CYCLIZATION DICHOTOMY OF D-*xylo*-HEX-5-ULOSONAMIDES AND SYNTHESIS OF PIPERIDINE ANALOGS OF ALDOHEXOSES AND ALDOHEXONO-1,5-LACTONES

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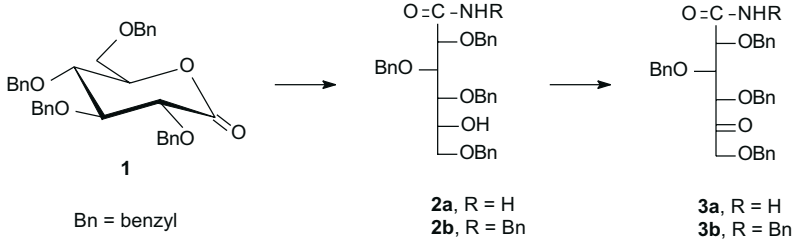
The preparation of 2,3,4,6-tetra-*O*-benzyl-5-D-*xylo*-hex-5-ulosonamides **3a** and **3b** and their cyclization to 5-amino-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-glucono-1,5-lactam (**4**) and 5-amino-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-talono-1,5-lactam (**5**) or to 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**9**), and also their direct transformation into 2,3,4,6-tetra-*O*-benzyl-D-talono-1,5-lactone (**6**), are described and discussed. The atypical boat conformation of D-talonolactam **5** and D-talonolactone **6** was found.

Key words: Carbohydrates; Azasugars; Hexonolactones; Synthetic methods; Rearrangements; Epimerizations.

Azasugars (*i.e.*, piperidine and pyrrolidine analogs of sugars) can affect glycosylation or catabolism of glycoproteins or inhibit the recognition of specific carbohydrates. This makes them interesting as potential therapeutics in the treatment of some metabolic disorders (*e.g.*, diabetes), cancer and some serious viral diseases, including AIDS (for review, see refs[1,2]). These considerations have led to a remarkable effort in the field of synthesis of novel compounds of this type. The synthesis of azasugars requires either a multi-step transformation of appropriate monosaccharide (*e.g.*, refs[3,4,5]) or, less frequently, enantioselective reactions starting from non-sugar precursors (*e.g.*, refs[6,7]). Transformations of suitably protected lactones of aldonic acids seemed to be an interesting tool for the synthesis of compounds possessing azasugar structure[8,9]. We focused our attention on the key step of this approach, *i.e.*, reductive cyclization of D-hex-5-ulosonamides into 5-amino-5-deoxy-D-hexono-1,5-lactams. In this contribution, we describe the influence of reaction conditions on the reaction course and population of products, with particular attention to possible side reactions, such as epimerization and reduction of D-hex-5-ulosonamides and their direct con-

version into target 5-amino-5-deoxy-D-hexopyranoses and 1,5-dideoxy-1,5-imino-D-hexitols and their *N*-substituted analogs.

As starting compounds we used 2,3,4,6-tetra-*O*-benzyl-D-*xylo*-hex-5-ulosonamide (**3a**) and its *N*-benzyl derivative (**3b**) (Scheme 1). Compound **3a** was obtained from 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**, ref.[10]) in two steps according to ref.[8]. An analogous procedure was used for



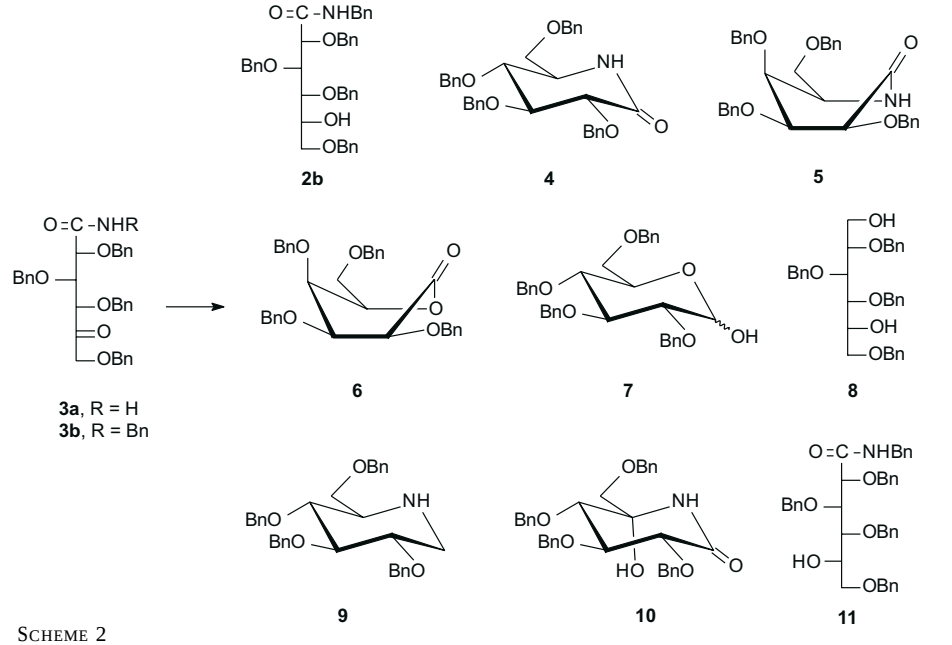
SCHEME 1

the preparation of *N*-benzyl derivative **3b**. Lactone **1** was opened by action of benzylamine in boiling toluene to afford *N*-benzyl-2,3,4,6-tetra-*O*-benzyl-D-gluconamide (**2b**) and its free 5-OH group was oxidized with a mixture of acetic anhydride and dimethyl sulfoxide to give compound **3b**.

Cyclizations of 2,3,4,6-tetra-*O*-benzyl-D-*xylo*-hex-5-ulosonamide) (**3a**) and *N*-benzyl-2,3,4,6-tetra-*O*-benzyl-D-*xylo*-hex-5-ulosonamide (**3b**) (Scheme 2) were performed under three alternative conditions differing in their reduction ability: (i) sodium cyanoborohydride in the presence of formic acid in boiling acetonitrile, (ii) sodium borohydride in the presence of trifluoroacetic acid in acetonitrile at ambient temperature and (iii) sodium cyanoborohydride in the presence of trifluoroacetic acid in acetonitrile at ambient temperature. A significant influence of acid catalysis on the reduction of amides, lactams and cyclic imides with sodium borohydrides is well known[11–13]. The results of this study are summarized in Table I.

Under conditions (i), the ketoamide **3a** afforded predominantly 5-amino-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-glucono-1,5-lactam (**4**, ref.[8]), *i.e.*, the expected product of the intramolecular reductive amination. As a side product, we isolated 5-amino-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-talono-1,5-lactam (**5**). Unexpected formation of D-talonolactam **5** from the D-*xylo* ketoamide **3a** can be explained by the following sequence of transformations (Scheme 3): epimerization in position C-4 *via* enol derivative **A**, reductive cyclization of the formed L-*arabino* ketoamide **B** to the D-galactonolactam **C**, and its epimerization in C-2 position *via* enol **D**. The

attempt to convert the ketoamide **3a** in one step into 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**9**, ref.[8]) under conditions (ii) led to a complex mixture of products in which the required compound **9** was present in a relatively low yield (30%). The other products were



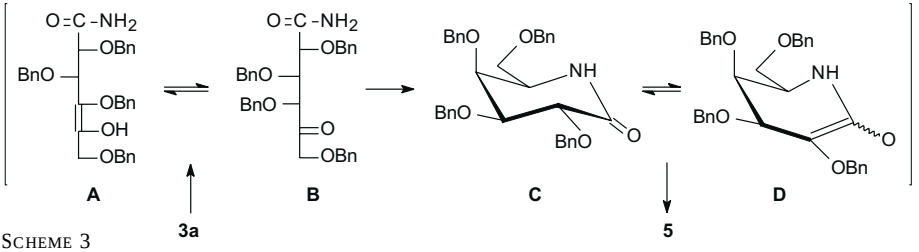
SCHEME 2

TABLE I
Reduction of compounds 3a and 3b; yield of products

Starting compound	Conditions[a]	Products, %								
		2b	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
3a	*a*) $NaBH_3CN$, HCOOH		83	3						
3a	*b*) $NaBH_4$, CF_3COOH				9	14	29	30		
3a	*c*) $NaBH_3CN$, CF_3COOH		33		3	32			12	
3b	*a*) $NaBH_3CN$, HCOOH	15			49					17
3b	*b*) $NaBH_4$, CF_3COOH	7			6					70

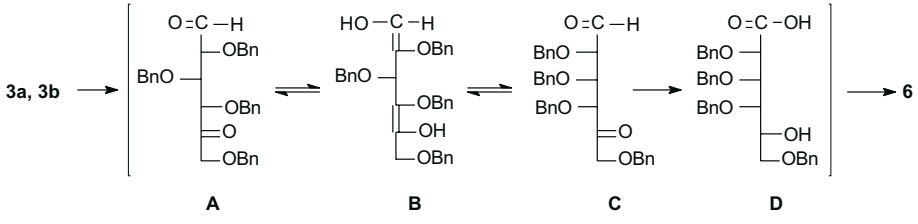
[a] *For* details see Experimental.

2,3,4,6-tetra-*O*-benzyl-D-talono-1,5-lactone (**6**), 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**7**, ref.[14]) and 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**8**, ref.[15]). The population of these products can be influenced by the concentration of trifluoroacetic acid. Thus, a higher concentration of trifluoroacetic acid led



SCHEME 3

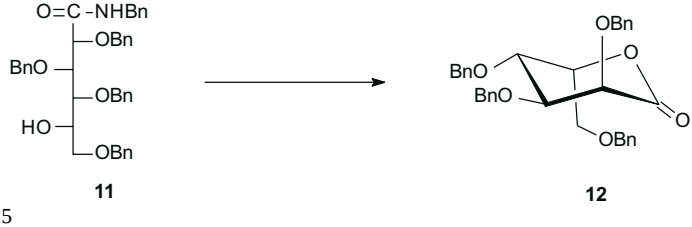
to a higher proportion of the formed side products **6** and **8**. Glucitol **9** is evidently a product of subsequent reduction of the intermediate D-gluconolactam **4** because we found that lactam **4** can be converted to the glucitol **9** by sodium borohydride in the presence of trifluoroacetic acid, *i.e.*, under conditions corresponding to conditions (ii). The formation of the side product **7** from the ketoamide **3a** proceeded by reduction of the keto group followed by reductive splitting of the amide function to give aldehyde group. Glucitol **8** arises as a product of reduction of D-glucopyranose **7** reduction with sodium borohydride[15]. Unexpected formation of talonolactone **6** can be explained by transformations which resemble intramolecular Cannizzaro reaction (Scheme 4). The amide function of the ketoamide **3a** is reduced to give the ketoaldehyde **A** with D-*xylo* configuration which subsequently epimerizes at position C-2 and C-4 *via* the enol **B** under the formation of the ketoaldehyde **C** with L-*ribo* configuration. Intramolecular Cannizzaro reaction then affords talonic acid **D** which spontaneously cyclizes to the talonolactone **6**. By reaction of ketoamide **3a** under condi-



SCHEME 4

tions (iii), the main products were D-gluconolactam **4** (33%) and D-glucopyranose **7** (32%); the other compounds obtained were the product of intramolecular addition of NH_2 group to the keto group giving 5-*C*-amino-2,3,4,6-tetra-*O*-benzyl-L-idono-1,5-lactam (**10**, refs[8,9]) and a trace amount of talonolactone **6**. The presence of glucitol **9** in the reaction mixture was not observed.

Contrary to the ketoamide **3a**, the attempted cyclization of *N*-substituted ketoamide **3b** under conditions (i) afforded, instead of the expected product of intramolecular reductive amination, D-talonolactone **6** (49%), as the main product. In the case of the *N*-substituted ketoamide **3b**, the transformations depicted in Scheme 4 were obviously the main process. The other products, *i.e.*, the epimeric *N*-benzyl 2,3,4,6-tetra-*O*-benzyl-D-gluconamide (**2b**) and *N*-benzyl-2,3,4,6-tetra-*O*-benzyl-L-idonamide (**11**), were formed by reduction of the keto group. Reaction of the ketoamide **3b** under conditions (ii) led predominantly to the reduction of its keto group and a significantly higher production of L-idonamide **11** (70%). The configuration of L-idonamide **11** was proved by its conversion (Scheme 5) to the conformationally stabilized 2,3,4,6-tetra-*O*-benzyl-L-gulono-1,5-lactone (**12**, ref.[16]) with the same configuration at position C-5. The alkaline conditions used for the hydrolysis of L-idonamide **11** to the corresponding aldonic acid led, at the same time, to the epimerization in position C-2 resulting in L-gulonolactone **12** as the final product. Base-catalyzed epimerization of aldonic acids and their derivatives is a common process[17] for the inversion of configuration at position C-2.



11 **12**

SCHEME 5

The conformation of D-talono derivatives **5** and **6** was studied using NMR methods based on the detailed analysis of coupling constants. The values of coupling constants and dihedral angles calculated from the Karplus equation[18] made also the occurrence of chair conformation in D-talono derivatives less probable. The results from 2D NMR ROESY experiments as well as from theoretical calculation of optimum geometry using MM2 (ref.[19]) and AM1 (ref.[20]) calculations supported a less typical boat conformation. The

presence of characteristic H-2/H-5 and H-2/H-3 cross-peaks and simultaneous absence of any cross-peak with H-4 in ROESY NMR spectrum, as well as the energy difference of the studied compounds in both chair and boat conformations (the energy of the boat conformation is 2.5 kcal mol^{-1} lower) also support our conclusion[21].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at 22 °C and are given in 10^{-1} deg cm^2 g^{-1}. The IR spectra were recorded on a Bruker IFS 88 (FTIR) spectrometer, wavenumbers are given in cm^{-1}. NMR spectra were recorded with a Varian UNITY-500 spectrometer in the FT mode at 499.8 MHz (^{1}H) and at 125.7 MHz (^{13}C) in deuteriochloroform, using tetramethylsilane as internal standard for the ^{1}H NMR spectrum and deuteriochloroform (δ 77.0) as standard for ^{13}C NMR spectrum. Chemical shifts are given in ppm and coupling constants in Hz. For uninterchangeable assignment of signals in ^{13}C NMR spectra of compounds **8**, **10**, **11** and **12a**, heterocorrelated 2D NMR spectra were measured by HMQC technique using the standard pulse sequence delivered by the producer. The following set of parameters was used: spectral width in both f_1 and f_2 dimensions 4 500 and 17 000 Hz, respectively, number of scans 32, number of increments in f_1 dimension 256, recycle delay 1 s, acquisition time 0.2 s, 90° pulse for ^{1}H was 22.5 ms, data matrix for processing 2 048 × 2 048 datapoints; no weighting function was used for processing. Positive-ion FAB mass spectra were measured on a BeqG-geometry mass spectrometer ZAB-EQ (VG Analytical, Manchester, U.K.), using an M-Scan FAB gun (Xe, energy 8 keV) at an accelerating voltage of 8 kV. Samples were dissolved in chloroform or methanol, a mixture of glycerol and thioglycerol or 3-nitrobenzyl alcohol was used as matrix. Thin-layer chromatography (TLC) was performed on Silufol UV_{254} sheets, and column chromatography on silica gel Silpearl (both Kavalier, Votice, Czech Republic). Analytical samples were dried at 6.5 Pa and 25 °C for 8 h.

N-Benzyl-2,3,4,6-tetra-*O*-benzyl-D-gluconamide (**2b**)

A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**, ref.[10]; 6.46 g, 12 mmol) and benzylamine (1.31 ml, 12 mmol) in dry toluene (90 ml) was refluxed for 5 h. The solvent was evaporated to give a syrupy residue, which was crystallized from toluene–petroleum ether. Yield 5.78 g (75%) of compound **2b**; m.p. 81 °C; $[\alpha]_D$ +18 (*c* 0.2, chloroform). IR (chloroform): 3 547 (OH); 3 417 (N–H, amide); 3 090, 1 497, 699 (aromatic); 1 672 (amide I); 1 522 (amide II). ^{1}H NMR: 7.16–7.35 m, 25 H (H-arom., Bn); 6.94 bt, 1 H, *J* = 5.9 (N**H**); 4.70 d, 1 H, *J* = 11.3 (CH_2-Ph); 4.65 d, 1 H, *J* = 11.3 (CH_2-Ph); 4.58 d, 1 H, *J* = 11.3 (CH_2-Ph); 4.56 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.51 d, 1 H, *J* = 11.3 (CH_2-Ph); 4.51 d, 1 H, *J* = 11.3 (CH_2-Ph); 4.51 d, 1 H, *J* = 11.3 (CH_2-Ph); 4.50 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.47 dd, 1 H, *J* = 6.3, 14.6 (CH_2-Ph); 4.33 d, 1 H, *J* = 3.2 (H-2); 4.26 dd, 1 H, *J* = 5.4, 14.6 (CH_2-Ph); 4.10 dd, 1 H, *J* = 3.2, 5.7 (H-3); 3.93 ddd, 1 H *J* = 3.1, 5.3, 7.7 (H-5); 3.87 dd, 1 H, *J* = 5.7, 7.7 (H-4); 3.66 dd, 1 H, *J* = 3.1, 9.9 (H-6b); 3.60 dd, 1 H, *J* = 5.3, 9.9 (H-6a). ^{13}C NMR: 170.81 s (C-1); 138.1 s, 138.07 s, 137.76 s (2C), 136.53 s, 128.64 d (2C), 128.57 d (2C), 128.46 d (2C), 128.34 d (2C), 128.28 d (2C), 128.26 d (2C), 128.12 d (4C), 127.98 d (4C), 127.81 d, 127.70 d,

127.64 d, 127.63 d, 127.48 d (C-arom., Bn); 80.64 d (C-3); 80.07 d (C-2); 77.41 d (C-4); 75.06 t (**C**H_2-Ph); 74.03 t (**C**H_2-Ph); 73.95 t (**C**H_2-Ph); 73.37 t (**C**H_2-Ph); 71.41 d (C-5); 71.06 t (C-6); 43.24 t (**C**H_2-Ph). For **2b** ($C_{41}H_{43}NO_6$) calculated: relative molecular mass 645.8, monoisotopic mass 645.3. FABMS, *m/z*: 646.1 $[M + H]^+$. For $C_{41}H_{43}NO_6$ (645.8) calculated: 76.25% C, 6.71% H, 2.16% N; found: 76.04% C, 6.71% H, 2.17% N.

N-Benzyl-2,3,4,6-tetra-*O*-benzyl-D-*xylo*-hex-5-ulosonamide (**3b**)

To a stirred solution of gluconamide **2b** (5.17 g, 8 mmol) in dry dimethyl sulfoxide (28 ml), acetic anhydride (17 ml) was added through septum and the mixture was stirred at room temperature for 15 h. The solution was poured under stirring to ice water (250 ml) and the mixture was stirred for 20 min. The product was extracted with toluene (2 × 150 ml) and the extracts were washed with water (4 × 60 ml), dried over anhydrous magnesium sulfate and concentrated in vacuum to give a syrupy residue, which was crystallized from toluene–petroleum ether. Yield 3.8 g (74%) of compound **3b**; m.p. 80–82 °C; $[\alpha]_D$ +3 (*c* 0.5, chloroform). IR (chloroform): 3 416 (N–H, amide); 3 090, 1 497, 699 (aromate); 1 731 (ketone); 1 673 (amide I); 1 522 (amide II). ^{1}H NMR: 7.11–7.36 m, 25 H (H-arom., Bn); 6.92 bt, 1 H, *J* = 6.0 (N**H**); 4.68 d, 1 H, *J* = 11.7 (CH_2-Ph); 4.58 d, 1 H, *J* = 11.7 (CH_2-Ph); 4.56 d, 1 H, *J* = 11.0 (CH_2-Ph); 4.55 d, 1 H, *J* = 11.0 (CH_2-Ph); 4.50 d, 1 H, *J* = 11.0 (CH_2-Ph); 4.45 dd, 1 H, *J* = 6.6, 14.7 (CH_2-Ph); 4.43 d, 1 H, *J* = 12.0 (CH_2-Ph); 4.40 d, 1 H, *J* = 12.0 (CH_2-Ph); 4.33 d, 1 H, *J* = 11.0 (CH_2-Ph); 4.31 d, 1 H, *J* = 17.6 (H-6b); 4.28 dd, 1 H, *J* = 5.4, 14.7 (CH_2-Ph); 4.24 d, 1 H, *J* = 17.6 (H-6a); 4.17-4.29 m, 3H (H-2, H-3, H-4). ^{13}C NMR: 205.91 s (C-5); 170.23 s (C-1); 137.71 s, 137.47 s, 137.31 s, 137.20 s, 136.50 s, 128.83 d (2C), 128.70 d (2C), 128.56 d (2C), 128.49 d (2C), 128.36 d (4C), 128.31 d, 128.17 d (2C), 128.11 d (2C), 128.04 d, 127.92 d, 127.87 d (2C), 127.82 d (2C), 127.77 d, 127.55 d (C-arom., Bn); 81.27 d (C-4); 80.60 d (C-2); 79.65 d (C-3); 75.21 t (**C**H_2-Ph); 74.58 t (**C**H_2-Ph); 74.17 t (**C**H_2-Ph); 73.52 t (**C**H_2-Ph); 73.22 t (C-6); 43.26 t (**C**H_2-Ph). For **3b** ($C_{41}H_{41}NO_6$) calculated: relative molecular mass 643.8, monoisotopic mass 643.3. FABMS, *m/z*: 644.3 $[M + H]^+$. For $C_{41}H_{41}NO_6$ (643.8) calculated: 76.49% C, 6.41% H, 2.17% N; found: 76.31% C, 6.47% H, 2.17% N.

Cyclization of 2,3,4,6-Tetra-*O*-benzyl-D-*xylo*-hex-5-ulosonamide (**3a**)

Method A). Sodium cyanoborohydride (32 g, 509 mmol) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-*xylo*-hex-5-ulosonamide (**3a**, ref.[8]; 82 g, 148 mmol) in a mixture of dry acetonitrile (2 000 ml) and formic acid (500 ml) and the mixture was stirred at ambient temperature for 1 h and refluxed for 2 h. After cooling, the mixture was concentrated to a quarter of the original volume and diluted with ethyl acetate (1 500 ml). The solution was extracted with saturated aqueous $NaHCO_3$ (3 × 300 ml) and water (300 ml), dried over anhydrous magnesium sulfate and the solvents were evaporated. Crystallization of the residue from toluene–petroleum ether afforded 54 g (68%) of compound **4**. The residue of the mother liquor was chromatographed on silica gel column (600 g). The column was eluted with a mixture of toluene–ethyl acetate (5 : 1) and the combined homogeneous fractions were evaporated to give 12 g (15%) of the crystalline **4** and 2.1 g (3%) of syrupy compound **5**.

Method B). Sodium borohydride (2.0 g, 52.8 mmol) and trifluoroacetic acid (6 ml, 78 mmol) were added to a stirred solution of ketoamide **3a** (5.54 g, 10 mmol) in dry acetonitrile (110 ml) and the mixture was stirred at ambient temperature for 16 h. The mixture was concentrated to a quarter of the original volume and diluted with toluene (500 ml). The

solution was extracted with saturated aqueous $NaHCO_3$ (3 × 60 ml) and water (60 ml), dried over anhydrous magnesium sulfate and the solvents were evaporated. The residue was chromatographed on a silica gel column (200 g). The column was eluted with a mixture of toluene–ethyl acetate (10 : 1) and the combined homogeneous fractions were evaporated to give 480 mg (9%) of the syrupy residue which, after crystallization from a mixture diethyl ether–petroleum ether, gave 300 mg (6%) of compound **6**. Further elution of the column with a mixture toluene–ethyl acetate (5 : 1) gave 770 mg (14%) of crystals which, crystallization from propan-1-ol to afforded 610 mg (11%) of compound **7**. Continued elution of the column with a mixture toluene–ethyl acetate (3 : 1) afforded 1.60 g (29%) of the syrupy compound **8**. Finally, the elution with a mixture toluene–ethyl acetate (2 : 1) gave 1.56 g (30%) of crystals, which were recrystallized from a mixture ethyl acetate ether–petroleum ether. Yield, 1.21 g (23%) of compound **9**.

The population of the above products is strongly dependent on the concentration of trifluoroacetic acid, doubling its amount afforded compound **6** (19%), compound **7** (6%), compound **8** (50%) and compound **9** (6%).

Method C). Sodium cyanoborohydride (2.0 g, 31.8 mmol) and trifluoroacetic acid (10 ml, 130 mmol) was added to a stirred solution of ketoamide **3a** (5.54 g, 10 mmol) in dry acetonitrile (140 ml) and the mixture was stirred at ambient temperature for 16 h. The reaction mixture was worked up as described in method *B*), to give 170 mg (3%) of syrupy residue of compound **6**, 1.74 g (32%) of crystalline compound **7**, 1.79 g (33%) of crystalline compound **4** and 680 mg (12%) of crystalline compound **10**. After crystallization compounds **4**, **6** and **7** were identical (m.p., $[\alpha]_D$, MS, IR and NMR spectra) with the respective compounds prepared by methods *A*) and *B*).

5-Amino-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-glucono-1,5-lactam (**4**)

M.p. 102–104 °C, $[\alpha]_D$ +105 (*c* 0.5, chloroform); ref.[8]: m.p. 100–102 °C, $[\alpha]_D$ +105.5 (*c* 0.51, chloroform). IR and NMR spectra agree with the data in ref.[8]. For **4** ($C_{34}H_{35}NO_5$) calculated: relative molecular mass 537.7, monoisotopic mass 537.2. FABMS, *m/z*: 538.0 $[M + H]^+$. For $C_{34}H_{35}NO_5$ (537.7) calculated: 75.95% C, 6.56% H, 2.61% N; found: 75.74% C, 6.25% H, 2.73% N.

5-Amino-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-talono-1,5-lactam (**5**)

Syrup; $[\alpha]_D$ +60 (*c* 0.1, chloroform). IR (chloroform): 3 389 (N–H, amide); 3 090, 1 497, 698 (aromate); 1 687 (amide I). ^{1}H NMR: 7.18–7.43 m, 20 H (H-arom., Bn); 5.90 bd, 1 H, *J* = 2.2 (NH); 5.11 d, 1 H, *J* = 11.7 (CH_2-Ph); 4.75 d, 1 H, *J* = 11.7 (CH_2-Ph); 4.66 d, 1 H, *J* = 11.7 (CH_2-Ph); 4.63 d, 1 H, *J* = 11.9 (CH_2-Ph); 4.57 d, 1 H, *J* = 11.7 (CH_2-Ph); 4.51 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.47 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.40 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.00 d, 1 H, *J* = 5.9 (H-2); 3.94 dd, 1 H, *J* = 5.1, 5.9 (H-3); 3.78 ddt, 1 H, *J* = 2.3, 3.8, 3.8, 8.6 (H-5); 3.69 dd, 1 H, *J* = 3.7, 5.1 (H-4); 3.62 t, 1 H, *J* = 9.1 (H-6a); 3.56 dd, 1 H, *J* = 4.0, 9.3 (H-6b). ^{13}C NMR: 170.54 s (C-1); 137.96 s, 137.80 s, 137.44 s, 137.41 s, 128.50 d (2C), 128.42 d (3C), 128.33 d (2C), 127.95 d, 127.93 d (2C), 127.91 d, 127.88 d (2C), 127.85 d, 127.78 d (2C) (C-arom., Bn); 78.87 d (C-3); 78.18 d (C-2); 75.29 d (C-4); 74.14 t (**C**H_2-Ph); 73.49 t (**C**H_2-Ph); 73.22 t (**C**H_2-Ph); 71.96 t (**C**H_2-Ph); 69.66 t (C-6); 52.07 d (C-5). For **5** ($C_{34}H_{35}NO_5$) calculated: relative molecular mass 537.7, monoisotopic mass 537.2. FABMS, *m/z*: 538.2 $[M + H]^+$. For $C_{34}H_{35}NO_5$ (537.7) calculated: 75.95% C, 6.56% H, 2.61% N; found: 75.81% C, 6.63% H, 2.55% N.

2,3,4,6-Tetra-*O*-benzyl-D-talono-1,5-lactone (**6**)

M.p. 77–80 °C; $[\alpha]_D$ +32 (*c* 0.5, chloroform). IR (chloroform): 3 090, 1 497, 699 (aromate); 1 763 (lactone). ^{1}H NMR: 7.15–7.48 m, 20 H (H-arom., Bn); 5.04 d, 1 H, *J* = 11.5 (CH_2-Ph); 4.63 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.63 d, 1 H, *J* = 11.5 (CH_2-Ph); 4.56 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.56 dt, 1 H, *J* = 1.7, 6.0, 6.0 (H-5); 4.53 d, 1 H, *J* = 12.1 (CH_2-Ph); 4.51 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.43 d, 1 H, *J* = 12.1 (CH_2-Ph); 4.31 d, 1 H, *J* = 12.1 (CH_2-Ph); 4.16 d, 1 H, *J* = 6.2 (H-2); 3.90 dd, 1 H, *J* = 1.7, 6.2 (H-3); 3.76 t, 1 H, *J* = 1.7 (H-4); 3.76 dd, 1 H, *J* = 5.9, 9.8 (H-6b); 3.62 dd, 1 H, *J* = 6.2, 9.8 (H-6a). ^{13}C NMR: 169.43 s (C-1); 137.46 s, 137.34 s, 137.05 s, 136.93 s, 128.47 d (2C), 128.44 d (2C), 128.43 d (2C), 128.41 d (2C), 128.39 d (2C), 128.05 d, 128.02 d (2C), 127.95 d (2C), 127.92 d (2C), 127.82 d (2C), 127.80 d (C-arom., Bn); 79.93 d (C-3); 78.53 d (C-2); 75.88 d (C-5); 75.21 d (C-4); 73.55 t (**C**H_2-Ph); 73.29 t (**C**H_2-Ph); 72.48 t (**C**H_2-Ph); 71.40 t (**C**H_2-Ph); 67.89 t (C-6). For **6** ($C_{34}H_{34}NO_6$) calculated: relative molecular mass 538.6, monoisotopic mass 538.2. FABMS, *m/z*: 539.3 $[M + H]^+$, 561.3 $[M + Na]^+$. For $C_{34}H_{34}NO_6$ (538.6) calculated: 75.81% C, 6.36% H; found: 75.74% C, 6.25% H.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**7**)

M.p. 150 °C, $[\alpha]_D$ +22 (*c* 2.0, chloroform); ref.[14]: m.p. 151–152 C, $[\alpha]_D$ +21.7 (*c* 2.19, chloroform). IR and NMR spectra agree with the data for the authentic sample prepared by procedure described in ref.[14]. For **7** (C34H36O6) calculated: relative molecular mass 540.7, monoisotopic mass 540.3. FABMS, *m/z*: 539.3 $[M - H]^+$, 563.3 $[M + Na]^+$. For $C_{34}H_{36}NO_6$ (540.7) calculated: 75.53% C, 6.71% H; found: 75.74% C, 6.25% H.

2,3,4,6-Tetra-*O*-benzyl-D-glucitol (**8**)

Syrup, $[\alpha]_D$ +19 (*c* 0.23, chloroform); ref.[15]: $[\alpha]_D$ +18 (*c* 0.6, chloroform). IR (chloroform): 3 568 (OH); 3 090, 1 497, 699 (aromatic). ^{1}H NMR: 7.21–7.37 m, 20 H (H-arom., Bn); 4.71 d, 1 H, *J* = 11.9 (CH_2-Ph); 4.67 d, 1 H, *J* = 11.6 (CH_2-Ph); 4.65 d, 1 H, *J* = 11.9 (CH_2-Ph); 4.62 d, 1 H, *J* = 11.6 (CH_2-Ph); 4.58 d, 1 H, *J* = 11.4 (CH_2-Ph); 4.55 d, 1 H, *J* = 11.9 (CH_2-Ph); 4.54 d, 1 H, *J* = 11.4 (CH_2-Ph); 4.50 d, 1 H, *J* = 11.9 (CH_2-Ph); 4.03 ddd, 1 H, *J* = 3.6, 4.9, 6.4, 7.0 (H-2); 3.89 dd, 1 H, *J* = 3.6, 6.5 (H-4); 3.80 dt, 1 H, *J* = 4.6, 4.6, 6.5 (H-5); 3.77 dd, 1 H, *J* = 3.6, 7.0 (H-3); 3.73 dd, 1 H, *J* = 4.4, 11.9 (H-6b); 3.65 dd, 1 H, *J* = 3.6, 9.9 (H-1b); 3.62 dd, 1 H, *J* = 4.9, 9.9 (H-1a); 3.56 dd, 1 H, *J* = 4.7, 11.9 (H-6a). ^{13}C NMR: 138.17 s, 138.00 s, 137.88 s, 137.86 s, 128.46 d (2C), 128.43 d (2C), 128.41 d (4C), 128.39 d (2C), 128.10 d (2C), 127.96 d (2C), 127.89 d, 127.87 d (2C), 127.81 d (2C), 127.75 d (C-arom., Bn); 79.49 d (C-4); 79.17 d (C-5); 77.40 d (C-3); 74.49 t (**C**H_2-Ph); 73.47 t (**C**H_2-Ph); 73.27 t (**C**H_2-Ph); 73.10 t (**C**H_2-Ph); 71.17 t (C-6); 70.74 d (C-2); 61.88 t (C-1). For **8** ($C_{34}H_{38}NO_6$) calculated: relative molecular mass 542.7, monoisotopic mass 542.3. FABMS, *m/z*: 543.4 $[M + H]^+$. For $C_{34}H_{38}NO_6$ (542.7) calculated: 75.25% C, 7.07% H; found: 75.02% C, 7.01% H.

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**9**)

M.p. 42–43 °C, $[\alpha]_D$ +25 (*c* 0.2, chloroform); ref.[8]: m.p. 43–45 °C, $[\alpha]_D$ +29.5 (*c* 0.6, chloroform). IR and NMR spectra correspond with the respective data of the authentic sample (ref.[8]). For **9** ($C_{34}H_{37}NO_4$) calculated: relative molecular mass 523.7, monoisotopic mass

523.3. FABMS, *m/z*: 524.4 $[M + H]^+$. For $C_{34}H_{37}NO_4$ (523.7) calculated: 76.25% C, 6.71% H, 2.16% N; found: 77.6% C, 7.20% H, 2.55% N.

5-*C*-Amino-2,3,4,6-tetra-*O*-benzyl-L-idono-1,5-lactam (**10**)

M.p. 95–100 °C, $[\alpha]_D$ +72 (*c* 0.1, chloroform); ref.[8]: m.p. 99–100 °C, $[\alpha]_D$ +78.6 (*c* 0.51, chloroform); ref.[9]: m.p. 103–104.5 °C, $[\alpha]_D$ +74.2 (*c* 1.03, ethanol). IR and NMR spectra correspond with the respective data in refs[8,9]. For **10** ($C_{34}H_{35}NO_6$) calculated: relative molecular mass 553.7, monoisotopic mass 553.2. FABMS, *m/z*: 554.6 $[M + H]^+$, 576.6 $[M + Na]^+$. For $C_{34}H_{35}NO_6$ (553.7) calculated: 73.76% C, 6.37% H, 2.53% N; found: 73.58% C, 6.51% H, 2.48% N.

Cyclization of *N*-benzyl 2,3,4,6-tetra-*O*-benzyl-D-*xylo*-hex-5-ulosonamide (**3b**)

Method A). Sodium cyanoborohydride (1.08 g, 17.2 mmol) was added to a solution of ketoamide **3b** (3.22 g, 5 mmol) in a mixture of dry acetonitrile (75 ml) and 98% formic acid (17 ml) and the mixture was stirred at ambient temperature for 1 h and refluxed for 2 h. After cooling, the mixture was concentrated to a quarter of its volume and diluted with ethyl acetate (300 ml). This solution was extracted with saturated aqueous $NaHCO_3$ (3 × 100 ml) and water (100 ml), dried over anhydrous magnesium sulfate and the solvents were evaporated. The residue was chromatographed on a silica gel column (80 g). The column was eluted first with a mixture of toluene–ethyl acetate (10 : 1) to give 1.32 g (49%) of the syrupy residue, which was crystallized from a mixture diethyl ether–petroleum ether. Yield 909 mg (34%) of compound **6** identical (m.p., $[\alpha]_D$, IR and NMR spectra) with the authentic sample described above. Further elution with a mixture of toluene–ethyl acetate (5 : 1) gave 298 mg (9%) of the crystalline starting material **3b**, identical (m.p., $[\alpha]_D$, IR and NMR spectra), after crystallization, with the authentic compound **3b**. Finally, the elution with toluene–ethyl acetate mixture (2 : 1) afforded 500 mg (15%) of crystalline compound **2b** and 537 mg (17%) of syrupy compound **11**. After crystallization, compound **2b** was identical (m.p., $[\alpha]_D$, IR and NMR spectra) with the authentic material **2b**.

Method B). Sodium borohydride (1.19 g, 31.68 mmol) and trifluoroacetic acid (7.2 ml, 93.6 mmol) was added to a stirred solution of ketoamide **3b** (3.86 g, 6 mmol) in dry acetonitrile (66 ml) and the mixture was stirred at ambient temperature for 16 h. The reaction mixture was worked up as described in a previous experiment to give 190 mg (6%) of syrupy compound **6**, 270 mg (7%) of crystals **2b** and 2.72 g (70%) of syrupy compound **11**. Compounds **6** and **2b** were, after crystallization, identical (m.p.,$[\alpha]_D$, MS, IR and NMR spectra) with the authentic materials (see above).

N-Benzyl 2,3,4,6-Tetra-*O*-benzyl-L-idonamide (**11**)

Syrup; $[\alpha]_D$ +10 (*c* 0.2, chloroform). IR (chloroform): 3 568 (OH); 3 417 (N–H, amide); 3 090, 1 497, 699 (aromate); 1 673 (amide I); 1 523 (amide II). ^{1}H NMR: 7.16–7.34 m, 25 H (H-arom., Bn); 6.93 dd, 1 H, *J* = 5.3, 6.3 (CH_2-Ph); 4.78 d, 1 H, *J* = 11.3 (CH_2-Ph); 4.59 d, 1 H, *J* = 11.2 (CH_2-Ph); 4.54 dd, 1 H, *J* = 6.3, 14.6 (CH_2-Ph); 4.51 d, 1 H, *J* = 11.3 (CH_2-Ph); 4.51 d, 1 H, *J* = 11.0 (CH_2-Ph); 4.50 d, 1 H, *J* = 11.2 (CH_2-Ph); 4.47 d, 1 H, *J* = 11.0 (CH_2-Ph); 4.45 d, 1 H, *J* = 11.9 (CH_2-Ph); 4.39 d, 1 H, *J* = 11.9 (CH_2-Ph); 4.22 dd, 1 H, *J* = 2.6, 8.1 (H-3); 4.21 dd, 1 H, *J* = 5.3, 14.6 (CH_2-Ph); 4.18 d, 1 H, *J* = 2.6 (H-2); 3.89 dd, 1 H, *J* = 2.3, 8.1 (H-4); 3.73 bdt, 1 H, *J* = 2.3, 6.3, 6.4 (H-5); 3.47 dd, 1 H, *J* = 6.4, 9.2 (H-6b); 3.34 dd, 1 H, *J* =

6.3, 9.1 (H-6a). ^{13}C NMR: 171.09 s (C-1); 138.06 s, 138.04 s, 137.97 s, 137.65 s, 136.27 s, 128.66 d (3C), 128.54 d (2C), 128.35 d, 128.33 d (3C), 128.31 d (3C), 128.24 d (2C), 128.18 d, 127.98 d (2C), 127.91 d (2C), 127.74 d (2C), 127.73 d (2C), 127.58 d, 127.53 d (C-arom., Bn); 80.40 d (C-3); 79.99 d (C-2); 78.06 d (C-4); 75.55 t (**C**H_2-Ph); 74.87 t (**C**H_2-Ph); 74.00 t (**C**H_2-Ph); 73.21 t (**C**H_2-Ph); 71.15 t (C-6); 69.31 d (C-5); 43.39 t (**C**H_2-Ph). For **11** ($C_{41}H_{43}NO_6$) calculated: relative molecular mass 645.8, monoisotopic mass 645.3. FABMS, *m/z*: 646.2 $[M + H]^+$. For $C_{41}H_{43}NO_6$ (645.8) calculated: 76.25% C, 6.71% H, 2.16% N; found: 76.03% C, 6.75% H, 2.20% N.

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**9**)

Sodium borohydride (300 mg, 8 mmol) and trifluoracetic acid (1 ml, 13 mmol) was added to a stirred solution of gluconolactam **4** (1.1 g, 2 mmol) in dry acetonitrile (24 ml) and the mixture was stirred at ambient temperature for 18 h. Additional sodium borohydride (300 mg, 8 mmol) and trifluoracetic acid (1 ml, 13 mmol) were added, the mixture was concentrated to a quarter of its volume and diluted with toluene (60 ml). The solution was extracted with saturated aqueous $NaHCO_3$ (3 × 10 ml) and water (10 ml), dried over anhydrous magnesium sulfate and the solvents were evaporated. Crystallization of the residue gave 255 mg (24%) of the starting compound **4**. Chromatography of the mother liquor on silica gel column (15 g) in toluene–ethyl acetate (2 : 1) afforded 220 mg (20%) of crystalline starting compound **4** and 520 mg (50%) of crystalline compound **9**; both compounds were, after recrystallization, identical (m.p., $[\alpha]_D$, MS, IR and NMR spectra) with the authentic compounds.

2,3,4,6-Tetra-*O*-benzyl-L-gulono-1,5-lactone (**12**)

A solution of L-idonoamide **11** (420 mg, 0.65 mmol) in 0.5 M KOH in methanol (8 ml) was stirred at 50 °C for 12 h. After cooling, the mixture was poured on a column of Dowex 50 in the pyridinium form (10 ml) and the column was washed with dioxane (50 ml). The eluate was concentrated and the residue coevaporated with benzene (3 × 5 ml). Chromatography of the residue on a silica gel column (15 g) in toluene–ethyl acetate (2 : 1) afforded 210 mg (60%) of the syrupy **12**, $[\alpha]_D$ –43 (*c* 0.6, chloroform); ref.[16] $[\alpha]_D$ –53 (*c* 1.1, dichloromethane). IR (chloroform): 3 090, 1 497, 699 (aromatic); 1 763 (lactone). ^{1}H NMR: 7.23–7.38 m, 20 H (H-arom., Bn); 5.07 d, 1 H, *J* = 12.2 (CH_2-Ph); 4.85 ddd, 1 H, *J* = 2.6, 5.9, 7.7 (H-5); 4.82 d, 1 H, *J* = 12.0 (CH_2-Ph); 4.64 d, 1 H, *J* = 12.2 (CH_2-Ph); 4.58 d, 1 H, *J* = 12.0 (CH_2-Ph); 4.55 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.48 d, 1 H, *J* = 11.8 (CH_2-Ph); 4.37 d, 1 H, *J* = 11.5 (CH_2-Ph); 4.35 d, 1 H, *J* = 2.9 (H-2); 4.31 d, 1 H, *J* = 11.5 (CH_2-Ph); 3.94 dd, 1 H, *J* = 2.9, 4.5 (H-3); 3.78 dd, 1 H, *J* = 2.6, 4.5 (H-4); 3.71 dd, 1 H, *J* = 7.7, 9.5 (H-6b); 3.67 dd, 1 H, *J* = 5.9, 9.5 (H-6a). ^{13}C NMR: 170.38 s (C-1); 137.65 s (2C), 137.57 s, 136.96 s, 128.47 d (2C), 128.44 d (2C), 128.40 d (2C), 128.37 d (2C), 128.12 d, 128.08 d (2C), 127.91 d, 127.89 d (4C), 127.84 d, 127.80 d, 127.77 d (2C) (C-arom., Bn); 77.56 d (C-5); 75.59 d (C-3); 74.13 d (C-2); 73.77 d (C-4); 73.64 t (**C**H_2-Ph); 73.54 t (**C**H_2-Ph); 73.38 t (**C**H_2-Ph); 72.96 t (**C**H_2-Ph); 67.44 t (C-6). For **12** ($C_{34}H_{34}NO_6$) calculated: relative molecular mass 538.7, monoisotopic mass 538.2. FABMS, *m/z*: 539.3 $[M + H]^+$. For $C_{34}H_{34}NO_6$ (538.7) calculated: 75.81% C, 6.36% H; found: 75.60% C, 6.48% H.

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