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Double Reductive Amination of L-*arabino*-Hexos-5-uloses: a Diastereoselective Approach to 1-Deoxy-D-galactostatin Derivatives(#)(°)

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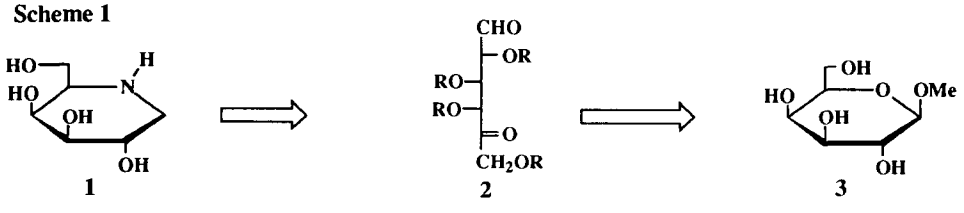
Abstract: The double reductive amination of L-*arabino*-hexos-5-ulose with benzhydrylamine and $NaBH_3CN$ takes place in a diastereospecific manner giving in moderate chemical yield (36 %) the galactosidase inhibitor 1-deoxy-D-galactostatin. The aminocyclization of 2,6-di-*O*-benzyl-L-*arabino*-hexos-5-ulose is more complicated giving results dependent from the type of amine: with ammonia or methylamine a mixture of C-5 epimeric 1-deoxyazapyranoses (D-*galacto*/L-*altro* ratio ≈ 4:1) is obtained in 45-65 % combined yield, while with benzhydrylamine substantial amounts of an acyclic 1-deoxy-1-benzydrylamino-hexitol (10 % yield) is isolated together with the expected 1-deoxy-azasugars of the D-*galacto* and L-*altro* series.

Polihydroxylated piperidines, also called azasugars for their formal derivation by replacement of the ring oxygen of monosaccharides by nitrogen, constitute a class of intensely investigated compounds, owing to their glycosidase inhibitory activity[2], that could be usefully exploited for the treatment of several diseases. A marked activity as galactosidase inhibitors is displayed by galacto-configurated azasugars[3], and, between them, by 1-deoxy-D-galactostatin **1**[4]. We present in this communication an expeditious and diastereoselective approach to **1**[5] and some of its derivatives by double reductive amination of a 1,5-dicarbonyl monosaccharide with $NaBH_3CN$ in the presence of a primary amine. The rationale of our synthetic procedure is depicted in the Scheme 1 and requires, as synthetic intermediates, L-*arabino*-hexos-5-uloses (**2**), easily obtained starting from methyl β-D-galactopyranoside **3**[6].

Scheme 1



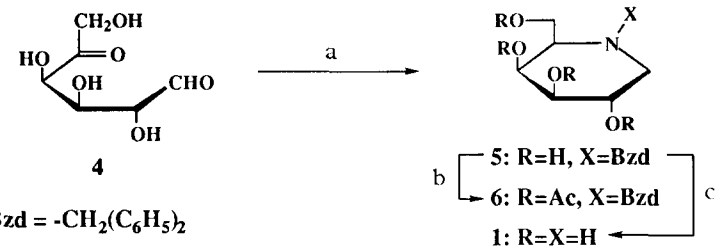
(#) Dedicated to the memory of Professor Giuseppe Bellucci.

(°) Part 7 of the series: "Rare and Complex Saccharides from D-Galactose and Other Milk Derived Carbohydrates". For part 6, see Ref 1.

The unprotected L-*arabino*-hexos-5-ulose (4)[6] was treated with $NaBH_3CN$ and benzhydrylamine under conditions that differ little from those used by Baxter and Reitz[7] for the aminocyclization of hexose-5-uloses of the D-*xylo* and D-*lyxo* series. The reaction product, isolated by simple partition between water and chloroform of the residue obtained after evaporation of the solvent from the reaction mixture, was constituted (^{13}C-NMR) of *N*-benzydryl-1-deoxy-D-galactostatin[§] (**5**) as the sole component, apart of about 20% of unreacted amine. A flash-chromatographic separation led to pure **5** (36 % isolated yield), showing NMR parameters (Tables 1 and 2) in good agreement with the proposed structure. Interestingly, the tetra-*O*-acetate **6**, obtained from **5** by conventional acetylation (Ac_2O/Py) showed a vicinal proton coupling constant pattern (Table 1) strongly different from that of **5**, pointing to a complete shift toward a $^1C_4$ conformation, characterized by the absence of high J values arising from trans-diaxial vicinal hydrogens. The transformation of **5** into the known parent azasugar **1** was achieved through hydrogenolytic *N*-deprotection with Pd on charcoal in MeOH containing an excess of HCl in order to avoid the *N*-methylation that, as demonstrated by Kato and coll.[8], is frequently encountered as side-reaction during the palladium-catalyzed hydrogenolysis of nojirymicin derivatives. Although we were not able to obtain good crystals of **1**, probably owing to its high hygroscopicity, their ^{13}C-NMR data (Table 2) were essentially identical with the reported ones[5e], fully confirming the proposed structure of **5**.

Despite the rather low yield, the aminocyclization of **4** provided an useful approach to **1** because of its high diastereoselectivity, that, within the accuracy of ^{13}C-NMR analysis, resulted complete. With respect to previous work,[7] the aldohexos-5-ulose of the L-*arabino* series, **4**, behave thus much more as the D-*xylo* (ratio of 1-deoxyazasugars D-gluco/L-ido = 96:4) than as the D-*lyxo* (D-manno/L-gulo 67:33) analogues, a fact that ruled out the hypothesis of a specific role played by the 4-hydroxyl group in the stereodetermining reaction step.

Scheme 2



Bzd = $-CH_2(C_6H_5)_2$

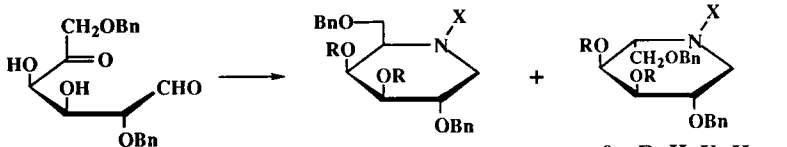
Reagents: a) Bzd-NH_2, $NaBH_3CN$/MeOH, -78°C-->r.t.; b) Ac_2O/Py; c) H_2/$Pd(OH)_2$-C/MeOH

After this result, we turned our attention to the aminocyclization of the 2,6-di-*O*-benzyl derivative **7**, in which the presence of the two liphophilic substituents could permit the use of primary amines with smaller alkyl substituents or even with ammonia, without isolation problems caused by the hydrophylicity of products. Following this idea, **7** was allowed to react with $NaBH_3CN$ and various ammonium salts (formiate, bromide, acetate) obtaining, as expected, the product of aminocyclization, the 1-deoxy-D-galactostatin derivative **8**, but in a non-diastereospecific way, its C-5 epimer, the 2,6-di-*O*-benzyl-1-deoxy-L-altrostatin (**9**), being also formed in amounts quite independent (**8**:**9** ratios from 80:20 to 85:25) of the type of the anionic counterpart of the salts.

[§]1-Deoxy-D-galactostatin (**1**) was also reported as 1-deoxy-D-*galacto*-nojirimycin, as [2R-(2α,3α,4α,5β)]-2-hydroxymethyl-3,4,5-piperidinetriol (Chemical Abstract indexing) and as 1,5-dideoxy-1,5-imino-D-galactitol; we prefer this latter systematic name preserving monosaccharide numbering.

The combined yield of the azasugar mixtures, simply obtained by extraction of the neutral by-products from the acidified residue followed by alkalinization and extraction with solvent, was in these cases, a more accettable 55% (isolated). The two C-5 epimers **8** and **9** were easily separated by flash-chromatography on silica and their structures inferred by NMR analysis.

Scheme 3



7

8 : R=H, X=H **9 : R=H, X=H**

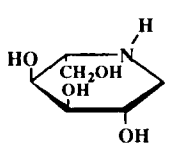
10: R=H, X=Me **11: R=H, X=Me**

12: R=Ac, X=Me **13: R=Ac, X=Me**

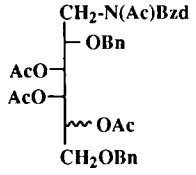
14: R=H, X=Bzd **15: R=H, X=Bzd**

16: R=Ac, X=Bzd **17: R=Ac, X=Bzd**

In the case of compund **8**, the high values of $J_{1',2}$ and $J_{2,3}$ (10.43 and 9.30 Hz, respectively) point to a practically complete preference for a $^4C_1$(D) conformation, whereas for the L-altro derivative **9**, a $^1C_4$(L) conformation was desumed from the $J_{4,5}$ value (10.03 Hz) in accordance with two trans-diaxial configurated hydrogens. This conformational difference between the two steric series is expected on the basis of the tendence of the more sterically demanding 6-hydroxymethyl group to assume an equatorial disposition. As a further structure confirmation, 2,6-di-*O*-benzyl derivative **8** was submitted to catalytic hydrogenolysis giving the unprotected azasugar **1**, identical to the previously prepared sample. Similarly, **9** was quantitatively transformed into the previously unreported 1,5-dideoxy-1,5-imino-L-altritol (1-deoxy-L-altrostatin, **18**), the NMR spectra of which in C_5D_5N at 80°C were completely solved (Tables 1 and 2) suggesting the prevalence of a $^1C_4$(L) conformation.



18



19

In order to improve the rather low yield, a rough screening of some reaction parameters (presence of crushed and activated 3 Å molecular sieves, careful control of pH during the reaction, etc.) was performed on the basis of previously reported aminocyclization methods,[9] without any apparent change. An appreciable yield increase was obtained using the reaction conditions recently reported for an interesting "tandem Michael addition-reductive amination" of 7-oxo-acrylates[10]. Thus, when **7** was treated with a large excess of CH_3COONH_4 and $NaBH_3CN$ at 60 °C, a rapid reaction took place and, after 2 h, the usual work-up and flash-cromatography led to a much more satisfactory isolated yield of **8** (48 %) and **9** (18 %). The ^{13}C-NMR analysis of the crude reaction product indicated, however, that at the higher reaction temperature, the diastereoselectivity dropped to a **8/9** ratio of 70:30.

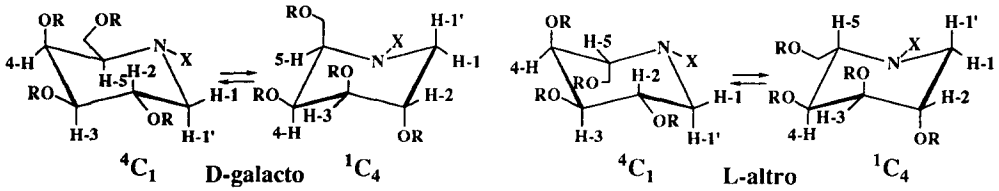
The extension of the reaction to a simpler primary amine, *i.e.* methylamine, gave results very close to those obtained with ammonia, in terms of diastereoselection (D-galacto/L-altro = 65:35 in the reaction at 60°C and

75:25 at room temp.), although less satisfactory yields were obtained (**10** and **11**, 35 and 15% respectively at 60°C and 32 and 13% at room temp.). NMR spectra of **10** and **11** were completely resolved (Tables 1 and 2); it was observed that the vicinal protonic *J* of the D-galacto derivative **10** differs very little, if any, from the values of the corresponding *N*-unprotected derivative **8**, pointing again to a $^4C_1$(D) conformation, while in the case of the L-altro analogue **11**, some differences in the *J* pattern with respect to **9** point to the presence of some minor conformational deviations. Finally, another interesting point arises from the remarkable deshielding of C-1 and C-5 ($\Delta\delta$ 7-11 ppm) induced both in the D-galacto and in L-altro series by *N*-methylation.

Table 1. Selected ^{1}H-NMR data (δ, ppm; *J*, Hz; CD3CN) of 1,5-dideoxy-1,5-imino-D-galactitol and 1,5-dideoxy-1,5-imino-L-altritol derivatives.

	5	**6**	**1**[a]	**8**	**10**	**12**	**9**	**11**	**13**	**18**[b]
H-1	2.94	2.97	3.06	3.25	3.01	3.16	2.84	2.67	2.83	3.51
H-1'	2.00	2.77	2.31	2.38	1.92	2.14	2.84	2.54	2.66	3.10[c]
H-2	3.73	4.72	3.70	3.62	3.63	3.86	3.52	3.52	3.67	4.26
H-3	3.33	5.13	3.41	3.45	3.32	4.77	3.96	3.77	5.23	4.46
H-4	4.06	5.37	3.94	3.87	3.85	5.50	3.69	3.74	5.25	4.39
H-5	2.66	3.52	2.68	2.91	2.20	2.50	2.78	2.40	2.66	3.40
H-6	3.92	4.60	3.58	3.57	3.65	3.65	3.71	3.69	3.68	4.25
H-6'	3.88	4.26	3.53	3.54	3.65	3.36	3.54	3.65	3.52	4.16
$J_{1,1'}$	11.94	14.49	12.65	12.47	11.10	11.27	--	12.50	12.54	13.15
$J_{1,2}$	3.89	2.23	5.26	5.08	4.89	4.95	2.18	4.29	5.18	2.11
$J_{1',2}$	7.57	2.88	10.79	10.43	10.25	10.34	--	2.96	3.38	3.02
$J_{2,3}$	7.32	4.06	9.64	9.30	9.30	9.93	3.80	4.61	5.66	4.10
$J_{3,4}$	3.40	3.28	3.14	3.07	3.39	3.55	3.32	2.95	3.12	3.40
$J_{4,5}$	3.32	5.50	1.21	1.46	1.70	1.85	10.03	7.70	7.05	9.14
$J_{5,6}$	5.33	7.97	6.62	6.78	5.31	5.20	3.30	3.65	3.83	4.30
$J_{5,6'}$	4.39	2.75	6.58	6.40	--	7.46	3.80	3.86	3.56	5.84
$J_{6,6'}$	11.62	12.34	11.20	n.d.	--	9.24	9.85	n.d.	10.58	10.43

[a]In D_2O with dioxane at 67.8 ppm as internal standard; [b]In C_5D_5N at 80°C; [c]A long range coupling ($J_{1',3}$ = 0.96 Hz) is also present.



Compounds **10** and **11** were also transformed into their 3,4-di-*O*-acetates, **12** and **13**, that were fully characterized by NMR spectroscopy (Tables 1 and 2). The conformational behaviour of these derivatives were again different: while the D-galacto derivative **12** shows *J* values in close accordance with a $^4C_1$(D) conformation, for the L-altro derivative **13** acetylation increases the deviations from the $^1C_4$(L) conformation. A

marked conformational change after acetylation of the hydroxyl groups was observed, as previously discussed, also for compound **5**; we intend to study further the interesting conformational features of these compounds and present the results in a separate paper.

Table 2. Selected ^{13}C-NMR data (δ, ppm; *J*, Hz; CD_3CN) of 1,5-dideoxy-1,5-imino-D-galactitol and 1,5-dideoxy-1,5-imino-L-altritol derivatives.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
5	51.11	69.70	74.89	70.94	61.59	60.34
6	46.36	68.31	71.46	70.30	55.99	60.13
1[a]	50.28	69.40	76.27	70.46	60.01	62.59
8	48.36	77.70	75.85	70.52	58.86	71.09
10	59.55	77.01	75.97	72.05	65.92	71.38
12	59.61	73.80	75.72	69.64	63.78	69.40
14	47.02	78.42	73.21	70.72	60.16	69.09
16	45.94	76.50	71.92	69.66	58.14	67.26
9	43.31	78.26	69.91	67.53	55.66	70.76
11	53.76	76.82	68.35	68.00	64.05	69.89
13	54.49	74.31	70.23	69.57	62.51	66.52
15	48.13	n.d.	73.07	71.53	59.94	66.54
17	48.34	73.60	73.43	71.55	58.02	66.83
18[b]	46.46	71.12	72.35	67.22	57.34	62.31

[a]In D_2O with dioxane at 67.8 ppm as internal standard; [b]In C_5D_5N at 80°C.

As a further structure confirmation, 2,6-di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-galactostatin, **8**, was transformed into **10**, by *N*-methylation with CH_2O and $NaBH_3CN$ (77 % yield of pure **10**) according to Borch.[11]

As an attempt to evidenciate some of the side-reactions causing the rather low yields, we finally studied the aminocyclization of **7** with benzydrylamine, in order to enhance the liposolubility of the by-products arising by incorporation of the amine reagent. The ^{13}C NMR spectrum of the crude reaction product showed four separated signals at δ 47.02, 48.13, 49.04, and 49.47 ppm (relative ratio ≈ 45:15:15:25), all giving negative signals in DEPT 135 experiments and evidently due to N-substituted methylene carbons. Unfortunatly, all attempts to separate the components of this mixture on silica were completely negative. Conversely, after standard acetylation (Ac_2O/pyridine), TLC analysis (hexane/AcOEt 75:25) showed two principal well separated spots (*Rf* 0.41 and 0.12) together with some minor components. A flash-chromatography allowed a complete separation of the two principal products. The faster moving product was constituted by an about 70:30 mixture (38% combined yield) of the two azasugars of the D-galacto (**16**) and L-altro (**17**), as confirmed by their ^{13}C NMR parameters (Table 2). The structure of **16** and **17** was fully confirmed by transesterification (MeONa/MeOH), giving a mixture of **14** and **15** (δ C-1 at 47.02 and 48.13 ppm), that was subjected to catalytic hydrogenolysis (H_2/Pd-C/MeOH-AcOH). An about 70:30 mixture of the parent azasugars **1** and **18** was thus finally obtained, giving spectral parameters identical to those of the previously prepared pure and separated samples.

The less mobile product was constituted by a sole compound giving in the ^{13}C NMR spectrum three acetoxy (δ 21.06, 21.19 and 21.32 ppm) and one *N*-acetyl signals (δ 22.90 ppm); the presence of these signals

and the J values (see Experimental) agree well with an acyclic structure **19**, arising from **7** by reductive amination of the aldehyde group and reduction of the keto one, and isolated in 10% yield. Although the assignement of the configuration at C-5 of **19** cannot be inferred from a simple NMR analysis and remains an open problem, if one thakes into account the composition of the crude aminocyclization product, one can conclude that the reduction at C-5 take place with a low stereoselectivity, the less abundant C-5 epimer of **19** being lost during flash-chromatography. The formation of similar products was observed by Baxter and Reitz[7c] during the aminocyclization of D-*xylo*-hexos-5-ulose with 4-fluoroaniline, and, to a lesser extent, with butylamine. Although the reduction of the carbonyl function with $NaBH_3CN$ was generally considered operative only at pH values of 3-4[9a], it is possible that in the case of polyhydroxylated compounds, an activation of the carbonyl group takes place, mainly in the presence of *O*-alkyl substituents, giving rise to acyclic compounds such as **19**, when the formation of the intermediate iminium ion is slowed down by steric interferences between the large substituents at the nitrogen atom and some of the protecting groups on the monosaccharide hydroxyl groups.

In conclusion, the usefulness of the aminocyclization of hexos-5-uloses for the obtention of biologically interesting azasugars is further demostrated with this work. Despite the moderate yield of the reaction, the complete diastereoselectivity of the reaction of the unsubstituted dicarbonyl L-*arabino* derivative **4** offers a new attractive approach to 1-deoxy-D-galactostatin derivatives. Interestingly, the protection as benzyl ethers of the OH-2 and OH-6 groups decreases the diastereoselectivity and, with a bulky primary amine, also the chemoselectivity of the reaction, suggesting an important role of steric factors in the formation of intermediate iminium ions.

EXPERIMENTAL

Melting points wee determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20±2°C; specific rotations are expressed in $deg \cdot cm^2 \cdot dag^{-1}$. ^1H-NMR spectra (internal TMS) were recorded with a Bruker AC 200 instrument at 200 MHz. First-order spectral analysis was performed whenever possible, otherwise spectra were simulated with PANIC (Bruker) or LAOCN-5 (QCPE QCMP 049) computer programs. Chemical shifts and coupling constants values were confirmed, when necessary, with COSY or J-RES experiments. ^{13}C-NMR spectra were recorded with the same spectrometer at 50 MHz. Assignments were made with the aid of DEPT and HETCOR experiments. All reactions were followed by TLC on Kieselgel 60 F_{254} with detection by UV light or with ethanolic 10% phosphomolibdic or sulphuric acid, and heating. Kieselgel 60 (Merck, 70-230 and 230-400 mesh, respectively) was used for column and flash cromatography. Solvents were distilled and stored over 4 Å molecular sieves activated at least 24 h at 400°C. $MgSO_4$ was used as the drying agent for solutions.

The following standard procedure was used for acetylations: a solution of the compound in a 2:1 (*v/v*) mixture (15 ml/mmol) of pyridine and Ac_2O was left at room temperature for 24 h, then repeatedly co-evaporated *in vacuo* with toluene and the residue was purified by chromatography on silica with the stated eluant system.

***N*-Benzhydryl-1,5-dideoxy-1,5-imino-D-galactitol (5) and its 2,3,4,6-tetra-*O*-acetyl derivative 6.**

To a solution of benzhydrylamine (0.45 ml, 2.61 mmol) and AcOH (0.23 ml, 4.02 mmol) in anhydrous MeOH (50 ml), cooled at -78°C under Ar, was slowly added a solution of **4**[1] (500 mg, 2.81 mmol) in anhydrous MeOH (30 ml) followed by a solution of $NaBH_3CN$ (411 mg, 6.54 mmol) in the same solvent (20 ml). The reaction mixture was stirred for 2 hr at -78°C, slowly allowed to reach room temperature and further stirred for 48

h, until TLC analysis showed a complete disappearance of the starting material. The solvent was evaporated under reduced pressure and the residue treated with satd aq. Na_2CO_3 (20 ml) and repeteadly extracted with $CHCl_3$ (6 x 30 ml); the combined extracts, dried and evaporated, left a semisolid residue constituted (TLC, $CHCl_3$/MeOH 9:1) by benzhydrylamine (R_f 0.61) and **5** (R_f 0.38). A flash-chromatography ($CHCl_3$/MeOH 19:2 + 0.2% sat. acq. NH_4OH) gave pure **5** (336 mg, 36% yield) as a crystalline solid, m.p. 180-1°C (from EtOH); $[\alpha]_D$ + 41.3 (*c* 0.6, $CHCl_3$); ^{1}H-NMR data (CD_3CN): see Table 1 and δ 5.30 (s, 1 H, -*CH*Ph_2, 7.20-7.40 (m, 10 H, 2 x C_6H_5); ^{13}C-NMR data: see Table 2 and δ 67.56 (*C*HPh_2); 127.6-130.2 (10 C, aromatic CH); 140.92 and 144.13 (2 x quatern. aromatics). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0; N, 4.3. Found: C, 69.5; H, 7.0; N, 4.5.

Routine acetylation of **5** (136 mg, 0.41 mmol), gave after column chromatography on silica (hexane/AcOEt 1:1), pure *2,3,4,6-tetra-O-acetyl-N-benzhydryl-1,5-dideoxy-1,5-imino-D-galactitol* (**6**) as a waxy solid (196 mg, 96 % yield); R_f 0.34 (hexane/AcOEt 6:4); $[\alpha]_D$ + 64.5 (*c* 0.6, $CHCl_3$); ^{1}H-NMR data (CD_3CN): see Table 1 and δ 2.04 and 2.13 (2 s, 12 H, 4 x *CH*$_3$COO), 5.09 (s, 1 H, *CH*Ph_2, 7.18-7.50 (m, 10 H, 2 x C_6H_5); ^{13}C-NMR data: see Table 2 and δ 21.26 and 21.00 (4 x *C*H_3COO), 69.33 (*C*HPh_2; 128.0-129.5 (10 C, aromatic CH), 143.38 and 144.73 (2 x quatern. aromatics), 170.31,170.53, 170.66 and 171.41 (4 x CH_3*C*OO). Anal. Calcd for $C_{27}H_{31}NO_8$: C, 65.2; H, 6.3; N, 2.8. Found: C, 65.8; H, 6.2; N, 3.0.

1,5-Dideoxy-1,5-imino-D-galactitol (1).

A solution of **5** (164 mg, 050 mmol) in anhydrous MeOH (5 ml) and 1% methanolic HCl (2 ml) containing 120 mg of 10 % Pd on charchoal was stirred at room temperature under H_2 for 2 h, until the starting material had disappeared (TLC analysis, $CHCl_3$/MeOH 19:1). The suspension was filtered over a small layer of Celite, neutralized with an excess IRA 400(OH^-) (2 ml, 10 min stirring), filtered over Celite and evaporated under reduced pressure; the residue was repeatedly extracted with hexane in order to eliminate the diphenylmethane, the semisolid residue (82 mg, quantitative yield) constituted by pure **1** (NMR) resisted to all attempts of crystallization; $[\alpha]_D$ + 40.5 (*c* 1.5, H_2O); lit.: $[\alpha]_D$ + 52.6 (*c* 1.3 H_2O)[5e]; NMR data: see Table 2.

2,6-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-galactitol (8) and 2,6-di-*O*-benzyl-1,5-dideoxy-1,5-imino-L-altritol (9).

A typical procedure for the aminocyclization of **7** with ammonium salts was the following. To a solution of ammonium formiate (54 mg, 0.86 mmol) in dry MeOH (10 ml), cooled at -78°C under Ar, was added in the order a solution of **7** (284 mg, 0.79 mmol) in dry MeOH (20 ml) and a solution of $NaBH_3CN$ (107 mg, 1.69 mmol) in MeOH (10 ml); after 2 h stirring at -78°C the reaction mixture was allowed to warm to room temperature and further stirred until the starting material had disappeared (TLC) (90 h). The reaction was quenched by successive additions of 1% methanolic HCl and stirred until a persistent pH 1 value was reached (3 h); the solution was reduced to about 5 ml, diluted with CH_2Cl_2 (40 ml) and washed with acqueous *1N* HCl (3 x 10 ml). The acid acqueous extracts were brought to pH 9-10 with aqueous *5N* NaOH and extracted with CH_2Cl_2 (3 x 20 ml). The organic layers were collected, dried ($MgSO_4$) and evaporated to leave a crude residue constitued (^{13}C-NMR) exclusively by a mixture of compounds **8** and **9** (150 mg, 55 % yield) in the ratio of 81:19, measured on the relative intensities of the ^{13}C-NMR signals [δ (CD_3CN) 48.36 and 43.31, respectively). A flash-chromatography on silica gel (AcOEt/hexane 9:1 followed by AcOEt/MeOH 95:5) allowed a complete separation of the components.

2,6-Di-O-benzyl-1,5-dideoxy-1,5-imino-D-galactitol (**8**, 83.2 mg, 30 % yield) is a syrup, R_f 0.41 (AcOEt/MeOH 95:5); $[\alpha]_D$ + 40.5 (*c* 0.8, $CHCl_3$); ^{1}H-NMR data (CD_3CN): see Table 1 and δ 4.49 and 4.61 (2 s, 4 H, 2 x

C*H*$_2$Ph), 7.25-7.38 (m, 10 H, aromatics); ^{13}C-NMR data: see Table 2 and δ 72.83 and 73.63 (2 x C*H*$_2$Ph), 128.2-129.2 (10 C aromatic CH), 139.43 and 140.13 (2 x quaternary aromatic). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 68.91; H, 7.57; N, 3.88.

2,6-Di-O-benzyl-1,5-dideoxy-1,5-imino-L-altritol (**9**, 22.0 mg, 8 % yield) is a syrup, R*f* 0.17 (AcOEt/MeOH 95:5); $[\alpha]_D$ + 24,0 (*c* 1,0, CHCl3); ^{1}H-NMR data (CD3CN): see Table 1 and δ 4.49 (s, 2 H, C*H*$_2$Ph), 4.56 (AB system, $J_{A,B}$= 11.88 Hz, C*H*$_2$Ph), 7.26-7.34 (m, 10 H, aromatics); ^{13}C-NMR data: see Table 2 and δ 71.44 and 73.86 (2 x C*H*$_2$Ph), 128.4-129.3 (10 C aromatic CH), 139.64 and 139.75 (2x quaternary aromatic). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.58; H, 8.11; N, 3.66.

The same reaction conducted with different amonium salts gave the following results: NH_4Br, 56 % yield of **8** + **9** (ratio: **8**:**9** = 82:18); CH_3COONH_4, 52 % yield of **8** + **9** (ratio: **8**:**9** = 85:15).

Alternatively, **7** (178 mg, 0.49 mmol) in MeOH (7 ml) was treated at room temp. in the order with CH_3COONH_4 (408 mg, 5.3 mmol, 15 ml of MeOH) and $NaBH_3CN$ (67 mg, 1.06 mmol, 7 ml of MeOH). The mixure was warmed for 2 h at 60°C and submitted to the same work-up as above. The crude reaction product (130 mg, 74 % yield) was a mixture of **8** + **9** in a ratio of 70:30). A flash-chromatography give pure samples of **8** and **9**, in 48 and 18% respective yield.

The hydrogenolysis of **8** (110 mg, 0.32 mmol) in MeOH (10 ml) and in the presence of 20% $Pd(OH)_2$ on charcoal (35 mg) as described for the hydrogenolysis of **5**, gave 1,5-dideoxy-1,5-imino-D-galactitol (**1**, 55 mg, quantit.) identical to the sample obtained above.

1,5-Dideoxy-1,5-imino-L-altritol (18).

A sample of **9** (128 mg, 0.37 mmol) was hydrogenolyzed by the method described above for **5**, giving 60 mg (quantitative yield) of 1,5-dideoxy-1,5-imino-L-altritol (**18**) as a syrup, pure by NMR spectroscopy (Tables 1 and 2); $[\alpha]_D$ -6.8 (*c* 0.5, MeOH).

2,6-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-*N*-methyl-D-galactitol (10), 2,6-di-*O*-benzyl-1,5-dideoxy-1,5-imino-*N*-methyl-L-altritol (11) and their 3,4-di-*O*-acetates (12 and 13).

The double reductive amination of **7** (284 mg, 0.79 mmol) with CH_3NH_3Cl (58.1 mg, 0.86 mmol) and $NaBH_3CN$ (107 mg, 1.7 mmol) was performed from -78°C to room temp. according to the procedure described above for the preparation of **1**. The crude residue obtained after work-up (281 mg) was constitued (^{13}C-NMR) by **10** and **11**, in a ratio of 75:25, measured on the relative intensities of the ^{13}C-NMR signals [δ (CD3CN) 59.55 and 53.76, respectively), and by some unidentified products. A chromatography on silica gel (AcOEt) allowed to a complete separation of the components.

2,6-Di-O-benzyl-1,5-dideoxy-1,5-imino-N-methyl-D-galactitol (**10**, 90 mg, 32 % yield) is a syrup, R*f* 0.45 (AcOEt/MeOH 95:5); $[\alpha]_D$ + 24.7 (*c* 1.0, CHCl3); ^{1}H-NMR data (CD3CN): see Table 1 and δ 2.22 (s,3 H, CH3), 4.49 and 4.64 (2 s, 4 H, 2 x C*H*$_2$Ph), 7.27-7.38 (m, 10 H, aromatics).^{13}C-NMR data: see Table 2 and δ 42,83 (CH3),72.73 and 73.68 (2 x C*H*$_2$Ph), 128.3-129.2 (10 C aromatic CH), 139.51 and 140.22 (quat. aromatic). Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N; 3.92. Found: C, 71.13; H, 7.23; N, 4.08.

The acetylation of **10** (124 mg, 0.41 mmol) according to the standard procedure, gave, after column chromatography on silica (CH_2Cl_2/Et_2O 1:1) pure **12** as a syrup (116 mg, 77 % yield); R*f* 0.57 (AcOEt/hexane 8:2); $[\alpha]_D$ + 0.89 (*c* 2.24, CHCl3); ^{1}H-NMR data (CD3CN): see Table 1 and δ 1.97 and 2.00 (2 s, 6 H, 2 x CH3COO), 2.25 (s, 3H, CH3); 4.59-4.66 (AB system, $J_{A,B}$= 11.94 Hz, C*H*$_2$C$_6$H$_5$),4.39-4.47 (AB system, $J_{A,B}$= 11.70 Hz, C*H*$_2$Ph) 7.23-7.41 (m, 10 H, 2 x C$_6$H$_5$); ^{13}C-NMR data: see Table 2 and δ 20.96 and 21.24

(2 x *C*H3COO), 42.072 (CH3);72.97 and 73.80 (2 x *C*H2Ph); 128.5-129.2 (10 C, aromatic CH), 139.21 and 139.80 (2 x quatern. aromatics), 171.05 and 171.16 (2 x CH3*C*OO). Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17. Found: C, 68.07; H, 7.53; N, 3.36.

*2,6-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-*N*-methyl-L-altritol* (**11**, 37 mg, 13 % yield) is an amorphous solid, R*f* 0.10 (AcOEt/MeOH 95:5); $[\alpha]_D$ + 27.3 (*c* 0.6, $CHCl_3$); ^{1}H-NMR data (CD_3CN): see Table 1 and δ 2.27 (s, 3 H, CH_3), 4.48 (s, 2 H, C*H*2C6H5), 4.52-4.57 (AB system, $J_{A,B}$= 11.56 Hz, C*H*2Ph), 7.28-7.36 (m, 10 H, aromatics) ^{13}C-NMR data: see Table 2 and δ 42.79 (CH_3), 71.77 and 73.71 (2 x *C*H2Ph). Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N; 3.92. Found: C, 68.87; H, 7.68; N, 3.68.

Routine acetylation of **11** (43 mg, 0.12 mmol) gave after chromatography (hexane/AcOEt 1:1) pure **13** (53 mg, quantit.) as a syrup, R*f* 0.15 (hexane/AcOEt 1:1); $[\alpha]_D$ -18.88 (*c* 3.33, $CHCl_3$); ^{1}H-NMR data (CD_3CN): see Table 1 and δ 1.93 and 2.00 (2 s, 6 H, 2 x C*H*3COO), 2.35 (s, 3H, CH_3), 4.55-4.60 (AB system, $J_{A,B}$= 11.78 Hz, C*H*2Ph), 4.43-4.52 (AB system, $J_{A,B}$= 11.86 Hz, C*H*2Ph) 7.29-7.37 (m, 10 H, 2 x C6H5); ^{13}C-NMR data: see Table 2 and δ 21.08 (2x *C*H3COO), 42.54 (CH_3), 72.02 and 73.74 (2 x *C*H2Ph); 128.54-129.27 (10 C, aromatic CH), 139.42 and 139.50 (2 x quatern. aromatics), 170.90 and 170.97 (2 x CH3*C*OO). Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17 Found: C, 68.49; H, 8.75; N, 2.81.

A pure sample of **10** was obtained from **8** according to Borch[11] as follows. A solution of **8** (83 mg, 0.24 mmol) in CH_3CN (4 ml) was treated at room temp with 40 % aqueous CH_2O (0.1 ml, 1.21 mmol), $NaBH_3CN$ (24 mg, 0.38 mmol), the reaction mixture was stirred with a constant pH control between 6 and 7, by addition of anhydrous AcOH. After 24 h stirring, the reaction mixture was diluted with Et_2O (10 ml), and the separated organic layer washed twice with 1*N* NaOH. After evaporation of the solvent, the crude residue was chromatographed on a short silica column (AcOEt as eluant) giving pure **10** (66 mg, 77% yield), identical to the sample described above.

Double reductive amination of 7 with benzhydrylamine

A solution of **7** (284 mg, 0.79 mmol) in MeOH (6 ml) was allowed to react with $BzdNH_2$ (0.144 ml, 0.83 mmol), CH_3COOH (0.047 ml, 0.83 mmoli), $NaBH_3CN$ (107 mg, 1.7 mmol) and 3 Å molecular sieves, according to the procedure described above for the preparation of **5.** The crude residue obtained after work-up (377 mg), analyzed by ^{13}C-NMR, showed 4 methylene signals (negative in DEPT experiments) in a ratio of 45:16:16:23 [δ (CD_3CN) 47.02, 48.13, 49.04 and 49.47 respectively].Several attempts to separate the components of the mixture through TLC, gave negative result. The above reaction product was acetylated to give a crude residue (442 mg), constituted (TLC, hexane/AcOEt 75:25) by two principal components with R*f* 0.41 and 0.12. A flash-chromatography on silica (hexane/AcOEt 75:25) allowed a complete separation of the components. The faster moving product (180 mg, 38 % yield) was a 70:30 mixture of **16** and **17**, and the less mobile one (54 mg, 10% yield) was pure **19**.

*3,4,5-Tri-*O*-acetyl-(*N*-acetyl-*N*-benzhydrylamino)-2,6-di-*O*-benzyl-1-deoxy-D-galactitol or -L-altritol (19)* was an amorphous solid, R*f* 0.15 (hexane/AcOEt 75:25); $[\alpha]_D$ - 50.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (CD_3CN): δ : 1.93, 194,1.95 and 1.96 (4 s, 12 H, 4 C*H*3COOH); 2.46 (d, 1H, $J_{2,3}$= 2.16, H-2); 3.30 (dd, 2 H, $J_{1,2}$=10.90 Hz, $J_{1,1'}$=15.95 Hz, H-1) ; 3.39 (m, 2 H, H-6 and H-6'); 3.41 (s, 1H, C*H*Ph2); 3.88 (dd, 1H, $J_{1',2}$=2.33 Hz H-1'); 4.03-4.32 (AB system, $J_{A,B}$= 10.07 Hz, C*H*2Ph); 4.36-4.44 (AB system, $J_{A,B}$= 11.66 Hz, C*H*2Ph); 4.74 (dd, 1 H, $J_{3,4}$=9.38 Hz, H-3); 5.11 (m, 1 H, $J_{5,6}$=5.98 Hz, $J_{5,6'}$=5.80 Hz H-5); 5.42 (dd, 1 H, $J_{4,5}$=2.38 Hz, H-4); 7.12-7.40 (m, 20H, aromatic).^{13}C NMR (CD_3CN): δ 21.06, 21.19 and 21.32 (3 x *C*H3COO), 22.90 (*C*H3CON), 48.45 (C-1), 62.19 (*C*HPh2), 69.02 (C-6, C-3 and C-4), 69.66 (C-5), 73.68

and 75.37 (2 x $CH_2C_6H_5$),76.69 (C-2) 128.0-132.9 (10 C, aromatic CH),138.64, 139.08, 140.90 and 141.21 (4 x quatern. aromatics) 170.62 (2 signals),170.87 and 173.20 (4 x CH_3CO). Anal. Calcd for $C_{41}H_{45}NO_9$: C, 70.77; H, 6.52; N; 2.01. Found: C, 69.79; H, 6.02; N, 1.90.

Compounds **16** and **17** were unseparable by TLC with several elution systems; their structures were inequivocally inferred from their ^{13}C-NMR data [Table 2 and δ (CD_3CN) for **16**: 21.10 (2 x CH_3CO), 69.42 ($CHPh_2$), 72.15 and 73.59 (2 x CH_2Ph), 127.6-144.7 (aromatic), 170.68 and 170.90 (2 x CH_3CO); for **17**: 21.05 and 21.25 (2 x CH_3CO), 71.73 ($CHPh_2$), 72.68 and 73.72 (2 x CH_2Ph), 127.6-144.7 (aromatic), 171.03 and 171.08 (2 x CH_3CO)] and by the following transformations. A solution of **16+17** (290 mg, 0.48 mmol) in MeOH (5 ml) was treated with 1N MeONa in MeOH (0.1 ml) and stirred at room temp. for 3 h. The solution was neutralized by a stream of CO_2 and evaporated to dryness *in vacuo*; the crude residue (230 mg, 92% yield) was flash-chromatographed (hexane/AcOEt 7:3 and then hexane/AcOEt 1:1) giving an about 70:30 mixture of **14** and **15** [^{13}C NMR data (CD_3CN), see Table 2 and δ for **14**: 68.71 ($CHPh_2$), 72.15 and 73.74 (2 x CH_2Ph), 127.6-129.3 (10 C, aromatic CH), 139.35, 140.16, 142.34 and 144.79 (4 x quatern. aromatics); for **15**: 71.31 ($CHPh_2$), 72.50 and 73.60 (2 x CH_2Ph), 127.5-145.2 (aromatic)]. The above mixture was hydrogenolyzed under conditions identical to those described above for **5**, giving quantitatively a mixture of **1** and **18** in a ratio (^{13}C-NMR) of about 75:25.

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