Synthesis of 4-Octuloses, V[+]

4-Octulose Derivatives as Key Intermediates in a New and Short Synthesis of Polyhydroxyindolizidines

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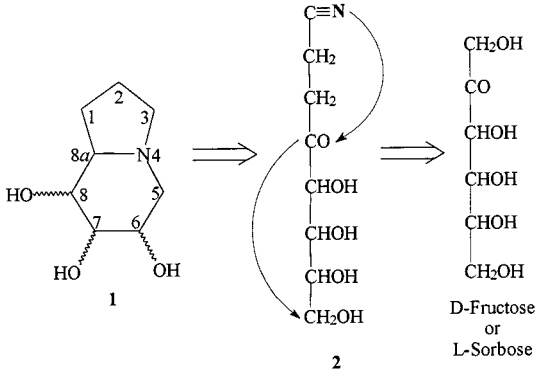
Reaction of **3** with (cyanomethylene)triphenylphosphorane in refluxing dichloromethane or methanol gave mixtures of **4a** and **4b** in ratios of about 3:1 and 1:3, respectively. The same reaction performed with the furanoid isomer **5** afforded **6a** and **6b** in (*E*)/(*Z*) ratios of approximately 9:1 and 1:2, respectively. Catalytic hydrogenation of the α,β-unsaturated nitriles **4** and **6** with either 10% Pd-C or Raney nickel afforded the saturated nitriles **7** and **9**, or the 1-amino-1,2,3-trideoxy-4-octulose derivatives **8** and **10**, respectively. In an attempt to transform **6a** into the appropriate polyhydroxylated branched-chain pyrrolidine **15**, (5*R*,8*S*,9*R*,10*S*)-8,9,10-trihydroxy-1-aza-6-oxaspiro[4.5]decane, which was identified as its peracylated derivative **16**, was isolated. Following an alternative synthetic strategy, partial hydrolysis of compound **9** afforded **17** which was regioselectively transformed into the corresponding derivative **22** via its 8-*O*-*p*-toluenesulfonyl derivative **18**. Removal of the 4,5-*O*-isopropylidene group in **22** with aqueous trifluroacetic acid gave the free octulose **23**, which was hydrogenated in the presence of 10% Pd-C, to afford the expected (6*S*,7*R*,8*R*,8*aR*)-6,7,8-trihydroxyindolizidine (1-deoxycastanospermine, **11**).

Introduction

Potent glycosidase inhibitors such as polyhydroxyindolizidines (**1**)[2] have received much attention in recent years because of their potential as antitumour, anti-HIV, antidiabetic agents, etc. Retrosynthesis of such molecules (see Scheme 1) clearly demonstrates that 4-octulosononitriles (**2**) could be excellent chiral synthetic intermediates, since all that would be necessary would be the transformation of CN to CH_2NH_2 to initially promote an internal reductive amination of the ketone at C-4 to give the required pyrrolidine, and subsequently another cyclization by internal nucleophilic displacement of the appropriate derivative, to form the indolizidine ring. Moreover, the cheap and readily available D-fructose and L-sorbose can be considered excellent starting chiral templates for the enantioselective synthesis of such 4-octulosononitriles en route to these inhibitors, depending on the required stereoisomers. The necessary extension of the sugar chain by two more carbon atoms at C-1, together with the introduction of a nitrogen function to afford the 4-octulosononitrile, could be achieved by Wittig methodology. Finally, the configurations of the stereogenic centres at C-6,7,8 in **1** would be predetermined by the starting hexulose.

Recently, our group has described the use of 4-octulose derivatives in the synthesis of tetra- and pentahydroxyindolizidines.[3]



Scheme 1. Retrosynthesis of **1**

Results and Discussion

The reaction of 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose[4] (**3**) with (cyanomethylene)triphenylphosphorane[5] in refluxing dichloromethane or methanol gave mixtures of (*E*)-**4a** and (*Z*)-**4b** in the ratios 3:1 and 1:3 (GLC analysis), respectively. On the other hand, the reaction of 2,3:4,6-di-*O*-isopropylidene-α-L-*xylo*-hexos-2-ulofuranose[6] (**5**) with the above Wittig reagent afforded (*E*)-**6a** and (*Z*)-**6b** in 9:1 and 1:2 ratios (GLC analysis), respectively. The ^{1}H-NMR spectra of **4a**−**6a** and **4b**−**6b** showed $J_{2,3}$ values of ca. 16 and 12 Hz, respectively, as expected for the (*E*) and (*Z*) configurations.

The above results were in agreement with those previously reported,[7] in which the stereoselectivity depended on the polarity of the solvent.

Catalytic hydrogenation of **4** and **6** in the presence of 10% Pd-C did not affect the cyano group and gave the corre-

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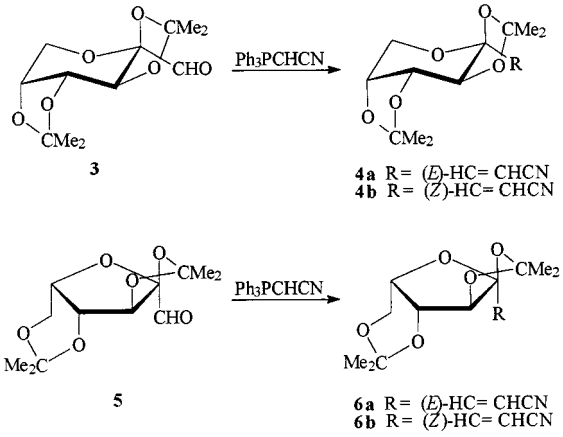
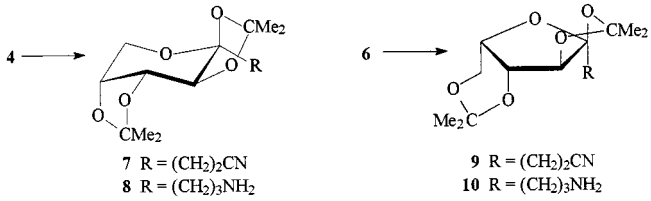


Scheme 2. Formation of 4-octulosononitrile derivatives by Wittig methodology

sponding saturated nitriles **7** and **9**, whereas hydrogenation in the presence of Raney nickel afforded the 1-amino derivatives **8** and **10**, respectively.

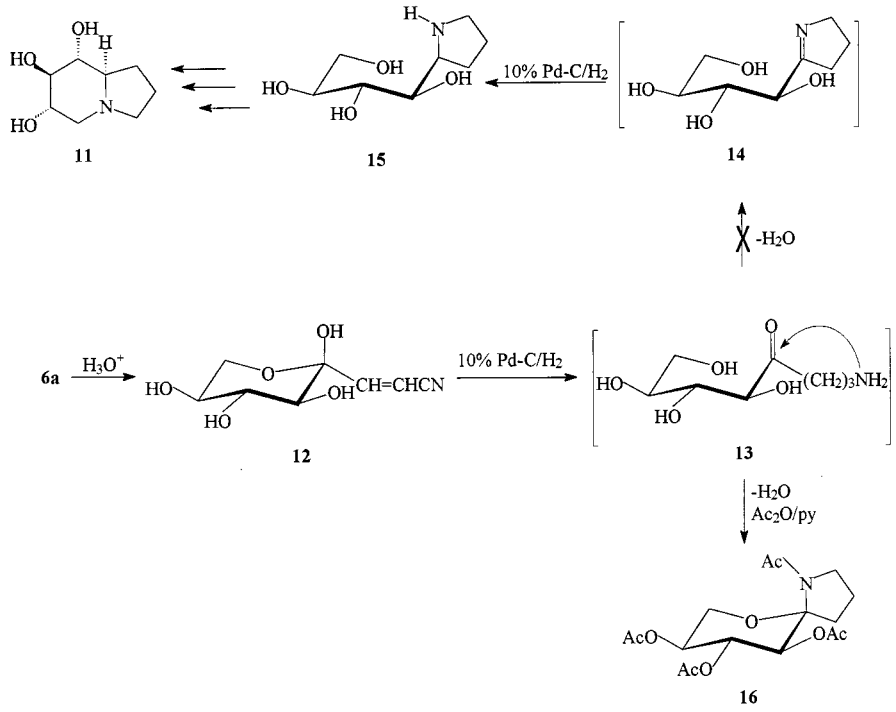


Scheme 3. Synthesis of 1-amino-1-deoxy-4-octulose derivatives

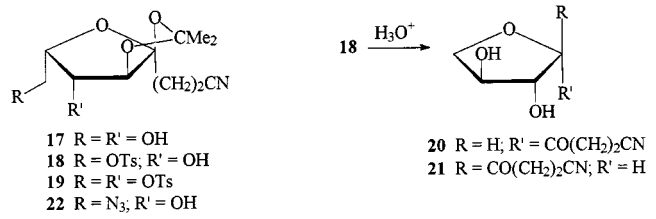
As an example of the potential of the above 4-octulosononitriles as important key intermediates in the synthesis of polyhydroxyindolizidines, an attempt to synthesize 1-deoxycastanospermine (**11**) from **6a**, was carried out. Thus, compound **6a** was deacetonated in an acid medium to give the corresponding (*E*)-**12**, which was subsequently hydrogenated to afford the intermediate 1-amino-1,2,3-trideoxy-L-*xylo*-4-octulose (**13**). Nucleophilic attack of the C-1 amino group at the C-4 carbonyl group in **13** would give the cyclic pyrroline intermediate **14**, which after subsequent hydrogenation, would produce the pyrrolidine **15** (see below, Scheme 4). This, in turn, could be transformed in three steps into the expected **11** according to our previous results.[3] However, the only compound obtained, which was isolated in very low yield and identified from the reaction mixture after peracetylation, was (5*R*,8*S*,9*R*,10*S*)-8,9,10-triacetoxy-1-*N*-acetyl-1-aza-6-oxaspiro[4.5]decane (**16**). An analogue of **16** has been described by Richardson et al.[8] as a byproduct in the synthesis of the corresponding trihydroxyindolizidine starting from an 1-azido-2,3-dideoxy-4-octulose.

On the basis of the above results, a new synthetic strategy was designed by introducing a good leaving group at C-8 that would be attacked by the nitrogen atom of the intermediate pyrrolidine, to form the bicyclic indolizidine skeleton. Thus, compound **9** was partially hydrolyzed to **17**, which was then regioselectively transformed into its 8-*O*-tosylate (**18**). When total deprotection of **18** occurred, an internal cyclization by a nucleophilic attack of 5-OH to C-8 took place (see Scheme 5) to give firstly **20**, which in turn epimerized to **21**.

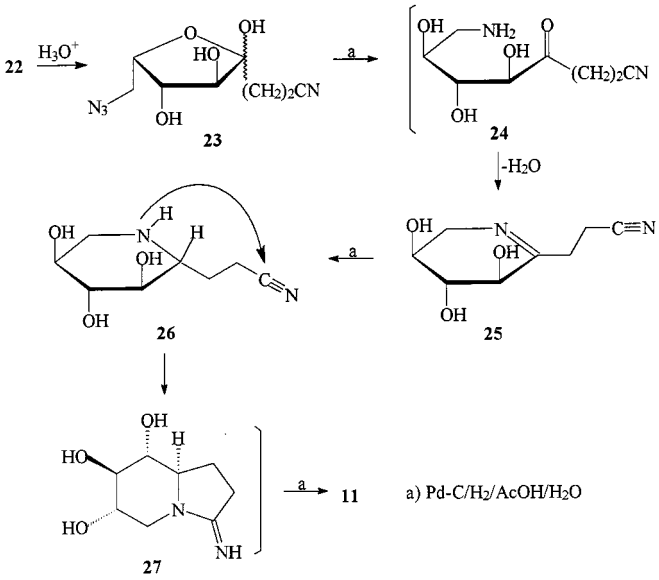
Treatment of **18** with sodium azide gave **22**, and by total deacetonation, the free 4-octulosononitrile **23** was obtained as a mixture of keto-, α- and β-furanose forms (^{13}C-NMR evidence). This was subjected to hydrogenation (Pd-C/H_2/



Scheme 4. Cyclization of **12** to spiroaminoketal **16**



Scheme 5. Formation of 5,8-anhydro-4-octulosononitrile derivatives (**20** and **21**) from **18**



Scheme 6. Double cyclization of **22** to 1-deoxycastanospermine (**11**)

methanol) to afford, after 4 h, the intermediate piperidine **26** together with 1-deoxycastanospermine (**11**) (^{13}C-NMR measurement of an aliquot). The latter was probably formed by a process similar to that found in the literature[9], in which an intermediate similar to **27** was aminated, presumably to be formed by nucleophilic addition of a piperidine moiety to the cyano group (see Scheme 6). Subsequent catalytic reductive deamination of **27** would lead to the indolizidine skeleton. When hydrogenation was carried out over a 24 h period, only **11** could be detected by ^{13}C-NMR spectroscopy.

On the other hand, the highly stereoselective formation of the new stereocentre (C-2) in the piperidine ring (only one isomer for **26** and **11** could be observed in the ^{13}C-NMR spectrum) was crucial for the whole process and accounted for the stereochemistry of the target molecule **11**. This result could be explained by a preferential attack of hydrogen from the bottom face (see Figure 1) of the Δ^1-piperidine (**25**), in accordance with those reported by other

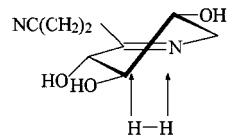


Figure 1. Stereochemical course for the hydrogenation of **25**

authors[10] in which analogous polyhydroxypiperidines were obtained.

Experimental Section

General Remarks: Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried with $MgSO_4$ before being concentrated under reduced pressure. The ^{1}H- and ^{13}C-NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin−Elmer 782 instrument and mass spectra with Fisons mod. Platform II and VG Autospec−Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. GLC was performed with a Perkin−Elmer 8410 gas chromatograph equipped with a flame-ionisation detector and a steel column (2 m × 0.125 in i.d.) packed with 5% OV-17 on Chromosorb W (100−120 mesh) at 200°C. The He flow rate was 30 mL/min, the injection port and the zone-detector temperatures were 250°C. TLC was performed on precoated silica-gel 60 F_{254} aluminium sheets and the spots were detected by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734).

(*E*)- and (*Z*)-2,3-Dideoxy-4,5:6,7-di-O-isopropylidene-β-D-*arabino*-oct-2-ene-4-ulo-4,8-pyranosononitrile (4a and 4b): a) A solution of **3**[4] (1.14 g, 4.4 mmol) and (cyanomethylene)triphenylphosphorane (1.86 g, 6.2 mmol) in dry CH_2Cl_2 (30 mL) was refluxed for 1 h. GLC showed that **3** had disappeared and that two new compounds in a ca. 3:1 ratio were present. The mixture was concentrated and the residue adsorbed onto silica gel and chromatographed (ether/hexane, 1:5) to afford firstly crystalline **4a** (710 mg, 57%), t_R = 4.74 min. − M.p. 87−88°C. − $[\alpha]_D^{26}$ = −26.4 (*c* = 1.14). − IR (KBr): $\tilde{\nu}$ = 2232 cm^{-1} (C≡N), 1387 and 1379 (CMe_2). − NMR data, see Tables 1−3. − $C_{14}H_{19}NO_5$ (281.30): calcd. C 59.77, H 6.81, N 4.98; found C 59.43, H 6.92, N 5.18. − Eluted secondly was crystalline **4b** (280 mg, 23%), t_R = 5.97 min. − M.p. 100−102°C. − $[\alpha]_D^{24}$ = −52 (*c* = 0.73). − IR (KBr): $\tilde{\nu}$ = 2226 cm^{-1} (C≡N), 1384 and 1374 (CMe_2). − NMR data, see Tables 1−3. − $C_{14}H_{19}NO_5$ (281.30): calcd. C 59.77, H 6.81, N 4.98; found C 59.51, H 7.28, N 4.62. − **b)** When reaction of **3** (970 mg, 3.8 mmol) with (cyanomethylene)triphenylphosphorane (1.7 g, 5.6 mmol) was carried out in refluxing dry methanol (30 mL) for 1.5 h, GLC also revealed the presence of **4a** and **4b** in a ca. 1:3 ratio. Resolution of the reaction mixture was performed as above to give **4a** and **4b** in a total yield of 890 mg (84%).

(*E*)- and (*Z*)-2,3-Dideoxy-4,5:6,8-di-*O*-isopropylidene-α-L-*xylo*-oct-2-ene-4-ulo-4,7-furanosononitrile (6a and 6b): a) A solution of **5**[6] (750 mg, 2.9 mmol) and (cyanomethylene)triphenylphosphorane (1.46 g, 4.85 mmol) in dry CH_2Cl_2 (30 mL) was refluxed for 1 h. GLC showed that **5** had disappeared and that two new compounds in a ca. 9:1 ratio were present. The mixture was concentrated and the residue adsorbed onto silica gel and chromatographed (ether/hexane, 1:4) to afford firstly syrupy **6a** (585 mg, 72%), t_R = 5.20 min. − $[\alpha]_D^{28}$ = +26 (*c* = 0.9).− IR (film): $\tilde{\nu}$ = 2231 cm^{-1} (C≡N), 1386 and 1377 (CMe_2). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m/z*: found 304.11595 [M^+ + Na]; calcd. 304.11609. − Eluted secondly was syrupy **6b** (70 mg, 8.6%), t_R = 6.14 min. − $[\alpha]_D^{22}$ = −7 (*c* = 1). − IR (film): $\tilde{\nu}$ = 2227 cm^{-1} (C≡N), 1387 and 1378 (CMe_2). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m/z*: 304.11598 [M^+ + Na]; calcd. 304.11609. − **b)** Reaction of **5** (810 mg, 3.14 mmol) with (cyanomethylene)triphenylphosphorane (1.32 g, 4.39 mmol) was carried out under the above conditions (dry methanol, 30 mL), and refluxed for 1.5 h.

GLC also revealed the presence of **6a** and **6b** in a ca. 1:2 ratio. Resolution of the reaction mixture was performed as above.

2,3-Dideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*arabino*-oct-4-ulo-4,8-pyranosononitrile (7): A solution of **4** (145 mg, 0.52 mmol) in dry methanol (10 mL) was hydrogenated at 1 atm in the presence of 10% Pd-C (55 mg) for 1 h. GLC then revealed the absence of **4** and the presence of a new compound with t_R = 5.22 min. The catalyst was collected, washed with methanol, and the combined filtrate and washings were concentrated. Column chromatography (ether/hexane, 2:1) of the residue gave syrupy **7** (126 mg, 86%). − $[\alpha]_D^{26} = -10$, $[\alpha]_{405}^{26} = -15$ (c = 1). − IR (film): $\tilde{\nu}$ = 2249 cm^{-1} (C≡N), 1383 and 1374 (CMe_2). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m/z*: found 306.13171 [M^+ + Na]; calcd. 306.13174.

1-Amino-1,2,3-trideoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*arabino*-oct-4-ulo-4,8-pyranose (8): a) Compound **4** (3.18 g, 11.3 mmol) in dry methanol (30 mL) containing ammonia was hydrogenated at 5 atm over Raney nickel (8 g) for 24 h. TLC (ether/hexane, 3:2) then revealed the absence of **7** and the presence of a non-mobile compound. The catalyst was filtered off, washed with methanol and the filtrate and washings concentrated to a residue that was subjected to column chromatography (ether/methanol, 5:1 with 0.15 mL of triethylamine) to afford syrupy **8** (2.63 g, 81%), R_f = 0.22 (ether/methanol, 3:2 with 0.15 mL of triethylamine). − $[\alpha]_D^{24} = -9.5$, $[\alpha]_{405}^{25} = -18$ (c = 1). − IR (film): $\tilde{\nu}$ = 3382 cm^{-1} (NH_2), 1382 and 1373 (CMe_2). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m/z*: found 310.16313 [M^+ + Na]; calcd. 310.16304. − **b)** A stirred solution of **7** (120 mg, 0.42 mmol) in anhydrous ether (5 mL) was treated with $LiAlH_4$ (40 mg). After 30 min, TLC (ether/methanol, 3:2 with 0.15 mL of triethylamine) then showed the presence of compound **8**. The excess hydride was destroyed by the cautious addition of aqueous 1 N sodium hydroxide, the organic phase was separated and the aqueous layer extracted with ether (5 mL). The combined extracts were concentrated to a residue that was chromatographed as above to yield **8** (70 mg, 58%).

2,3-Dideoxy-4,5:6,8-di-*O*-isopropylidene-α-L-*xylo*-oct-4-ulo-4,7-furanosononitrile (9): A solution of **6** (160 mg, 0.57 mmol) in dry methanol (5 mL) was hydrogenated at 1 atm in the presence of 10% Pd-C (66 mg) for 1 h. GLC then revealed the absence of **6** and the presence of a new compound with t_R = 5.80 min. The catalyst was collected and washed with methanol, and the combined filtrate and washings were concentrated. Column chromatography (ether/hexane, 2:1) of the residue gave crystalline **9** (141 mg, 88%). − M.p. 99−100°C. − $[\alpha]_{405}^{24} = +9.5$ (c = 1). − IR (KBr): $\tilde{\nu}$ = 2249 cm^{-1} (C≡N), 1383 and 1374 (CMe_2). − NMR data, see Tables 1−3. − $C_{14}H_{21}NO_5$ (283.32): calcd. C 59.35, H 7.47, N 4.94; found C 59.41, H 7.59, N 4.73.

1-Amino-1,2,3-trideoxy-4,5:6,8-di-*O*-isopropylidene-α-L-*xylo*-oct-4-ulo-4,7-furanose (10): a) Compound **6** (1.17 g, 4.16 mmol) was hydogenated at 5 atm in methanol (30 mL) in the presence of Raney nickel (6 g) for 36 h, as above. TLC (ether/hexane, 3:2) then revealed the presence of a non-mobile compound. The catalyst was removed, washed with methanol and the filtrate and washings were concentrated. Column chromatography (see above) afforded syrupy **10** (980 mg, 82%), R_f = 0.20. − $[\alpha]_D^{24} = +3$, $[\alpha]_{405}^{25} = +7$ (c = 1.7). − IR (film): $\tilde{\nu}$ = 3376 cm^{-1} (NH_2), 1384 and 1374 (CMe_2). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m/z*: found 310.16307 [M^+ + Na]; calcd. 310.16304. − **b)** Compound **9** (73 mg, 0.26 mmol) was reduced with $LiAlH_4$ (40 mg) in ether (5 mL) as above. After 30 min, TLC (ether/methanol, 3:2 with a few drops of triethylamine) showed the presence of **10**. Work-up of the reaction mixture as above, followed by column chromatography gave **10** (62 mg, 84%).

(*E*)-2,3-Dideoxy-L-*xylo*-oct-2-ene-4-ulo-4,8-pyranosononitrile (12): A solution of **6a** (2 g, 7.1 mmol) in aqueous 70% trifluoroacetic acid (20 mL) was heated at 50°C for 1 h. TLC (chloroform/methanol, 5:1) revealed the presence of a slower running compound. The mixture was concentrated and repeatly codistilled with water and then toluene. Column chromatography of the residue (chloroform/methanol, 10:1) gave syrupy **12** (950 mg, 67%). − IR (film): $\tilde{\nu}$ = 3445 cm^{-1} (OH) and 2235 (C≡N). − ^{1}H NMR data ([D_4]MeOH): δ = 3.13 (d, 1 H, $J_{5,6}$ = 10.2 Hz, 5-H), 3.48 (dt, 1 H, 7-H), 3.58−3.72 (m, 3 H, 6,8,8′-H), 5.86 (d, 1 H, 2-H), 6.82 (d, 1 H, $J_{2,3}$ = 16.4 Hz, 3-H). − For ^{13}C NMR data see Table 3.

(5*R*,8*S*,9*R*,10*S*)-1-*N*-Acetyl-8,9,10-triacetoxy-1-aza-6-oxaspiro-[4.5]decane (16): A solution of **12** (750 mg, 3.73 mmol) in dry meth-

Table 1. ^{1}H-NMR chemical shifts (δ) with multiplicities for compounds **4**, **6**−**10**, and **17**−**22**

	1-H	2-H	3-H	5-H	6-H	7-H	8-H	8′-H	CMe_2
4a	−	5.89 d	6.65 d	4.14 d	4.59 dd	4.22 ddd	3.87 dd	3.77 dd	1.54 s, 1.45 s, 1.34 s, 1.32 s
4b	−	5.53 d	6.40 d	4.24 d	4.66 dd	4.29 br. d	3.96 dd	3.86 d	1.64 s, 1.53 s, 1.51 s, 1.38 s
6a	−	6.03 d	6.74 d	4.30 br. s	4.34 br. d	4.13 dd	← 4.06 d →		1.51 s, 1.41 s, 1.34 s, 1.33 s
6b	−	5.51 d	6.50 d	4.39 br. s	4.37 br. d	4.80 dd	← 4.06 d →		1.56 s, 1.48 s, 1.42 s, 1.36 s
7	−	2.61 m	2.16 m, 2.02 m	4.06 s	4.54 d	4.18 d	3.77 d	3.67 d	1.49 s, 1.44 s, 1.32 s, 1.31 s
8	2.83 br. t	← 1.95−1.70 m →		4.09 d	4.56 dd	4.20 br. d	3.83 dd	3.71 d	1.51 s, 1.47 s, 1.35 s, 1.33 s
9	−	2.66 m	2.30 m	4.29 s	4.27 d	4.03 t	4.06 dd	3.99 d	1.47 s, 1.42 s, 1.36 s, 1.34 s
10	2.75 m	← 2.05−1.71 2 m →		← 4.25 br. s →			← 4.04 m →		1.47 s, 1.42 s, 1.36 s, 1.34 s
17	−	2.69 t	2.34 br. t	4.32 s	4.22 s	4.39 br. d	4.27 dd	4.10 d	1.51 s, 1.37 s
18	−	2.52 m	2.21 m		← 4.40−4.29 m →			4.12 dd	1.46 s, 1.34 s
19	−	2.47 m	2.15 t	4.48 s	4.77 d	4.39 dt	4.03 dd	3.99 d	1.43 s, 1.32 s
20	−	2.52 t	3.02 dt, 2.90 dt	4.12 s	4.04 d	3.91 br. s	3.96 dd	3.82 d	
21	−	2.55 t	2.89 dt, 2.80 dt	4.40 d	4.17 t	4.00 br. s	4.06 dd	3.68 d	
22	−	2.62 m	2.25 t	4.31 s	4.23 d	4.32 dt	← 3.57 d →		1.48 s, 1.34 s

anol (20 mL) was hydrogenated at 5 atm in the presence of 10% Pd-C (370 mg) overnight. The catalyst was collected and washed with methanol, and the combined filtrate and washings were concentrated. Conventional acetylation of the residue in dry pyridine (5 mL) with acetic anhydride (2.5 mL) followed by usual work-up of the reaction mixture and column chromatography (ether/hexane, 10:1) gave syrupy **16** (100 mg, 8%). − ^{1}H NMR ([D$_4$]MeOH): δ = 1.97, 2.00 and 2.04 (3 s, 9 H, 3 OAc), 2.12 (s, 3 H, NAc), 2.00−2.20 (m, 4 H, 3,3′,4,4′-H), 2.46 (ddd, 1 H, $J_{2',3}$ = 5.7, $J_{2',3'}$ = 8.5 Hz, 2′-H), 2.69 (dt, 1 H, $J_{2,3}$ = $J_{2,3'}$ = 9.5, $J_{2,2'}$ = 18 Hz, 2-H), 3.92 (dd, 1 H, 7*e*-H), 5.01 (ddd, 1 H, $J_{7a,8}$ = 10.8, $J_{7e,8}$ = 6 Hz, 8-H), 5.09 (d, 1 H, 10-H), 5.42 (t, 1 H, $J_{8,9}$ = $J_{9,10}$ = 9.8 Hz, 9-H). − ^{13}C NMR ([D$_4$] MeOH): δ = 20.58, and 20.63 (3 *Me*COO), 27.35 (2-C), 29.86 (3,4-C), 30.89 (*Me*CON), 61.37 (7-C), 68.62 (8-C), 70.85 (9-C), 71.04 (10-C), 106.11 (5-C),169.71, 169.90, 169.93 and 174.37 (4 Ac). − $C_{16}H_{23}NO_8$ (357.35): calcd. C 53.77, H 6.49, N 3.92; found C 53.81, H 6.59, N 4.12.

2,3-Dideoxy-4,5-*O*-isopropylidene-α-L-*xylo*-oct-4-ulo-4,7-furanosononitrile (17): A solution of **9** (3.73 g, 13.2 mmol) in 50% aqueous acetic acid (20 mL) was stirred at room temperature for 24 h. TLC (ether) then revealed the presence of a slower running product. The mixture was neutralized with solid sodium carbonate, concentrated, extracted with dichloromethane and the combined extracts were concentrated. Column chromatography (ether/hexane, 4:1) of the residue gave crystalline **17** (2.47 g, 77%). − M.p. 103−104°C (from ether). − $[\alpha]_D^{24}$ = +17 (*c* = 1).− IR (KBr): $\tilde{\nu}$ = 3323 cm^{-1} (OH), 2251 (C≡N), 1383 and 1375 (CMe$_2$). − NMR data, see Tables 1−3. − $C_{11}H_{17}NO_5$ (243.26): calcd. C 54.31, H 7.04, N 5.76; found C 54.20, H 7.17, N 5.86.

2,3-Dideoxy-4,5-*O*-isopropylidene-8-*O*-*p*-toluenesulfonyl-α-L-*xylo*-oct-4-ulo-4,7-furanosononitrile (18): To a stirred solution of **17** (2.34 g, 9.62 mmol), Et$_3$N (3.2 mL, 23 mmol), and DMAP (50 mg), in dry dichloromethane (40 mL), *p*-toluenesulfonyl chloride (2.75 g, 14.4 mmol) was added portionwise, and the mixture kept at room temperature for 24 h. TLC (ether) revealed the presence of a faster running product. Methanol (10 mL) was then added to the reaction mixture and after 3 h, the mixture was concentrated. The residue was partitioned in ether/water, the organic phase was separated and the aqueous phase extracted with ether (3 × 20 ml). Concentration of the organic extracts followed by column chromatography (ether/hexane, 1:2) of the residue gave crystalline **18** (3.16 g, 83%). − M.p. 119−120°C (from ether). − $[\alpha]_D^{24}$ = +0.6, $[\alpha]_{405}^{24}$ = −6.5 (*c* = 1.22). − IR (KBr): $\tilde{\nu}$ = 3430 cm^{-1} (OH) and 2249 (C≡N). − NMR data, see Tables 1−3. − $C_{18}H_{23}NO_7S$ (397.43): calcd. C 54.39, H 5.83, N 3.53, S 8.07; found C 54.60, H 5.86, N 3.58, S 7.77. A small amount (300 mg) of the syrupy 6,8-di-*O*-*p*-toluenesulfonyl derivative (**19**) was also obtained. − $[\alpha]_D^{24}$ = +16.3 (*c* = 1.6). − IR (film): $\tilde{\nu}$ = 2251 cm^{-1} (C≡N), 1599 (aromatic), and 1373 (CMe$_2$). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m*/*z*: found 574.11816 [M$^+$ + Na]; calcd. 574.11815.

Table 2. ^{1}H-NMR coupling consants (*J*) in Hz for compounds **4**, **6**−**10**, and **17**−**22**

	$J_{1,2}$	$J_{2,3}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$		$J_{7,8'}$	$J_{8,8'}$
4a	−	16.1	2.6	7.9	1.9		0.7	13
4b	−	11.8	2.6	7.9	1.7		0.0	13
6a	−	16.0	0.0	2.4		← 1.8 →		0.0
6b	−	11.8	0.0	2.3		← 1.9 →		0.0
7	−	−	0.0	8.0	0.0		0.0	13
8	6.8	−	2.5	7.9	1.8		0.0	13
9	−	−	0.0	2.1	2.1		0.0	13.3
10	−	−	−	−	−		−	−
17	−	7.0	0.0	0.0	3.4		0.0	12
18	−	−	−	−	−		4.9	9.5
19	−	7.6	0.0	2.8	6.3		5.9	11
20[a]	−	6.8	0.0	0.0	3.1		0.0	9.1
21[b]	−	6.8	3.9	0.0	3.3		0.0	9.1
22	−	7.7	0.0	2.7		← 6.1 →		0.0

[a] $J_{3,3'}$ = 19, $J_{6,OH}$ = 4, $J_{7,OH}$ = 2.5 Hz. − [b] $J_{3,3'}$ = 18.7, $J_{6,OH}$ = 4.5, $J_{7,OH}$ = 3.3 Hz.

Hydrolysis of 18: A solution of **18** (200 mg, 0.5 mmol) in aqueous 70% trifluoracetic acid (1 mL) was kept at room temperature for 60 h. TLC (ether) revealed a slower running compound. The mixture was neutralized with Na_2CO_3, concentrated and the residue was thoroughly extracted with ethyl acetate, then filtered, adsorbed onto silica gel and chromatographed (ether/methanol, 20:1) to afford firstly 5,8-*anhydro*-2,3-dideoxy-L-*xylo*-oct-4-ulosononitrile (**20**) as a syrup. − $[\alpha]_D^{26}$ = +3, $[\alpha]_{405}^{24}$ = +19 (*c* = 0.4). − IR (film): $\tilde{\nu}$ = 3459 and 3384 cm^{-1} (OH), 2252 (C≡N), and 1724 (C=O). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m*/*z*: found 208.05859 [M$^+$ + Na]; calcd. 208.05858. Eluted secondly was syrupy 5,8-*anhydro*-2,3-dideoxy-L-*lyxo*-oct-4-ulosononitrile (**21**). − $[\alpha]_D^{25}$ = −61 (*c* = 0.54). − IR (film): $\tilde{\nu}$ = 3446 and 3395 cm^{-1} (OH), 2251 (C≡N), 1733 and 1720 (C=O). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m*/*z*: found 208.058557 [M$^+$ + Na]; calcd. 208.058578. − The same results were obtained when hydrolysis was performed with 80% aqueous acetic acid at 80°C for 13 h.

8-Azido-2,3,8-trideoxy-4,5-*O*-isopropylidene-α-L-*xylo*-oct-4-ulo-4,7-furanosononitrile (22): To a stirred solution of **18** (2 g, 5 mmol) in dry DMF (15 mL), NaN_3 (1 g, 15.4 mmol) was added and the mixture heated at 90°C for 5 h. TLC (ether) revealed the presence of a faster running compound. The reaction mixture was concentrated, diluted with water (30 mL) and extracted with ether (4 × 25 mL). The combined extracts were washed with brine, then water and concentrated to a residue that was chromatographed (ether/hexane, 1:2) to afford syrupy **22** (1.19 g, 88%). − $[\alpha]_D^{24}$ = +22.5 (*c* = 1.5). − IR (KBr): $\tilde{\nu}$ = 3456 cm^{-1} (OH), 2252 (C≡N), and 2106 (N_3). − NMR data, see Tables 1−3. − HRMS (LSIMS); *m*/*z*: found 291.107085 [M$^+$ + Na]; calcd. 291.106925.

(6*S*,7*R*,8*R*,8a*R*)-6,7,8-Trihydroxyindolizidine (1-Deoxycastanospermine) (11): A solution of **22** (1.1 g, 4.1 mmol) in aqueous 50% trifluoroacetic acid (10 mL) was stirred at room temperature for 24 h. TLC (ether) showed the presence of a slightly moving compound. Work-up of the reaction mixture as above gave after column chromatography (chloroform/methanol, 35:1) 8-azido-2,3,8-trideoxy-L-*xylo*-4-octulosononitrile (**23**, 805 mg, 86%) as a syrup. − $[\alpha]_D^{26}$ = −9.7 (*c* = 0.45). − IR (film): $\tilde{\nu}$ = 3419 cm^{-1} (OH), 2254 (C≡N), 2109 (N_3), and 1724 (C=O). − ^{13}C NMR ([D$_4$]MeOH): δ = 11.64 (2-C, α-f), 12.11 (2-C, β-f), 12.46 (2-C, keto form), 31.67 (3-C, keto form), 35.26 (3-C, α-f), 35.94 (3-C, β-f), 52.01 (8-C, β-f), 52.45 (8-C, α-f), 54.51 (8-C, keto form), 72.05, 73.92, 77.23, 77.81, 78.32, 80.77, 81.09 and 81.63 (5,6,7-C, α-f, β-f and keto form), 102.73 (4-C, β-f), 107.62 (4-C, α-f), 120.82 (1-C, keto form), 121.40 and 121.46 (1-C, α-f and β-f), 210.39 (C-4, keto form). − HRMS (LSIMS); *m*/*z*: found 251.075588 [M$^+$ + Na]; calcd. 251.075625. − Compound **23** (650 mg, 2.85 mmol) in aqueous 20% acetic acid (25 mL) containing NaOAc (1 g) was hydrogenated at 4 atm in the presence of 10% Pd-C (100 mg) for 15 h to afford the title compound (**11**, 285 mg, 58%) as white needles. − M.p. 179−180°C (dec.) (ref.[11] m.p. 178−181°C). − $[\alpha]_D^{29}$ = +50 (*c* = 1.2, MeOH) {ref.[11] $[\alpha]_D^{29}$ = +50.6 (*c* = 0.2, MeOH)}. − IR (KBr): $\tilde{\nu}$ = 3379 and 3265 cm^{-1} (NH and OH). − ^{1}H NMR ([D$_4$]MeOH) (inter alia): δ = 2.01 (t, 1 H, $J_{5\alpha,5\beta}$ = $J_{5\alpha,6}$ = 10.5 Hz, 5α-H), 2.23 (q, 1

Table 3. ^{13}C-NMR data for compounds **4**, **6**−**10**, **12**, and **17**−**22**

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	CMe$_2$	CMe_2
4a	116.60	101.86	151.93	100.59	73.18	69.80	70.21	61.50	109.43, 109.38	26.15, 25.91, 24.77, 24.11
4b	115.16	99.80	148.95	100.67	73.31	69.72	70.20	61.34	110.03, 109.24	26.66, 25.82, 24.61, 24.10
6a	116.64	102.93	150.47	113.23	87.72	73.40	73.05	60.21	111.18, 97.62	27.04, 26.16, 29.05, 18.59
6b	115.17	100.28	147.95	114.04	88.27	73.54	73.22	60.17	111.38, 97.56	27.25, 26.11, 28.94, 18.76
7	120.03	11.60	36.80	102.11	73.62	70.22	70.51	61.05	108.98, 108.09	26.20, 25.83, 24.86, 23.98
8	42.36	27.38	38.06	103.96	73.70	70.51	70.73	60.84	108.77, 107.35	26.34, 25.77, 25.08, 24.00
9	119.96	12.50	33.98	113.33	86.60	73.47	72.29	60.30	111.58, 97.53	27.25, 26.46, 28.95, 18.67
10	42.04	35.07	34.94	115.49	86.53	73.67	71.95	60.48	111.03, 97.35	27.52, 26.77, 28.99, 18.77
12	118.04	102.15	154.82	96.93	75.58	71.18	75.52	63.54		
17	120.91	12.45	33.81	113.21	87.51	79.44	77.23	61.43	111.57	27.21, 26.34
18	119.86	12.16	33.56	113.33	86.84	78.42	74.16	66.53	111.97	27.19, 26.36
19	119.18	11.97	33.66	113.11	84.83	81.25	76.80	65.80	112.91	26.94, 26.43
20	120.26	10.52	33.78	209.02	89.79	80.63	74.95	74.17		
21	120.30	10.36	35.40	207.07	85.81	78.02	76.24	74.20		
22	119.96	12.26	33.87	113.17	87.15	79.32	75.16	49.28	111.91	27.24, 26.42

H, $J_{3\alpha,3\beta} = J_{2\alpha,3\alpha} = J_{2\beta,3\alpha} = 9$ Hz, 3α-H), 3.02 (dt, 1 H, 3β-H), 3.12 (dd, 1 H, $J_{5\beta,6} = 5.2$ Hz, 5β-H), 3.58 (ddd, 1 H, $J_{6,7} = 9.2$ Hz, 6-H). − ^{13}C NMR ([D$_4$]MeOH): δ = 22.67 (1-C), 29.14 (2-C), 54.51 (3-C), 57.40 (5-C), 69.24 (8*a*-C), 72.06 (6-C), 76.43 (8-C), 80.81 (7-C). − HRMS (LSIMS); *m/z*: found 196.094987 [M$^+$ + Na]; calcd. 196.094963.

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