONa–MeOH, 0 °C, 60%; (b) LiN_3–anhyd DMF, 90 °C, quantitative; (c) 50% aqueous TFA, rt, 75%; (d) H_2, 10% Pd–C, MeOH, 70 psi, rt; (e) H_2, 10% Pd–C, AcOH–AcONa–H_2O (pH=3.9), 70 psi, rt (two steps 25%).

cyano group in **18** eventually led to the indolizidine ring of **2** by reductive deamination of intermediate **B**.

The configuration at the new C-8a stereogenic centre in the indolizidine ring may be rationalized on the basis of a preferential attack of hydrogen from the less hindered face of the planar imine intermediate **A** (see Fig. 2). As expected, only the *R* epimer was isolated after catalytic hydrogenation of **17**, in agreement with previous results reported by us[8a,b] and other authors.[10]

From the coupling constants of H-6,7,8 and 8a ($J_{6,7}$=$J_{7,8}$=$J_{8,8a}$=9.0 Hz) in the ^1H NMR spectrum of **2**, it can be deduced that the six-membered ring adopts a chair-like conformation ($^8C_5$). The hydroxyl groups at C-6,7 and 8 are displayed in equatorial positions and the piperidinic ring is trans-fused with the five-membered ring (see Fig. 3). This result is in agreement with those reported by Mulzer et al.[7f] for the tetrabenzylated derivative of **2**.

3. Conclusions

In conclusion, 4-octulosononitrile derivative **8** was shown to be a good precursor for the stereoselective synthesis of (+)-1-*epi*-castanospermine (**2**), which was achieved in 11 synthetic steps from L-sorbose. The key reaction in this sequence was the catalytic

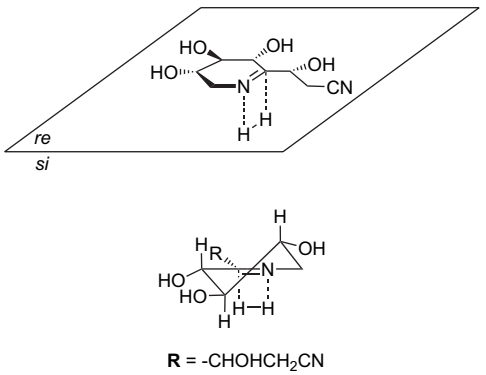


Figure 2. Proposed *si*-face hydrogen approach for the reduction of intermediate **A**.

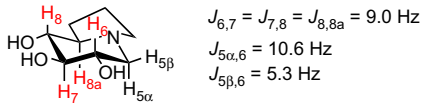


Figure 3. Chair-like spatial disposition of the piperidinic ring of (+)-1-*epi*-castanospermine (**2**).

reductive amination of azide **17** to afford diastereoselectively a single piperidine intermediate **18**. We come to show here the versatility of such octulosononitrile derivatives in the stereoselective synthesis of polyhydroxyindolizidine alkaloids.

4. Experimental

4.1. General

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 Me_4Si). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet and br, broad. IR spectra were recorded with a Perkin–Elmer FT-IR Spectrum One instrument and mass spectra were recorded with a Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured, unless otherwise stated, 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 detected by employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulfuric acid containing 0.8% cerium sulfate (w/v) and heating. Column chromatography was performed on silica gel (Merck, 7734). The non-crystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR and HRMS (LSIMS).

*4.1.1. 3-O-Benzoyl-2-deoxy-4,5-O-isopropylidene-α-L-gulo-oct-4-ulo-4,7-furanosononitrile (**8**)*

A stirred solution of compound **7**[9] (3.5 g, 8.6 mmol) in 50% aqueous acetic acid (25 mL) was heated to 50 °C for 4 h. TLC (ether) revealed the absence of **7** and the presence of a lower R_f compound. The mixture was concentrated and repeatedly codistilled with water and toluene. Column chromatography of the residue (ether–hexane, 3:2→ether) gave **8** (2.87 g, 92%) as a white foam. R_f=0.52 (ether). $[\alpha]_D^{24}$ +13 (*c* 1.5). IR: ν_{max}/cm^{-1} 3453 (OH), 3066 (aromatic), 2257 (CN) and 1728 (C=O). ^1H NMR (400 MHz): δ 8.10 (d, 2H*ortho*, Bz), 7.61 (t, 1H*para*, Bz), 7.47 (t, 2H*meta*, Bz), 5.64 (t, 1H, $J_{2,3}$=$J_{2',3}$=5.2 Hz, H-3), 4.40 (m, 2H, H-5,6), 4.33 (br s, 1H, H-7), 4.13 (br dd, 1H, $J_{7,8}$=2.8 Hz, $J_{8,8'}$=12.8 Hz, H-8), 4.04 (br dd, 1H, $J_{7,8'}$=2.8 Hz, H-8′), 3.12 (dd, 1H, $J_{2,2'}$=17.2 Hz, H-2), 3.03 (dd, 1H, H-2′), 1.39 and 1.51 (2s, 6H, CMe_2). ^{13}C NMR: δ 165.56 (Ph*C*O), 134.3, 130.3, 130.2 and 128.9 (*Ph*CO), 117.7 (C-1), 113.5 and 113.3 (C-4, *C*Me$_2$), 85.9 and 77.0 (C-5,6), 80.9 (C-7), 69.9 (C-3), 61.2 (C-8), 26.9 and 27.8 (C*Me*$_2$) and 19.2 (C-2). HRMS (LSIMS): *m*/*z* 386.1219 [M^++Na]. For $C_{18}H_{21}O_7NNa$ 386.1215 (deviation −0.9 ppm).

*4.1.2. 3-O-Benzoyl-2-deoxy-4,5-O-isopropylidene-8-O-p-toluenesulfonyl-α-L-gulo-oct-4-ulo-4,7-furanosononitrile (**9**)*

To a stirred solution of **8** (2.1 g, 5.75 mmol) in anhydrous CH_2Cl_2 (20 mL) were added Et_3N (2 mL, 14.4 mmol), DMAP (50 mg) and TsCl (1.32 g, 6.9 mmol). The reaction mixture was stirred at rt for 1.5 h. TLC (ether) showed the presence of a faster moving compound. The mixture was concentrated and chromatographed (ether–hexane, 1:1) to give **9** (2.7 g, 91%) as a white foam. R_f=0.89 (ether). $[\alpha]_D^{23}$ +7 (*c* 1). IR: ν_{max}/cm^{-1} 3502 (OH), 2257 (CN) and 1730 (C=O). ^1H NMR (400 MHz): δ 7.81 and 8.08 (2d, 4H, *J*=8.6 Hz, Ts), 7.61 (t, 1H*para*, Bz), 7.46 (t, 2H*ortho*, Bz), 7.38 (d, 2H*meta*, Bz), 5.60 (dd, 1H, $J_{2,3}$=5.6 Hz, $J_{2',3}$=6.4 Hz, H-3), 4.51 (dt, 1H, $J_{6,7}$=2.8 Hz, $J_{7,8}$=$J_{7,8'}$=6.4 Hz, H-7), 4.38 (s, 1H, H-5), 4.30 (dd, 1H, H-8), 4.33 (d, 1H, H-6), 4.15 (dd, 1H, $J_{8,8'}$=10.4 Hz, H-8), 2.95 (d, 1H, H-2), 2.94 (d, 1H, H-2′), 2.47 (s, 3H, *Me* Ts), 1.35 and 1.49 (2s, 6H, CMe_2). ^{13}C NMR: δ 165.7 (Ph*C*O), 145.6, 134.8, 134.2, 132.7, 130.2, 128.8, 28.5, 128.4, 128.3 (*Ph*CO and Ts), 116.7 (C-1), 113.9 and 113.3 (C-4, *C*Me$_2$), 85.0 and 74.2 (C-5,6), 79.9 (C-7), 68.9 (C-3), 66.8 (C-8), 27.7 and 26.8 (C*Me*$_2$), 21.9 (*Me* Ts) and 18.8 (C-2). HRMS (LSIMS): *m*/*z* 540.1304 [M^++Na]. For $C_{25}H_{27}O_9NSNa$ 540.1299 (deviation −0.9 ppm).

*4.1.3. 3-O-Benzoyl-2,8-dideoxy-8-iodo-4,5-O-isopropylidene-α-L-gulo-oct-4-ulo-4,7-furanosononitrile (**10**)*

To a solution of I_2 (1.22 g, 4.8 mmol), PPh_3 (1.26 g, 4.8 mmol) and imidazole (0.60 g, 8.8 mmol) in toluene (15 mL) was added a solution of **8** (1.45 g, 4 mmol) in toluene (10 mL). The reaction mixture was stirred at 100 °C for 2 h. TLC (ether) revealed the absence of the starting material and the presence of a new product of higher R_f. The mixture was concentrated, the residue dissolved in CH_2Cl_2 (15 mL) and washed with 10% aqueous $Na_2S_2O_3$ and water. The solvent was evaporated and the residue chromatographed (ether–hexane, 1:1) to give **10** (1.6 g, 85%) as a colourless syrup. R_f=0.33 (ether–hexane, 3:2). $[\alpha]_D^{28}$ +31 (*c* 0.34). IR: ν_{max}/cm^{-1} 3425 (OH), 2257 (CN) and 1729 (C=O). ^1H NMR (400 MHz): δ 8.08 (d, 2H*ortho*, Bz), 7.60 (t, 1H*para*, Bz), 7.50 (t, 2H*meta*, Bz), 5.58 (dd, 1H, $J_{2,3}$=4.8 Hz, $J_{2',3}$=7.2 Hz, H-3), 4.57 (m, 1H, H-7), 4.44 (s, 1H, H-5), 4.24 (s, 1H, H-6), 3.34–3.26 (m, 2H, H-8,8′), 3.07 (dd, 1H, $J_{2,2'}$=17.2 Hz, H-2), 3.01 (dd, 1H, H-2′), 1.53 and 1.36 (2s, 6H, CMe_2). ^{13}C NMR: δ 165.8 (Ph*C*O), 134.2, 130.3, 128.9 and 128.8 (*Ph*CO), 116.9 (C-1), 113.8 and 113.8 (C-4, *C*Me$_2$), 85.2 and 74.6 (C-5,6), 83.0 (C-7), 69.1 (C-3), 27.8 and 26.9 (C*Me*$_2$), 19.0 (C-2) and 1.0 (C-8). HRMS (LSIMS): *m*/*z* 458.0107 [M^+−Me]. For $C_{17}H_{17}O_6NI$ 458.0101 (deviation −1.3 ppm).

*4.1.4. Reaction of **10** with LiN_3*

To a solution of **10** (300 mg, 0.63 mmol) in anhydrous DMF (3 mL) was added LiN_3 (62 mg, 1.26 mmol) and the reaction mixture stirred for 3 h at 50 °C. TLC (ether–hexane, 2:3) revealed the presence of a new product of slightly lower R_f. The mixture was concentrated to a residue that was chromatographed in ether yielding an inseparable mixture of **11** and **12** (88 mg).

This mixture was dissolved in anhydrous MeOH (5 mL) and 2 M MeONa (0.2 mL) was added. After stirring at rt for 18 h, TLC (ether–hexane, 3:1) revealed the presence of two new compounds of lower R_f. This mixture was neutralized by addition of AcOH and evaporated to a residue that was chromatographed (ether–hexane, 2:3→3:1) to yield two compounds.

Firstly was eluted compound **13** (33 mg). R_f=0.38 (ether–hexane, 3:1). $[\alpha]_D^{27}$ +27 (*c* 1.3, MeOH). IR: ν_{max}/cm^{-1} 3492 and 3420 (OH), 2261 (CN) and 2101 (N_3). ^1H NMR (400 MHz, MeOH-d_4): δ 4.84 (s, 1H, H-5), 4.35 (m, 1H, H-7), 4.11 (d, 1H, $J_{6,7}$=2.5 Hz, H-6), 3.99 (dd, 1H, $J_{2,3}$=3.1 Hz, $J_{2',3}$=9.4 Hz, H-3), 3.51 (dd, 1H, $J_{8,8'}$=12.9 Hz, $J_{7,8}$=7.4 Hz, H-8), 3.42 (dd, 1H, $J_{7,8'}$=5.1 Hz, H-8′), 2.87 (dd, 1H, $J_{2,2'}$=17.2 Hz, H-2), 2.65 (dd, 1H, H-2′), 1.38 and 1.47 (2s, 6H, CMe_2). ^{13}C NMR: δ 118.6 (C-1), 114.9 and 112.9 (C-4, *C*Me$_2$), 85.5 and 74.2 (C-5,6), 81.1 (C-7), 68.3 (C-3), 49.7 (C-8), 26.8 and 25.8 (C*Me*$_2$) and 20.1 (C-2). HRMS (LSIMS): *m*/*z* 269.0886 [M^+−Me]. For $C_{10}H_{13}O_5N_4$ 269.0886 (deviation 0.0 ppm).

Secondly was eluted compound **14** (20 mg). $[\alpha]_D^{25}$ +19 (*c* 2). IR: ν_{max}/cm^{-1} 3451 (OH), 2252 (CN) and 2105 (N_3). ^1H NMR (400 MHz): δ 4.42 (s, 1H, H-5), 4.34–4.30 (m, 1H, H-7), 4.08 (br d, 1H, $J_{6,OH}$=9.4 Hz, H-6), 3.68 (s, 3H, OMe), 3.68 (dd, 1H, H-3), 3.51 (dd, 1H, $J_{8,8'}$=18.9 Hz, $J_{7,8}$=7.1 Hz, H-8), 3.46 (dd, 1H, $J_{7,8'}$=5.9 Hz, H-8′), 3.29 (d, 1H, OH), 2.86 (dd, 1H, $J_{2,2'}$=17.4 Hz, $J_{2,3}$=3.5 Hz, H-2), 2.75 (dd, 1H, $J_{2',3}$=8.0 Hz, H-2′), 1.51 and 1.38 (2s, 6H, CMe_2). ^{13}C NMR: δ 118.1 (C-1), 113.4 and 113.2 (C-4, *C*Me$_2$), 86.7 (C-5), 81.2 (C-7), 80.1

(C-3), 74.7 (C-6), 60.4 (C-8), 49.6 (OMe), 27.4 and 26.4 (CMe_2), 18.4 (C-2). HRMS (LSIMS): *m/z* 283.1042 [M^+−Me]. For $C_{11}H_{15}O_5N_4$ 283.1049 (deviation +2.4 ppm).

4.1.5. 2-Deoxy-4,5-O-isopropylidene-8-O-p-toluenesulfonyl-α-L-gulo-oct-4-ulo-4,7-furanosononitrile (**15**)

To a solution of **9** (1.14 g, 2.20 mmol) in anhydrous MeOH (15 mL) was added 2 M MeONa in MeOH (0.5 mL) and the reaction mixture was stirred for 3 h at 0 °C. TLC (ether) revealed the presence of a new product of lower R_f. The reaction mixture was evaporated and the residue chromatographed (ether–hexane, 2:1 → ether–MeOH, 10:1) to give **15** (1.3 g, 60%) as a white foam. R_f=0.30 (ether–hexane, 2:1). $[\alpha]_D^{24}$ +42 (*c* 0.2). IR: ν_{max}/cm^{-1} 3490 (OH) and 2252 (CN). ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.80 and 7.45 (2d, 4H, *J*=8.3 Hz, Ts), 4.41 (s, 1H, H-5), 4.34 (dt, 1H, $J_{6,7}$=$J_{7,8}$=3.3 Hz, $J_{7,8'}$=7.5 Hz, H-7), 4.28 (dd, 1H, $J_{8,8'}$=11.1 Hz, H-8), 4.10 (dd, 1H, H-8′), 4.09 (d, 1H, H-6), 3.82 (dd, 1H, $J_{2,3}$=3.0 Hz, $J_{2',3}$=9.7 Hz, H-3), 2.66 (dd, 1H, $J_{2,2'}$=17.1 Hz, H-2), 2.53 (dd, 1H, H-2′), 2.47 (s, 3H, *Me* Ts), 1.40 and 1.34 (2s, 6H, CMe_2). ^{13}C NMR: δ 143.7, 134.3, 131.1, 129.2 (Ts), 119.7 (C-1), 114.2 and 116.3 (C-4, CMe_2), 86.4 and 75.2 (C-5,6), 80.9 (C-7), 70.3 (C-8), 69.4 (C-3), 27.9 and 26.9 (CMe_2), 21.6 (*Me* Ts) and 21.2 (C-2). HRMS (LSIMS): *m/z* 436.4315 [M^++Na]. For $C_{18}H_{23}O_8NSNa$ 436.4319 (deviation +0.9 ppm).

4.1.6. 8-Azido-2,8-dideoxy-4,5-O-isopropylidene-α-L-gulo-oct-4-ulo-4,7-furanosononitrile (**13**)

To a stirred solution of **15** (800 mg, 1.93 mmol) in anhydrous DMF (12 mL) was added LiN_3 (170 mg, 3.4 mmol) and the mixture was heated to 90 °C for 5 h. TLC (ether) revealed the presence of a new product of slightly higher R_f. The reaction mixture was evaporated and the residue chromatographed (ether) to give **13** (550 mg, quantitative) as a white foam.

4.1.7. 8-Azido-2,8-dideoxy-α-L-gulo-oct-4-ulo-4,7-furanosononitrile (**17**)

A solution of **13** (200 mg, 0.67 mmol) in 50% aqueous TFA (10 mL) was stirred at rt for 17 h. The mixture was evaporated and codistilled with water and toluene several times. The final residue was chromatographed (ether) to give **17** (124 mg, 75%) as a colourless syrup. R_f=0.36 (ether–methanol, 10:1). $[\alpha]_D^{27}$ +4 (*c* 2.5, MeOH). IR: ν_{max}/cm^{-1} 3401 (OH), 2257 (CN) and 2107 (N_3). ^{1}H NMR (400 MHz, MeOH-d_4): δ 4.24 (dt, 1H, $J_{7,8}$=$J_{6,7}$=4.6 Hz, $J_{7,8'}$=6.6 Hz, H-7), 4.11 (m, 2H, H-5,6), 3.91 (dd, 1H, $J_{2,3}$=3.1 Hz, $J_{2',3}$=9.3 Hz, H-3), 3.46–3.30 (m, 2H, H-8,8′), 2.83 (dd, 1H, $J_{2,2'}$=17.1 Hz, H-2) and 2.66 (dd, 1H, H-2′). ^{13}C NMR: δ 118.9 (C-1), 103.5 (C-4), 78.2, 76.8 and 76.9 (C-5,6,7), 70.7 (C-3), 50.5 (C-8) and 20.0 (C-2). HRMS (LSIMS): *m/z* 267.1948 [M^++Na]. For $C_8H_{12}O_5N_4Na$ 267.1944 (deviation −1.5 ppm).

4.1.8. (1R,6S,7R,8R,8aR)-1,6,7,8-Tetrahydroxyindolizidine [(+)-1-epi-castanospermine, **2**]

A solution of compound **17** (72 mg, 0.3 mmol) in MeOH (12 mL) was hydrogenated at 70 psi over 10% Pd–C (20 mg) for 24 h. TLC (ether–MeOH, 10:1) showed the presence of a single compound of lower mobility. The catalyst was filtered off, washed with MeOH and the filtrate evaporated to a residue that was dissolved in 1% AcOH (12 mL). Then NaOAc (24 mg) and 10% Pd–C (12 mg) were added. The mixture was hydrogenated at 70 psi for 24 h. TLC (CH_2Cl_2–MeOH, 1:1) revealed the presence of a single compound. The catalyst was filtered off, washed with water and MeOH and evaporated. The residue was chromatographed (CH_2Cl_2–MeOH, 2:1) and the product obtained was transferred to a Dowex® 50Wx8 (200–400 mesh) column that was eluted with MeOH (15 mL), H_2O (10 mL) and 5% NH_4OH (40 mL) consecutively to afford **2** (14 mg, 25%) as a white solid. R_f=0.36 (CH_2Cl_2–MeOH, 1:1). $[\alpha]_D^{27}$ +10 (*c* 0.25, MeOH, pH 6) [lit.:[7a] $[\alpha]_D^{22}$ +3.8 (*c* 0.54, MeOH)]. ^{1}H NMR (400 MHz, D_2O): δ 4.07 (ddd, 1H, $J_{1,8a}$=6.5 Hz, $J_{1,2}$=3.7 Hz, $J_{1,2'}$=8.6 Hz, H-1), 3.45 (ddd, 1H, $J_{5\beta,6}$=5.3 Hz, $J_{5\alpha,6}$=10.6 Hz, $J_{6,7}$=9.0 Hz, H-6), 3.22 (t, 1H, $J_{7,8}$=$J_{8,8a}$=9.0 Hz, H-8), 3.17 (t, 1H, H-7), 2.98 (dd, 1H, $J_{5\alpha,5\beta}$=10.9 Hz, H-5β), 2.78 (dt, 1H, $J_{2',3}$=1.5 Hz, $J_{2,3}$=9 Hz, H-3), 2.40 (q, 1H, $J_{3,3'}$=$J_{2,3'}$=$J_{2',3'}$=9.1 Hz, H-3′), 2.14 (dq, 1H, $J_{2,2'}$=14.1 Hz, H-2), 2.07 (t, 1H, H-5α), 1.95 (dd, 1H, H-8a) and 1.52 (dddd, 1H, H-2′). ^{13}C NMR: δ 83.9 (C-7), 78.9 (C-1), 78.5 (C-8), 78.0 (C-8a), 75.1 (C-6), 60.0 (C-5), 56.0 (C-3) and 37.6 (C-2). HRMS (LSIMS): *m/z* 190.1080 [M^++H]. For $C_8H_{16}O_4N$ 190.1079 (deviation −0.5 ppm).

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