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Cycloaddition Reactions of Carbohydrate Derivatives. Part VI.[1] Quinolizidine Analogs of Castanospermine

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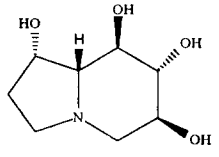
Abstract: Octahydroquinolizine-1,2,3,8-tetraols 12, 16 and 23, analogs of castanospermine, were synthesized from D-glucose, L-arabinose and D-mannose, respectively, using hetero-Diels-Alder reactions of sugar-derived azomethines as the key step.

Castanospermine (1), a hydroxyindolizidine alkaloid-antibiotic isolated first from *Castanospermum australe*[2] exhibits many interesting biological activities such as inhibition of glycosidase enzymes[3], and antimetastatic[4], antiviral properties[5]. Therefore, in recent years much effort has been devoted to the synthesis of 1 and its analogs[6,7]. We have elaborated new approaches to the synthesis of hydroxyindolizidines via hetero-Diels-Alder reactions of sugar-based azomethines[1,8] and by 1,3-dipolar cycloadditions of chiral, cyclic nitrones[9]. As an extension of our [4+2] approach we decided to prepare some quinolizidine analogs of **1**. To our knowledge, only a few examples are known of such castanospermine analogs[10-12].



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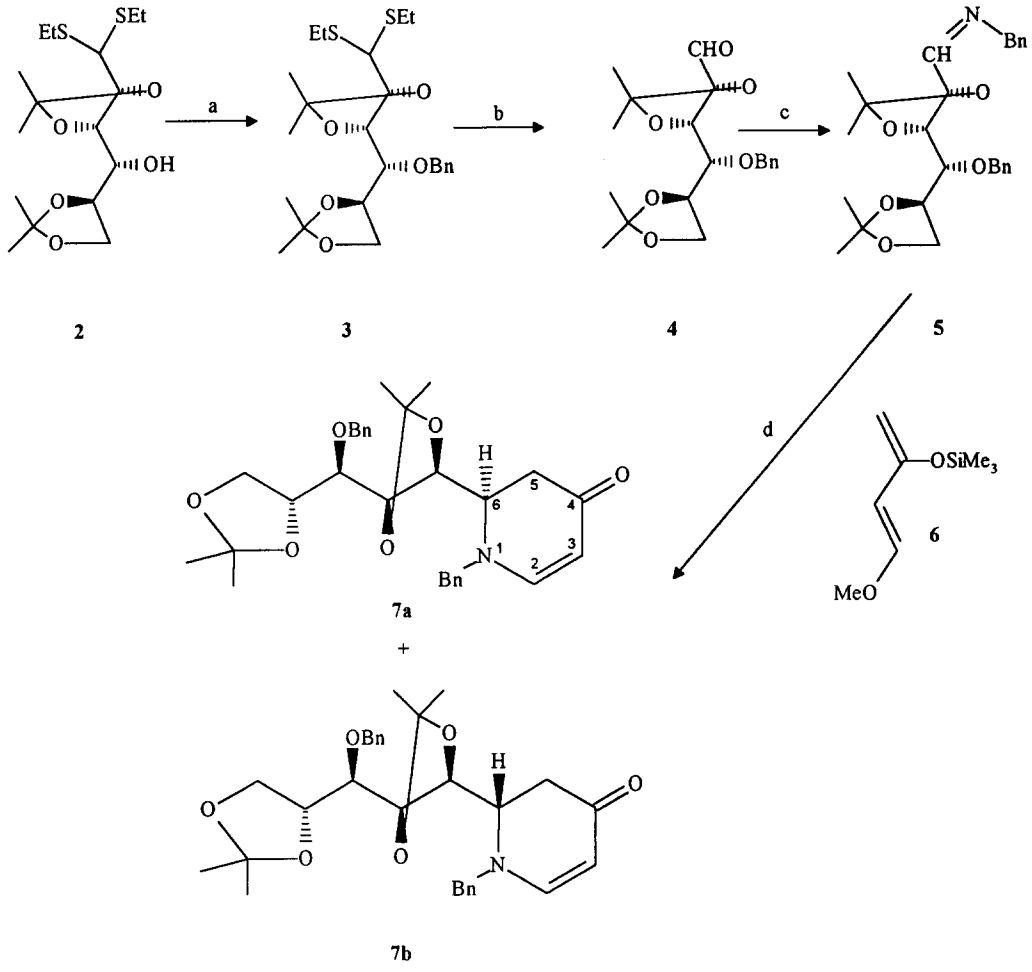
The azomethine dienophile **5** was prepared from D-glucose. The diisopropylidene mercaptal **2**[13] was benzylated (**3**) followed by mercury salt promoted demercaptalization[14] to give **4**. The latter was condensed with benzylamine and the azomethine **5** was allowed to react with Danishefsky's diene **6**, in the presence of zinc chloride (Scheme 1.).

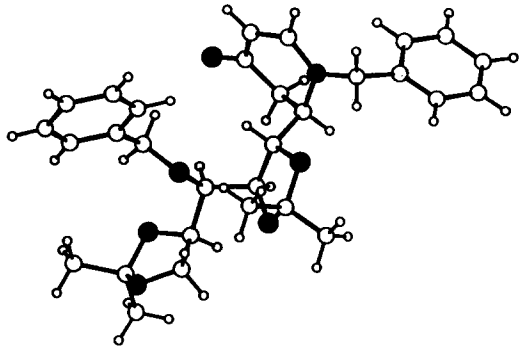
A mixture (9:1) of diastereomeric piperidones **7a** and **7b** was formed and could be easily separated by chromatography. As expected[1], the major isomer proved to be the 6R product **7a**. The configuration of the newly formed chiral center could be determined by circular dichroism spectroscopy. **7a** exhibited a



Scheme 1

a) BnBr, NaH, DMF, r.t, 16 h; b) HgO, Et_2OBF_3, H_2O-THF, r.t.; c) $BnNH_2$, THF, r.t., 1 h; d) $ZnCl_2$, dioxane, 3 h.

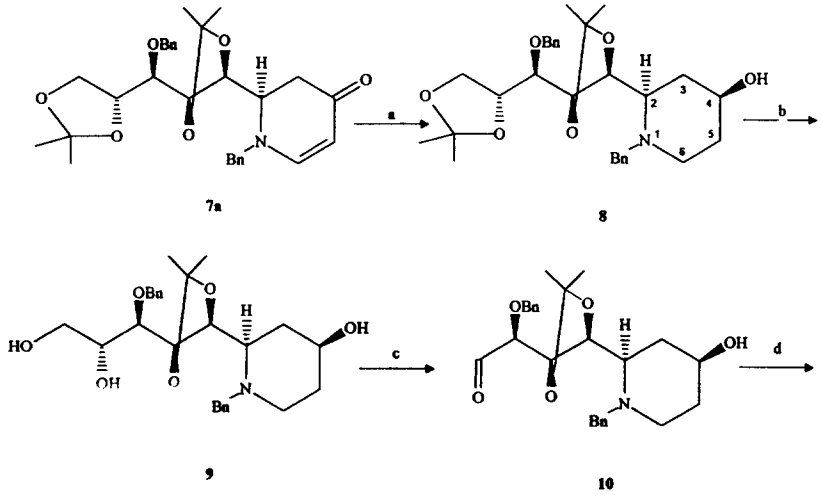
positive Cotton effect at 330 nm, therefore, according to our previous findings[1] for similar compounds **7a** must be the 6R isomer. We were able to confirm the configuration of this compound by X-ray crystallography (see diagram and reference 17) as well.



X-ray structure of **7a**.

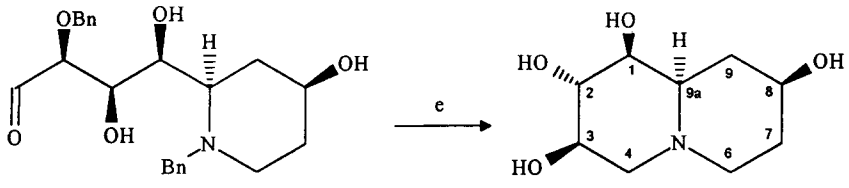
7a was treated with 10 equivalents of sodium tetrahydridoborate in ethanol leading to simultaneous reduction of the keto function and the CC double bond in the heterocycle. As expected on the basis of our previous experience[1], the single diastereomer **8** was only formed in this reaction. This high stereoselectivity can be explained by the strong shielding effect of the sugar chain on one side of the ring.

The terminal dioxolane grouping of **8** was subsequently hydrolized to give **9**; the glycol system of the latter was cleaved by lead(IV)acetate (**10**) and the acetonide hydrolized to give **11**. Finally this was catalytically hydrogenolized affording quinolizidine **12**. NOESY experiments revealed spatial proximity of 8 and 9a protons in **12** supporting the proposed structure.



Scheme 2

a) $NaBH_4$, EtOH, 20 h, b) AcOH, H_2O, 50 °C, c) $Pb(OAc)_4$, PhH, d) CF_3COOH, H_2O, e) H_2, Pd(C), AcOH

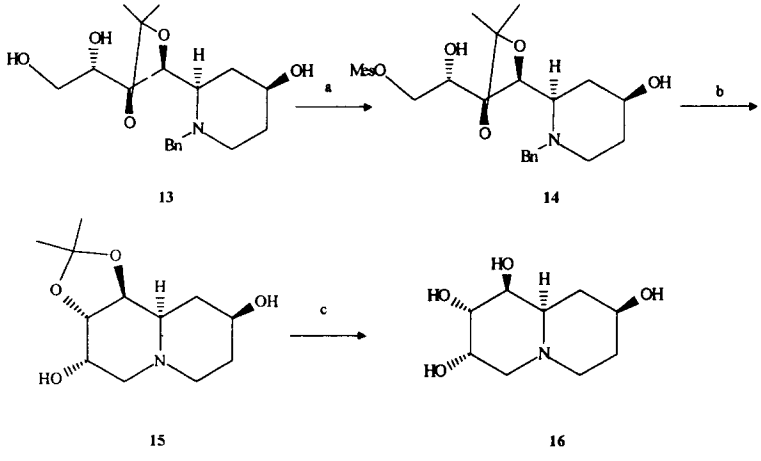


11 12

Scheme 2.

(Continued) e) H_2, Pd(C), AcOH

Another quinolizidine **16** could be prepared from **13** which, in turn, was synthesized[1] from L-arabinose. Mesitylenesulfonyl was reported to be a good leaving group in the synthesis of castanospermine analogs[15]. In our case, mesisylation of **13** afforded **14** in a reasonable yield (64%). Cyclization of **14** was accomplished by removing of the N-benzyl protective group using catalytic hydrogenolysis. Subsequent intramolecular alkylation led to **15**. Hydrolysis of the dioxolane ring resulted in another quinolizidine analog **16** of castanospermine.



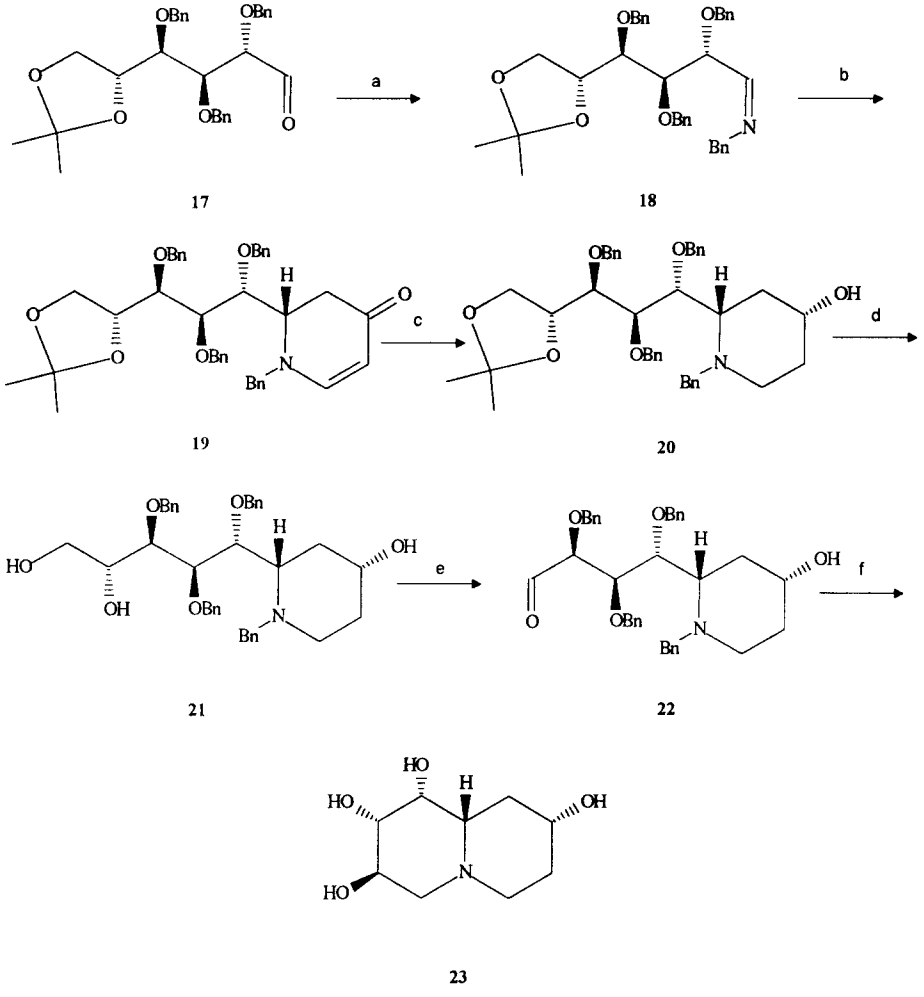
13 14 15 16

Scheme 3

a) MesCl, pyridine; b) TsCl, pyridine; c) H_2, Pd(C), EtOH, $NaHCO_3$, 12 h; d) TFA, H_2O, 40°C, 24 h.

A third tetrahydroxyquinolizidine diastereomer (**23**) was prepared from **17**[16]. The cycloaddition reaction of azomethine **18** afforded **19** as a single product. Reduction of the enone system of the latter with sodium

tetrahydridoborate resulted in one diastereomeric piperidinol only, **20**. The latter was transformed into **23** by the routine reaction sequence: hydrolysis (**22**), glycol cleavage (**23**) and hydrogenolysis.



Scheme 4.

a) **6**, $ZnCl_2$, MeCN, 3 h; b) $NaBH_4$, EtOH, 24 h then 85 % TFA, CH_2Cl_2, 2 h; c) $Pb(OAc)_4$, $PhCH_3$, 0.5 h; d) H_2, Pd(C), AcOH, 16h. e) $Pb(OAc)_4$ f) H_2, Pd(C), AcOH.

In conclusion, our [4+2] synthetic approach proved to be effective for the preparation of polyhydroxyindolizidines and quinolizidines. Various biological activities of the end-products will be tested in the near future.

Experimental

General methods. Adsorption chromatography was carried out using Kieselgel 60. For TLC precoated aluminium-backed plates (Kieselgel 60 F203) were used. Melting points were determined on a Kofler electric hot stage and were not corrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. I.R. spectra were recorded on a Perkin-Elmer 283D spectrometer im KBr pellets. ^1H and ^{13}C NMR spectra were obtained with Bruker WP200SY, WP250, WP300 and WP400 instruments. CI-MS spectra were recorded with a AEI-SM-9 spectrometer using isobutane at 220°C, FAB spectra were obtained with an SM-80 instrument.

4-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-D-glucose diethyl dithioacetal (3). To a stirred solution of **2** (5.0 g, 13.6 mmol) in dry dimethylformamide (50 mL) a 80% suspension of sodium hydride in oil (1.0 g) was added at 0 °C. After 0.5 h the alkoxide solution was treated with benzyl bromide (2.43 mL, 20.4 mmol) for 16 h at room temperature. A few mL of methanol and water was added and the mixture was poured in water, extracted with dichloromethane and dried ($MgSO_4$). After evaporation the crude product was purified by column chromatography (hexane-ethyl acetate 9:1) affording **3** (5.0 g, 80%). $[\alpha]_D$ -15.9 (c 1.0, $CHCl_3$). ^1H-NMR (200 MHz, $CDCl_3$) δ 7.4 (m, 5H, phenyl), 4.8 (q, 2H, J_{AB}= 11 Hz, OCH_2Ph), 3.85 (d, 1H, $J_{1,2}$= 6 Hz, H-1), 2.8 and 2.6 (2q, 4H, 2 SCH_2),. MS (EI):m/z 456 (M^+). Anal. Calcd for $C_{23}H_{36}O_5S_2$: C, 60.53; H, 7.89 S, 14.05. Found: C, 60.68; H, 7.99; S, 14.32.

4-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose (4). To a well stirred suspension of red mercury oxide (3.13 g, 14.46 mmol) in tetrahydrofuran-water mixture (85:15; 25 mL) boron trifluoride etherate (1.78 mL, 14.46 mmol) was added, followed by dropping a solution of 3 (3.3 g, 7.23 mmol) in THF (5 mL). After 20 min of stirring the mixture was diluted with ether (60 mL) and filtered. The organic phase was washed with saturated sodium hydrogen carbonate solution and dried ($MgSO_4$). The evaporation residue was chromatographed (hexane-ethyl acetate 8:2) giving **4** (1.92 g, 76%) as an oil. $[\alpha]_D$ -0.8 (c 1.84, $CHCl_3$). ^1H-NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H, -CHO), 7.4 (m, 5H, phenyl). MS (EI): m/z 350 (M^+). Anal. Calcd for $C_{19}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.45; H, 6.90.

***N*-Benzyl-(6R,1'S,2'R,3'R,4'R)-6-(3'-*O*-benzyl-1',2':5',6'-di-*O*-isopropylidene-1',2',4',5'-pentahydroxy-1'-pentyl)-2,3-didehydropiperidine-4-one (7a)** and its 6S isomer **7b**. A solution of **4** (1.9 g, 5.42 mmol) in THF (60 mL) was treated with benzylamine (0.6 mL, 5.42 mmol) in the presence of 3 A molecular sieves (1 g). After 1 hour the mixture was filtered and the solvent was evaporated. The residue was dissolved in dioxane (75 mL), **6** (21.7 mmol) and anhydrous zinc chloride (0.74 g, 5.4 mmol) were added under stirring. After 3 h agitation the solution was neutralized with the addition of saturated NaHCO3 solution and evaporated to dryness. The residue was extracted with dichloromethane, the solution was washed with brine, dried (MgSO4) then separated by column chromatography (hexane-ether-acetone 3:1:1).

7a. 1.8 g (65.7%). Mp. 113 °C. $[\alpha]_D$ +215.5 (c 1.0, $CHCl_3$). ^1H-NMR (200 MHz, $CDCl_3$) δ 7.40 (m, 10H, 2 phenyl), 7.10 (d, 1H, $J_{2,3}$= 7.5 Hz, H-2), 5.0 (d, 1H, H-3), 4.4-4.8 (m, 5H, -OCH_2Ph+ -NCH_2Ph+ H-1'), 4.21 (dd, 1H, $J_{3',4'}$= 13 Hz, H-4'), 4.02 (m, 2H, 5'-CH_2), 3.93 (dd, 1H, $J_{1',2'}$= 7 Hz, H-2'), 3.65 (dd, 1H, H-3'), 3.52 (t, 1H, $J_{5,6}$=$J_{6,1'}$=7.5 Hz, H-6), 2.8 (m, 1H, H-5ax), 2.1 (m, 1H, H-5eq), 1.3 (m, 12H, 4 CH_3). MS (EI): m/z 507 (M^+). Anal. Calcd for $C_{30}H_{37}NO_6$: C, 71.17; H, 7.17; N, 2.77.

Found: C, 71.46; H, 7.19; N, 2.83.

7b. 0.2 g (7.3%). $[\alpha]_D$ -98.5 (c 1.0, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.32 (m, 10H, 2 phenyl), 7.10 (d, 1H, $J_{2,3}$= 7.5 Hz, H-2), 5.05 (d, 1H, $J_{2,3}$= 7.5 Hz, H-3), 4.52-4.80 (m, 4H, -OCH_2Ph -NCH_2Ph), 4.44 (m, 1H, H-1'), 4.20 (dd, 1H, $J_{3',4'}$= 7 Hz, $J_{4',5'}$= 11 Hz, H-4'), 4.01 (m, 3H, 5'-CH_2+H-2'), 3.75 (m, 1H, H-6), 3.62 (m, 1H, H-3'), 2.65 (m, 1H, H-5ax), 2.40 (dd, 1H, H-5eq), 1.32 (m, 12H, 4 CH_3). MS (FAB) : m/z 514 $(M+Li)^+$. Anal. Calcd for $C_{30}H_{37}NO_6$: C, 71.17; H, 7.17; N, 2.83. Found: C, 71.52; H, 7.22; N, 2.88.

***N*-Benzyl-(2R,4S,1'S,2'R,3'R,4'R)-4-hydroxy-2-(3'-*O*-benzyl-1',2':5',6'-di-*O*-isopropylidene-1',2',3',4',5'-pentahydroxy-1'-pentyl)piperidine (8)**. **7a** (1.4 g, 2.76 mmol) in ethanol (75 mL) was reduced with sodium tetrahydridoborate (1.04 g, 27.6 mmol) for 20 h at room temperature, then the solution was neutralized with 0.1 M HCl and evaporated to dryness. The residue was extracted with dichloromethane and this solution was washed with water and dried. The product (1.3 g, 92%) was obtained after column chromatography (hexane-ether-acetone 3:2:1). $[\alpha]_D$ -5.0 (c 0.76, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 10 H, 2 phenyl), 4.6 (dd, 2H, J_{AB}= 11 Hz, -OCH_2Ph), 3.61 (dd, -NCH_2Ph), 3.74 (m, 1H, H-4), 3.20 (m, 1H, H-6), 2.82 (m, 1H, H-2), 1.30 (4s, 12H, 4CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 109.1, 108.2 (2 CMe_2), 78.6-76.3 (C-1', C-2', C-3', C-4'), 74.5 (OCH_2Ph), 67.3 (C-4), 65.4 (C-5'), 57.6 (C-2), 57.3 (NCH_2Ph), 48.1 (C-2), 33.2, 30.8 (C-3, C-5), 27.4-25.3 (4 CH_3). MS (EI): m/z 496 $(M-CH_3)^+$. Anal. Calcd for $C_{30}H_{41}NO_6$:C, 70.42; H, 8.08; N, 2.74. Found: C, 70.53; H, 8.10; N, 2.80.

***N*-Benzyl-(2R,4S,1'S,2'R,3'R,4'R,)-4-hydroxy-2-(3'-*O*-benzyl-1',2'-*O*-isopropylidene-1',2',3',4',5'-pentahydroxy-1'-pentyl)piperidine (9)** **8** (2.3 g, 2.54 mmol) was kept in acetic acid-water 3:1 solution (70 mL) at 50 °C for 24 h. The solvent was distilled off and the residue was purified on a silica gel column using dichloromethane-ether-methanol 18:2:1 mixture as eluant to give 1.06 g (83%) of **9** as an oil. $[\alpha]_D$ -17.2 (c 0.87, $CHCl_3$). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.3 (m, 10H, 2 phenyl), 4.55 (q, 2H, J_{AB}= 11 Hz, -OCH_2Ph), 4.2 (m, 1H, H-1'), 3.9 (m, 1H, H-3'), 3.75 (m, 4H, H-4, H-4', 5'-CH_2), 3.7 (dd, 2H, -NCH_2Ph), 3.3 (dd, 1H, $J_{2',3'}$= 1 Hz, $J_{1',2'}$= 5.5 Hz, H-2'), 3.1 (ddd, 1H, H-2eq), 2.5 (m, 1H, H-6), 2.3 (m, 1H, H-2ax), 2.05 (m, 1H, H-5), 1.8 (m, 1H, H-3), 1.3 (m, 8H, 1 H-3, 1 H-5, 2 -CH_3). MS (CI) m/z: 472 (MH^+). Anal. Calcd for $C_{27}H_{37}NO_6$: C, 68.76; H, 7.91; N, 2.97. Found: C, 68.82; H, 7.96; N, 2.90.

(1S,2S,3R,8S,9aR)-Octahydroquinolizine-1,2,3,8-tetraol (12). **9** (960 mg, 2.04 mmol) was treated with lead(IV)acetate (885 mg, 2.24 mmol) in dry toluene (50 mL) for 20 min. The reaction mixture was washed with 0.5 M NaOH solution, then with brine and dried ($MgSO_4$). The crude aldehyde **10** was transformed without purification. MS (EI) m/z: 424 $(M-CH_3)^+$. **10** (0.8 g) was hydrolyzed in a 3:1 trifluoroacetic acid-water mixture (16 mL) at 0 °C for 16 h. It was evaporated to dryness and toluene was distilled off five times to remove the traces of acid. Crude **11** was used for the next step without further purification. The latter compund (727 mg) was hydrogenated in acetic acid in the presence of palladium on charcoal (900 mg) for 24 h. The mixture was filtered through celite, evaporated, the residue was dissolved in water (10 ml) and treated with Serdolit Blue anion exchange resin. After filtration and evaporation the product **12** was obtained by column chromatography (toluene-methanol 1:1). Yield: 270 mg (73%). $[\alpha]_D$ -24.5 (c 1.14, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 3.70 (m, 1H, H-2), 3.62 (s, 1H, H-3), 3.53 (m, 1H, H-8), 3.41 (m, 1H, H-1), 2.85 (dd, 1H, $J_{6,7}$= 3 Hz, H-6), 2.72 (dd, 1H, $J_{3,4}$= 3 Hz, H-4), 2.53 (m, 1H, H-4'),

2.45 (m, 1H, H-9a), 2.20 (m, 1H, H-6'), 1.70-1.40 (m, 4H, H-7, H-9). ^{13}C-NMR (50 MHz, CD_3OD) δ 74.0 (C-1), 71.4 (C-2), 70.1 (C-3), 69.8 (C-8), 59.8 (C-9a), 56.7 (C-4), 55.2 (C-6), 36.8 (C-9), 34.6 (C-7). MS (FAB) m/z: 204 $(MH)^+$, 226 $(M+Na)^+$. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 53.25; H, 8.55; N,6.95.

***N*-Benzyl-(2R,4S)-2-((1'S,2'R,3'S)-1',2'-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-4'- *O*-(2,4,6 trimethylbenzenesulfonyl)-1'-butyl)-4-hydroxypiperidine (14).** **13**[1] (410 mg, 1.17 mmol) was dissolved in dry pyridine (15 mL) and 2,4,6-trimethylbenzenesulfonyl chloride (510 mg, 2.34 mmol) was added at 0 °C. After 10 min it was allowed to warm to room temperature and after 16 h the solvent was evaporated, the residue was extracted with chloroform, and that solution was washed successively with 0.1 N hydrochloric acid, with sodium hydrogen carbonate solution. The product (**14**) was obtained with the use of column chromatography (dichloromethane-methanol 95:5). Yield: 400 mg, 64%. $[\alpha]_D$ +24.0 (c 0.96, $CHCl_3$). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.3 (m, 5H, phenyl), 7.03 (s, 2H, mesisyl aromatic), 4.30 (m, 2H, -NCH_2Ph), 3.50 (dd, 2H, 4'-CH_2), 2.62 (s, 6H, 2 Me, mesisyl), 2.32 (s, 3H, Me, mesisyl), 1.38 (s, 6H, 2 Me). MS (FAB) m/z: 534 $(MH)^+$. Anal Calcd for $C_{28}H_{39}NO_7S$: C, 63.02; H, 7.37; N, 2.62. Found: C, 63.12; H, 7.45; N, 2.75.

(1S,2S,3S,8S,9aR)-1,2-*O*-isopropylidene-1,2,3,8-tetrahydroxy-octahydroindolizine (15)
Compound **14** (280 mg, 0.53 mmol) was hydrogenated in ethanol (15 mL) in the presence of $NaHCO_3$ (0.5 g) and palladium on charcoal (10%). After 12 h the mixture was filtered through a celite pad and the filtrate was kept at 60 °C for 4 h. The solvent was evaporated, the residue was dissolved in water (10 mL) and the pH of the solution was adjusted to 10-12 with 1 N NaOH. The product was extracted with ethyl acetate giving rise to **15** (55 mg, 43%). $[\alpha]_D$ +38.9 (c 1.1, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.25 (d, 1H, $J_{2,3}$=4.5 Hz, H-3), 4.10 (dd, 1H, $J_{1,9a}$= 10 Hz, $J_{1,2}$= 12 Hz, H-1), 3.71 (m, 1H, H-8), 3.63 (dd, 1H, $J_{2,3}$= 4.5 Hz, $J_{1,2}$= 12 Hz, H-2), 3.20 (m, 1H, $J_{9,9a}$= 3 Hz, $J_{9',9a}$= 16 Hz, H-9a), 3.02 (m, 3H, 2H-6, H-4), 2.60 (dd, 1H, $J_{3,4}$=4.5 Hz, H-4), 1.70 (m, 2H, 2H-9), 1.40 (m, 2H, 2H-7), 1.33, 1.35 (2s, 6H, 2 Me). ^{13}C-NMR (65 MHz, $CDCl_3$) δ 110.5 (CMe_2), 75.2 (C-1), 72.1 (C-2), 69.8 (C-8), 66.1 (C-3), 57.6 (C-9a), 51.8, 51.3 (C-4, C-6), 29.8, 27.9 (C-7, C-9), 26.7, 26.8 (2 CH_3). MS (FAB) m/z: 244 $(MH)^+$. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.29; H, 8.71; N, 5.76. Found: 59.42; H, 8.85; N, 5.72.

(1S,2S,3S,8S,9aR)-Octahydroquinolizine-1,2,3,8-tetraol. (16) Compound **15** (33 mg) was hydrolyzed in a 2:1 trifluoroacetic acid-water mixture (1.5 mL) for 24 h at 40 °C. After evaporation the residue was dissolved in water and treated with Serdolit Blue anion exchange resin to give chromatographically homogeneous **16** (25 mg, 92%). $[\alpha]_D$ -6.0 (c 1.0, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 4.25 (d, 1H, $J_{2,3}$= 7 Hz, H-3), 3.92 (m, 2H, H-8, H-2), 3.70, (d, 1H, $J_{1,9a}$= 4 Hz, H-1eq), 3.42 (m, 2H, H-4, H-9a), 2.83 (m, 2H, H-4', H-6), 2.75 (t, 2H, H-6ax), 1.95 (d, 1H, J_{gem}= 12 Hz, H-7eq), 1.80 (d, 1H, J_{gem}= 12 Hz, H-9eq), 1.62 (t, 1H, H-9ax), 1.45 (m, 1H, H-7ax). ^{13}C-NMR (65 MHz, CD_3OD) δ 71.5 (C-1), 70.0 (C-2), 66.4 (C-3), 63.8 (C-8), 60.3 (C-9a), 54.4 (C-4), 53.5 (C-6), 35.7 (C-9), 32. 9 (C-7). Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 53.23; H, 8.65; N, 6.83.

***N*-Benzyl-(6S,1'R,2'R,3'R,4'R)-6-(1',2',3'-tri-*O*-benzyl-4',5'-*O*-isopropylidene-1',2',3',4',5'-pentahydroxy-1'-pentyl)-2,3-didehydropiperidine-4-one. (19)** This compound was prepared from **18** described previously[1] for similar compounds. Syrup. Yield: 86%. $[\alpha]_D$ -101.3 (c 1.0, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 20H, aromatic), 6.92 (m, 1H, H-2), 4.88 (d, $J_{2,3}$= 7 Hz,H-3), 2.52 (m, 1H, H-5), 2.25 (m, 1H, H-5), 1.27 and 1.43 (2s, 6H, 2 Me),. ^{13}C-NMR (65 MHz, $CDCl_3$) δ 190.1 (C-4), 152.7 (C-2), 96.9 (C-3), 79.8 , 76.8, 76.5 (C-1', C-2', C-3'), 66.4 (C-5'), 60.9 (NCH_2Ph), 56.0 (C-6), 38.3 (C-5), 26.3 and 24.5 ($C(CH_3)_2$). MS (FAB): m/z: 654 $(M+Li)^+$; 648 $(M+H)^+$. Anal. Calcd for $C_{41}H_{45}NO_6$: C, 76.01; H, 7.0; N,2.16. Found: C, 75.95; H, 6.96; N, 2.13.

***N*-Benzyl-(2S,4R,1'R,2'R,3'R,4'R)-2-(1',2',3'-tri-*O*-benzyl-4',5'-*O*-isopropylidene-1',2',3',4',5'-pentahydroxy-1'-pentyl)-4-hydroxypiperidine (20).** Compound **19** was reduced with sodium tetrahydridoborate as described earlier[1] for such compounds. Yield. 91%. Syrup. $[\alpha]_D$ + 0.7 (c 1.0, $CHCl_3$): δ 7.3 (m, 20H, aromatic), 5.07-4.49 (m, 6H, OCH_2Ph), 3.68 (m, 1H, H-4), 3.O2(m, 1H, H-2), 2.87 (m, 1H, H-6eq), 2.25 (m, 1H, H-6ax) 1.88 (m, 2H, H-3), 1.62 (m, 2H, H-5), 1.37 and 1.32 (2s, 6H, isopropylidene). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 108.3 (CMe_2), 81.7, 79.4, 79.3, 76.5 (C-1', C-2', C-3', C-4'), 74.4, 74.3, 72.9 (-OCH_2Ph), 70.3 (C-4), 66.8 (C-5'), 59.6 (C-2), 52.8 (-NCH_2Ph), 48.5 (C-6), 34.7 (C-3), 29.8 (C-5) 26.6 and 25.1 ($C(CH_3)_2$). MS (FAB) m/z: 652 $(M+H)^+$. Anal. Calcd for $C_{41}H_{49}NO_6$: C, 75.55; H, 7.58; N, 2.15. Found: C, 76.02; H, 7.67; N, 2.16.

***N*-Benzyl-(2S,4R,1'R,2'R,3'R,4'R)-2-(1',2',3'-tri-*O*-benzyl-1',2',3',4',5'-pentahydroxy-1'-pentyl)-4-hydroxypiperidine (21).** Compound **20** was hydrolyzed in dichloromethane (100 ml) with 85% trifluoroacetic acid (5 mL) for 2 h at room temperature. The mixture was evaporated to dryness, toluene was distilled from the residue, then it was dissolved in dichloromethane (100 mL) and that solution was washed with 0.3 N NaOH in brine and ultimately with brine to give, after evaporation, the product **21** (2.86 g, 81% as a foam. $[\alpha]_D$ +7.6 (c 0.86, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.3 (m, H20, aromatic), 4.86-4.50 (2s, q, 6H, OCH_2Ph), 4.19 (m, 3H, H-4, H-5'), 3.02 (m, 1H, H-2), 2.89 (m, 1H, H-6eq), 2.25 (m, 1H, H-6ax), 1.90 (m, 2H, H-3), 1.60 (m, 2H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 81.9 (C-1'), 78.3 (C-2', C-3'), 74.6, 73.9, 73.1 (OCH_2Ph), 72.3 (C-4'), 64.1 (C-5'), 60.4 (C-2), 53.8 (-NCH_2Ph), 48.4 (C-6), 34.2 (C-3), 30.0 (C-5). MS (CI) m/z: 612 $(M+H)^+$.Anal. Calcd for $C_{38}H_{45}NO_6$: C, 74.60; H, 7.41; N, 2.29. Found: C, 75.02; H, 7.48; N, 2.25.

(1R,2S,3R,8R,9aS)-Octahydroquinolizine-1,2,3,8-tetraol (23). A well stirred solution of **21** (1.35 g, 2.2 mmol) in toluene (30 mL) was treated with lead(IV)acetate (1.06 g, 2.4 mmol) for 0.5 h. After filtration the mixture was washed with saturated $NaHCO_3$ and dried ($MgSO_4$). After evaporation the residue was hydrogenated for 16 h in acetic acid (20 mL) in the presence of palladium on charcoal (10%) catalyst (0.5 g). The product (262 mg, 55%) was isolated by chromatography (dichloromethane-methanol-NH_4OH 14:6:1). M.p. 75-77 °C. $[\alpha]_D$ -8.5 (c 0.85, MeOH). ^{1}H-NMR (300 MHz, CD_3OD): δ 3.86 (m, 1H, $J_{3ax,4eq}$= 4.5 Hz, H-3ax), 3.60 (m, 2H, H-1eq, H-8ax), 3.25 (dd, 1H, $J_{1eq,2ax}$= 3.5 Hz, $J_{2ax,3ax}$ = 10 Hz, H-2ax), 3.00 (m, 2H, H-4eq, H-6eq), 2.35 (m, 2H, H-6ax, H-9-ax), 2.10 (t, 1H, $J_{4ax,4eq}$= $J_{4ax,3ax}$= 11.0 Hz, H-4ax), 1.85 (m, 2H, H-7eq, H-9eq), 1.58 (ddd, 1H, $J_{9ax,9aax}$= $J_{8ax,9ax}$= $J_{9ax,9eq}$= 11-12 Hz, H-9ax), 1.42 (m, 1H, H-7ax). ^{13}C-NMR (75 MHz, CD_3OD): δ 77.0 (C-2), 73.2 (C-1), 68.9 (C-8), 68.2 (C-3), 64.9 (C-9a), 60.6 (C-4), 55.0 (C-6), 37.9 (C-9), 34.9 (C-7). Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 53.29; H, 8.62; N, 6.95.

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17. X-Ray crystal Structure Determination of compound **7a**:
    Crystal data : C_{30} H_{37} N O_6 , M_w = 507.75. ; orthorhombic, P $2_12_12_1$, a= 8.941 (5), b= 11.642 (7), c= 26.724 (15) A, V= 2782 (3) A^3, d_c= 1.21 g cm^{-3}, Z= 4, λ (Cu Ka)= 1.5418 A, F(000)= 1084, μ= 6.4 cm-1 (absorption ignored).
    Data collected from a small crystal (0.02x0.13x0.23 mm^3) on a Cad-4 Nonius diffractometer, using graphite monochromated Cu Kα radiation and the θ - 2θ scan technique up to θ= 60°. From the 2227 measured reflections , 824 were considered as observed having I> 2σ(I), σ(I) from counting statistics, and kept in refinement calculations. The structure was solved by direct methods (ref. 18) and refined by full-matrix least-squares, minimizing the function Σ $(Fo - Fc)^2$ (ref. 19). The phenyl substituents were treated as rigid groups. The hydrogen atoms were introduced at theoretical positions (d C-H = 1.00 A) and affected an isotropic thermal factor equivalent to that one of the bonded atom, plus 10%. Convergence was reached at R= 0.067, Rw= 0.064 (with R_w= $\{\Sigma w(Fo- Fc)^2/ \Sigma wFo^2\}^{1/2}$ and w= $1/(\sigma^2(Fo)+ 0.00044\ Fo^2)$. No residual higher than 0.26 e A-3 in the final difference map.
    Supplementary material available: tables of atomic coordinates, bond lengths, selected bond and torsion angles.
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