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A Facile Transformation of Sugar Lactones to Azasugars

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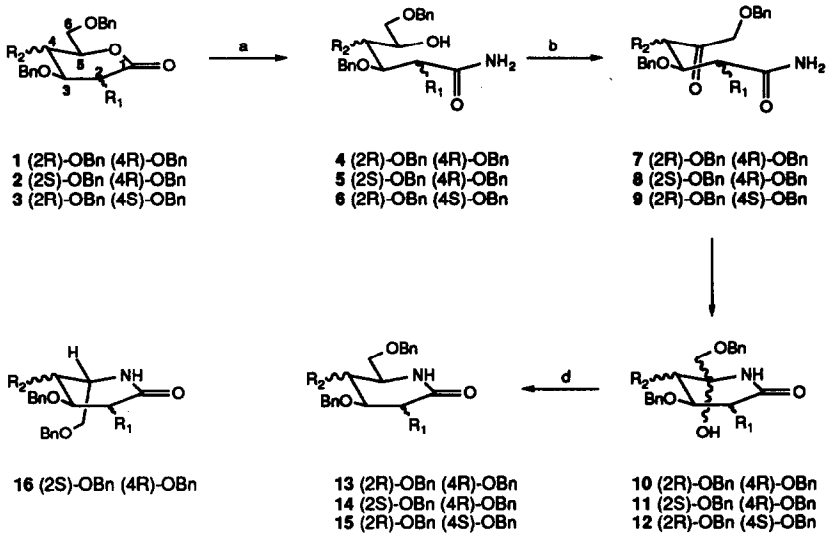
Abstract: The synthesis of pyrano- and furano- sugar lactams from the corresponding lactones, in a five step sequence, is described.

The action of azasugars as inhibitors of glycosidases has recently aroused a great deal of attention in view of the significance of *cleavage* or *formation* of the glycoside bond in a large number of important biological processes[3]. Azasugars can alter the glycosylation or catabolism of glycoproteins or inhibit the recognition of specific carbohydrates. This makes them of considerable potential therapeutic interest. The natural monocyclic azasugar antibiotics nojirimycin and deoxynojirimycin are known to exhibit biological activities in a number of areas[4].

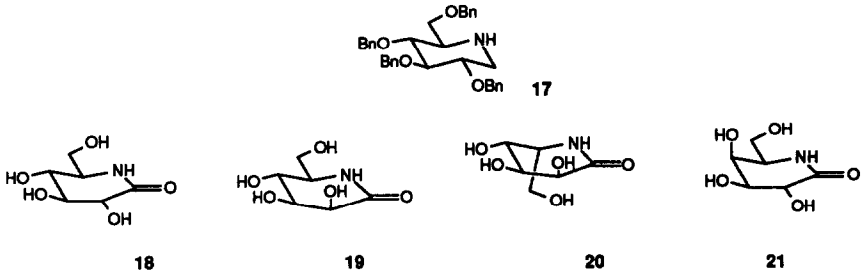
At present there are about 25 known natural azasugar glycosidase inhibitors; however, their isolation in the pure form from natural sources is a laborious and expensive exercise. In the light of these considerations there has recently been a spate of vigorous activity, devoted to the chemical synthesis of, in particular, modified azasugars[5], in search of new inhibitors of specific steps mediated by the glycosidases.

In connection with a programme on the development of catalytic antibodies, we required a facile access to δ-gluconolactam and its reduction product, the natural antibiotic 1-deoxy-nojirimycin; which has become an accepted model molecule for studies on glycosidase inhibitors. An expedient synthesis of these compounds from the readily available gluconolactone was reported in a preliminary communication from this laboratory[6]. We now present the details of this synthesis and the application of the synthetic strategy to a number of other six- and five-ring azasugars.

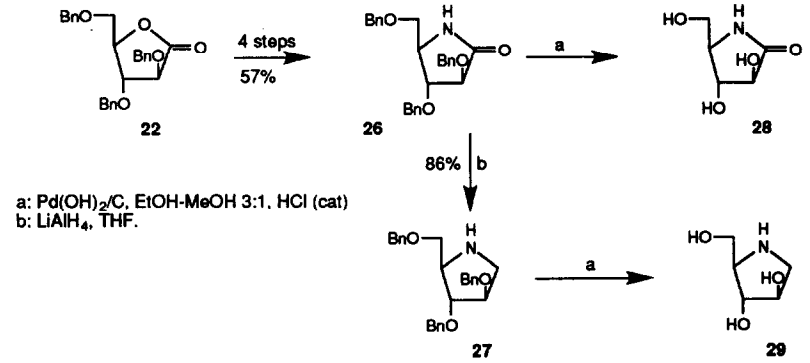
The synthesis of six-membered azasugars, namely, gluconolactam[7] (**18**), mannolactam[8] (**19**), isomannolactam (**20**) and galactonolactam[9] (**21**) is described in Scheme 1. The sequence started with the benzylated lactones **1** - **3**, which are conveniently available starting materials[10a]. Reaction of these with methanolic ammonia gave the stereochemically related hydroxy amides **4** - **6**, which were subsequently oxidized ($DMSO/Ac_2O$) to the corresponding keto amides **7** - **9**. Treatment of the latter with methanolic ammonia gave, in each case, a mixture of two isomeric hydroxy lactams described by structures **10** - **12**. When the individual mixtures of the C(5)-epimers of **10** and **12** were reduced with sodium cyanoborohydride, in the presence of formic acid, each pair led to the formation of a single lactam [**13** and **15**, respectively]. In contrast, reduction under the same conditions of the diastereomers corresponding to **11**, resulted in a mixture of lactams **14** and **16** (2:3). The lactams **13** - **16** were debenzylated by catalytic reduction [H_2, Pd/C (10%), $MeOH/H_2O/AcOH$] to give the azasugars **18** - **21**. Gluconolactam **13** could be reduced to the known[11] tetrabenzyldeoxynojirimycin **17**, which can be used for the synthesis of several N-alkylated derivatives[5c].



a: NH_3, MaOH, b: DMSO, Ac_2O, c: NH_3, MeOH, d: $NaCNBH_3$, HCO_2H



Scheme 1

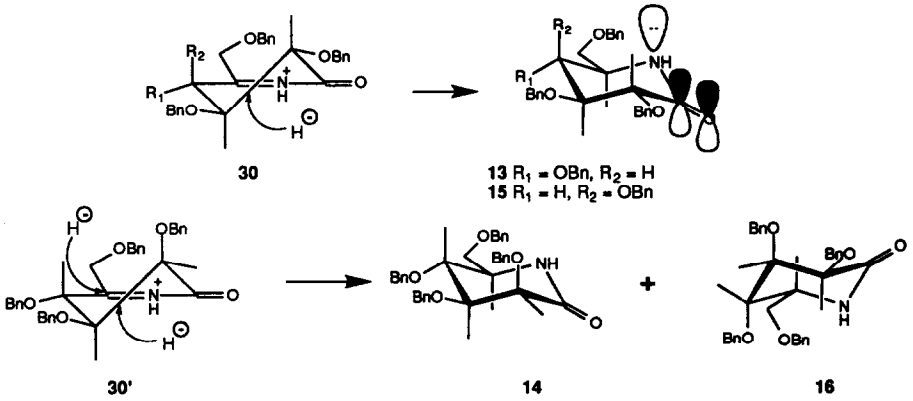


a: $Pd(OH)_2/C$, EtOH-MeOH 3:1, HCl (cat)
b: $LiAlH_4$, THF.

Scheme 2

An analogous sequence of transformations was also employed for conversion of the five-ring arabinolactone (**22**)[10b] via the corresponding arabinoamide (**23**), 4-dehydro-4-oxo-D-arabinoamide **24** and the 4-dehydro-4-hydroxy arabinolactam isomers **25** to the corresponding lactam (**26**), which was subsequently debenzylated to **28** (Scheme 2). The structure of **26** was derived from its NMR data and securely established by its conversion, via **27**, to the known 1,4-dideoxy-1,4-imino-arabinitol **29**[12].

The stereochemical course of reduction of the lactams **10** - **12** deserves comment. The mechanism of this step presumably involves a hydride donation by the sodium cyanoborohydride reagent to the acyliminium ion (**30**), initially formed by an acid catalyzed dehydration of the enantiomeric mixtures of the hydroxy lactam substrates (**10** - **12**). In case of **10** and **12**, the reduction of such an intermediate leads to the products expected on the basis of the stereoelectronically controlled transition states. The hydride approaches the α-face of the ring, thus generating that configuration of the developing nitrogen electron-pair, which allows the most effective overlap with the orbitals of the lactam carbonyl. A similar reasoning applies to the reduction step in the synthesis of **26**.



Scheme 3

The fact that acyliminium ion **30'** (scheme 3), from hydroxy lactam **11**, gives a mixture of **14** and **16**, in which **14** is the predominant product, implicates the steric features of the transition state of the hydride addition to the intermediate. An α-attack by hydride on **30'** results in a transition state in which the generated product (**14**) bears a sterically unfavored axial C(2)-benzyloxy substituent. A β-attack at the iminium carbon of **30'** requires that when the ideal overlap between the developing nitrogen lone-pair and the carbonyl orbitals is attained, the transition state bears two substituents (C(3)- and C(4)- benzyloxy groups) in the axial positions. Thus, the steric factors in the transition states of the two pathways, while allowing the operation of a β-attack, still favor the approach of the hydride on the α-face of the molecule. It may therefore be concluded that the selectivity of the reduction step of the synthetic sequence can be anticipated, provided due attention is paid to the relevant stereoelectronic factors which operate in the transition state of the reaction.

The biological evaluation of the synthesized compounds is currently in progress and will be presented elsewhere.

Experimental

General methods and materials

Infrared (IR) spectra were recorded on a Perkin Elmer 1310 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) were recorded on a Bruker WM-250 or a Bruker ARX 400 instrument. The NMR spectra recorded in $CDCl_3$ are recorded with tetramethylsilane as reference; the NMR spectra in D_2O were recorded with

sodium 3-(trimethylsilyl)propionate 2,2,3,3-d_4 as reference. Attached proton tests (APT) spectra were recorded at the Bruker ARX 400 instrument at 100.61 MHz. Thin layer chromatography (TLC) was performed on silicagel coated plastic sheets (Merck silicagel 60 F_{254}). Flash chromatography was performed on Silicagel 0.035-0.070 mm (Janssen Chimica). Optical rotations were measured on a Perkin Elmer 241 polarimeter. Elemental analysis were performed by Dornis u. Kolbe Microanalytisches Laboratorium, Mülheim a.d. Ruhr, Germany. Mass spectra were recorded on a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer using the Fast Atom Bombardment (FAB) technique. Melting points (m.p.) were determined on a Leitz melting point microscope and are uncorrected.

2,3,4,6-tetra-O-benzyl-D-glucono-δ-lactone 1[10a]

A solution of 10.1 gram 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (18.8 mmol) in 50 ml dimethyl sulfoxide and 30 ml acetic anhydride was stirred for 12 hours under nitrogen atmosphere. The reaction was quenched by adding 200 ml water; the resulting mixture was stirred for another 15 minutes during which the product precipitated as an oil. The water layer was removed and the resulting crude oil was washed for three times with water in the same way. The residue was then dissolved in dichloromethane and washed with water (3x). The collected organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* .The product was used for further reactions without further purification. Yield 10.53 g crude oil (R_f in ethyl acetate / petroleum ether 1:1 is 0.64). IR ($CHCl_3$): 1750 (δ-lactone), 1490, 1450, 1360, 690 (Ar). ^{1}H NMR ($CDCl_3$): 3.71 (2xdd, 2H, C-6; J5-6 = 2.5 and 3.0 Hz; J6-6 = 11.1 Hz), 3.84-4.01 (m, 2H, C-3, C-4), 4.14 (d, 1H, C-2; J2-3 = 6.7 Hz), 4.4-4.8 (m, 8H, C-5 and $PhCH_2$), 5.0 (d, 1H, $PhCH_2$; J = 11.4 Hz), 7.1-7.4 (m, 20H, ArH).

2,3,4,6-tetra-O-benzyl-D-mannono-δ-lactone 2

2,3,4,6-tetra-O-benzyl-D-galactopyranose (1.05 g; 1.93 mmol) was allowed to react with 5 ml dimethyl sulfoxide and 3 ml acetic anhydride. Work up procedure as for **1** and crystallisation from ethyl acetate and petroleum ether yielded 719 mg white crystals of **2** (1.38 mmol; 71%). Rf in petroleum ether / ethyl acetate 4:1 is 0.17. IR ($CHCl_3$): 1765 (δ-lactone), 690 (Ar).M.p. 83.5-85°C. ^{1}H-NMR ($CDCl_3$): 3.64 (d, 2H, C-6; J_{56}=4.5 Hz), 3.78 (dd, 1H, C-4; J4-3 = 1.4 Hz, J4-5 = 7.3 Hz), 4.06 (dd, 1H, C-3; J3-2 = 2.6 Hz, J3-4 = 1.4 Hz), 4.21-4.37 (m, 4H, C-2, C-5, $PhCH_2$), 4.54 (s, 2H, $PhCH_2$), 4.59 (d, 1H, $PhCH_2$; J = 11.9 Hz), 4.65 (d, 1H, $PhCH_2$; J = 11.2 Hz), 4.86 (d, 1H, $PhCH_2$; J = 11.2 Hz), 5.07 (d, 1H, $PhCH_2$; J = 11.9 Hz), 7.07-7.41 (m, 20H, ArH).

2,3,4,6-tetra-O-benzyl-D-galactono-δ-lactone 3

2,3,4,6-tetra-O-benzyl-D-galactopyranose (1.0 g; 1.85 mmol) was allowed to react with 5 ml dimethyl sulfoxide and 3 ml acetic anhydride as described for **1**. Flash chromatography with petroleum ether 60-80 / ethyl acetate 3:1 (Rf = 0.31) gave 893 mg of a white syrup of **3** (1.66 mmol; 90%). IR ($CHCL_3$): 1740 (δ-lactone), 690 (Ar). ^{1}H-NMR ($CDCl_3$): 3.65 (dd, 1H, C-6; J5-6 = 5.6 Hz, J6-6 = 9.2 Hz), 3.72 (dd, 1H, C-6; J5-6 = J6-6 = 9.1 Hz), 3.89 (dd, 1H, C-3; J3-2 = 9.6 Hz, J3-4 = 2.2 Hz), 4.17 (dd, 1H, C-4; J4-3 = J4-5 = 1.8 Hz), 4.39 (ddd, 1H, C-5; J5-4 = 1.5 Hz, J5-6 = 6.0 and 9.0 Hz), 4.45-4.53 (m, 3H, C-2; $PhCH_2$), 4.61, 4.70, 4.77, 4.79, 4.92, 5.19 (5x d, $PhCH_2$; J=10.7-11.9 Hz), 7.21-7.43 (m, 20H, ArH).

2,3,4,6 tetra-O-benzyl-D-gluconamide 4

4.02 gram gluconolactone **1** was dissolved in 50 ml of an 8N ammonia-solution in methanol. After stirring for 1.5 hour under nitrogen atmosphere the reaction mixture was concentrated *in vacuo* . Crystallization of the resulting white solid from ethyl acetate and petroleum ether 60-80 afforded 3.4 gram of white crystals of **4** (6.1 mmol). R_f in petroleum ether / ethyl acetate 1:1 is 0.22. Yield 86% in 2 steps from tetrabenzylglucose. M.p. 74-77°C. $[\alpha]_D$ +26.7 (c 0,53; $CHCl_3$) (Lit[7c]: M.p. 89-90°C. $[\alpha]_D$ +24.5. IR ($CHCl_3$): 3600-3500 (b, OH), 3500, 3400 (NH_2), 3000, 2920, 2820, 1680 (amide), 1560, 1490, 1450, 695 (Ar). ^{1}H NMR ($CDCl_3$): 2.85 (d, 1H, OH; J = 2.9 Hz), 3.63 (2x dd, 2H, C-6; J5-6 = 2.3 and 4.7 Hz; J6-6 = 10.5 Hz), 3.80-4.00 (m, 2H, C-4, C-5), 4.08 (dd, 1H, C-3; J3-2 = 3.2 Hz; J3-4 = 4.0 Hz), 4.26 (d, 1H, C-2; J2-3 = 3.2 Hz), 4.4-4.8 (m, 8H, $PhCH_2$), 5.62 (bs, 1H, NH), 7.0-7.5 (m, 20H, ArH). MS (FAB): 556 (M+1). Analysis calcd for $C_{34}H_{37}NO_6$: C, 73.49; H, 6.70; N, 2.52. Found: C, 73.55; H, 6.71; N, 2.48.

2,3,4,6-tetra-O-benzyl-D-mannonamide 5

Lactone **2** (497 mg; 0.92 mmol) was allowed to react with 10 ml 8N ammonia in methyl alcohol as described for **2**. Yield 510 mg of **5** as a white solid (0.92 mmol; 100%). Rf in petroleum ether 60-80 / ethyl acetate 1:1 is 0.25). $[\alpha_D]$ +15.8 (c 0.55; $CHCl_3$). M.p. 132-134° C. IR ($CHCl_3$): 3505, 3400 (OH, NH), 1680 (amide), 690 (Ar). ^1H NMR ($CDCl_3$): 3.25 (d, 1H, OH; J = 6.0 Hz), 3.64 (d, 2H, C-6; J5-6 = 4.1 Hz), 3.88 (dd, 1H, C-4; J4-3 = 5.6 Hz, J4-5 = 7.3 Hz), 3.97-4.02 (m, 1H, C-5), 4.13 (dd, 1H, C-3; J3-4 = 5.3 Hz, J3-2 = 3.8 Hz), 4.35 (d, 1H, C-2; J2-3 = 3.6 Hz), 4.47-4.72 (m, 8H, $PhCH_2$), 5.57 (bs, 1H, NH), 6.57 (bs, 1H, NH), 7.15-7.33 (m, 20H, ArH). MS (FAB): 556 (M+1).

2,3,4,6-tetra-O-benzyl-D-galactonamide 6

Lactone **3** (881 mg; 1.64 mmol) was allowed to react in 15 ml of 8N ammonia in methyl alcohol as described for **4**. Crystallization from ethyl acetate and petroleum ether 60-80 gave 738 mg of white crystals of **6** (1.33 mmol, yield 81%). Rf in petroleum ether 60-80 / ethyl acetate 2:1 is 0.20. $[\alpha_D]$ -2.46 (c 0.33; $CHCl_3$). M.p. 118-121°C. IR ($CHCl_3$): 3550, 3500, 3395 (OH, NH), 1680 (amide), 690 (Ar). ^1H NMR ($CDCl_3$): 2.52 (d, 1H, OH; J = 8.3 Hz), 3.52 (dd, 1H, C-6; J5-6 = 6.5 Hz, J6-6 = 9.4 Hz), 3.59 (dd, 1H, C-6; J5-6 = 6.5 Hz, J6-6 = 9.4 Hz), 3.89 (dd, 1H, C-3, J3-2 = 8.2 Hz, J3-4 = 1.5 Hz), 4.11-4.20 (m, 3H, C-2, C-4, C-5), 4.35 (d, 1H, $PhCH_2$; J = 11.5 Hz), 4.40 (d, 1H, $PhCH_2$; J = 11.5 Hz), 4.45 (d, 1H, $PhCH_2$; J = 11.4 Hz), 4.47 (d, 1H, $PhCH_2$; J = 11.4 Hz), 4.56 (d, 1H, $PhCH_2$; J = 11.9 Hz), 4.61 (d, 2H, $PhCH_2$; J = 11.0 Hz), 4.70 (d, 1H, $PhCH_2$; J = 11.0 Hz), 5.60 (bs, 1H, NH), 6.61 (bs, 1H, NH), 7.16-7.36 (m, 20H, ArH).

2,3,4,6-tetra-O-benzyl-5-dehydro-5-oxo-D-gluconamide 7

A solution of 1.93 gram **2** (3.5 mmol) in 12.5 ml dimethyl sulfoxide and 7.5 ml acetic anhydride was stirred under a nitrogen atmosphere for 12 hours. 50 ml water was added and the mixture was stirred for another 15 minutes during which a yellow oil precipitated. The water layer was then removed and the residue was extracted with water (3x). The residue was dissolved in dichloromethane and extracted with brine (2x). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. The product without further purification was used for the subsequent reactions. Yield 2.9 g of a yellow syrup of **7** (R_f in petroleum ether 60-80 / ethyl acetate 1:1 is 0.26). M.p. 114-116°C. IR ($CHCl_3$): 3500, 3400 (NH_2), 3000, 2920, 2820, 1725 (C=O), 1685 (amide), 1560, 1490, 1450, 695 (Ar). ^1H NMR ($CDCl_3$): 4.1-4.7 (m, 13H, C-2, C-3, C-4, C-6, $PhCH_2$), 5.52 (bs, 1H, NH), 6.59 (bs, 1H, NH), 7.1-7.4 (m, 20H, ArH). MS (FAB): 556 (M+1).

2,3,4,6-tetra-O-benzyl-5-dehydro-5-oxo-D-mannonamide 8

A solution of 925 mg of amide **5** (1.67 mmol) was allowed to react with 5 ml dimethyl sulfoxide and 3 ml acetic anhydride as described for compound **7**. Crystallization from ethyl acetate gave 846 mg of white crystals of **8** (2.53 mmol; 92%). Rf in ethyl acetate / petroleum ether 60-80 1:1 is 0.30. IR ($CHCl_3$): 3510, 3410 (NH_2), 1730 (carbonyl), 1700 (amide), 695 (Ar). ^1H NMR ($CDCl_3$): 4.11 (d, 1H; J = 4.3 Hz), 4.10-4.31 (m, 3H), 4.33 (d, 1H, J = 5.4 Hz), 4.42-4.66 (m, 8H), 5.39 (bs, 1H, NH), 6.40 (bs, 1H, NH), 7.18-7.34 (m, 20H, ArH). MS (FAB): 554 (M+1).

2,3,4,6-tetra O-benzyl-5-dehydro-5-hydroxy-D-glucono- and L-idonolactam 10

Compound **7** (273 mg; 0.49 mmol) was dissolved in 10 ml of a solution of ammonia in methyl alcohol (8M ammonia). The mixture was stirred for 2 hours after which it was concentrated *in vacuo*. The residue was purified with flash chromatography (eluent: petroleum ether 60-80 / ethyl acetate 2:1). Yield of two products: 135 mg of a white solid of **10a** (0.24 mmol; 59%; R_f in the same eluent is 0.16) and 77 mg of a yellow syrup of **10b** (0.14 mmol; 33%; R_f is 0.08). **10a**: m.p. 99-101° C. $[\alpha]_D$ +78,6 (c 0,51; $CHCl_3$). IR ($CHCl_3$): 3550 (OH), 3380 (NH), 1685 (δ-lactam), 1490, 1450, 690 (Ar). ^1H NMR ($CDCl_3$): 3.24 (d, 1H, C-6; J6-6 = 9.5 Hz), 3.33 (d, 1H, C-6; J6-6 = 9.5 Hz), 3.74 (d, 1H,C-4; J3-4 = 9.5 Hz), 4.01 (d, 1H, C-2; J2-3 = 8.5 Hz), 4.22 (dd, 1H, C-3; J2-3 = 8.8 Hz; J3-4 = 9.2 Hz), 4.53 (d, 2H, $PhCH_2$; J = 8.9 Hz), 4.74 (d, 1H, $PhCH_2$; J =

11.2 Hz), 4.77 (d, 1H, $PhCH_2$; J = 11.0 Hz), 4.89 (d, 1H, $ArCH_2$; J = 11.0 Hz), 5.17 (d, 1H, $PhCH_2$; J = 11.1 Hz), 6.35 (bs, 1H, NH), 7.10-7.50 (m, 20H, ArH). **10b**: IR ($CHCl_3$): 3550 (w, OH), 3380 (w, NH), 1685 (s, δ-lactam), 1490, 1450, 690 (Ar). ^1H NMR ($CDCl_3$): 3.53 (d, 1H, C-6; J6-6 = 9.2 Hz), 3.64 (d, 1H, C-6; J6-6 = 9.2 Hz), 3.77 (d, 1H, C-4; J3-4 = 4.4 Hz), 3.93 (dd, 1H, C-3; J3-4 = 4.4 Hz; J2-3 = 6.8 Hz), 4.36 (d, 1H, C-2; J2-3 = 6.8 Hz), 4.42 (d, 1H, $PhCH_2$; J = 11.5 Hz), 4.50-4.80 (m, 6H, v), 5.12 (d, 1H, $PhCH_2$; J=11.3 Hz), 6.65 (bs, 1H, NH), 7.10-7.50 (m, 20H, ArH). Based on the NMR-spectra the major produkt is assigned to the gluconolactam-structure **10a** and the minor produkt to the idonolactam-structure **10b**.

Isomeric lactams (11, C5-epimers)
Amide **8** (474 mg; 0.86 mmol) was stirred in a solution of 8N ammonia in methyl alcohol for 2 hours. After evaporation a yellow syrup was obtained which contained a mixture of the hydroxy lactams. The mixture was used for the subsequent reactions without separation. Rf in petroleum ether 60-80 / ethyl acetate 2:1 is 0.08 and 0.15. IR ($CHCl_3$): 3510 (OH), 3380 (NH), 1685 (δ-lactam), 695 (Ar). MS (FAB): 554 (M+1).

Isomeric lactams (12, C5-epimers)
Amide **6** (694 mg; 1.25 mmol) was allowed to react with 6 ml dimethyl sulfoxide and 4 ml acetic anhydride as described for compound **4**. The resulting oxoamide cyclised directly giving the two hydroxy lactams which were used for the following step without separation. Yield 574 mg of a yellow syrup (1.04 mmol; 83%). Rf in petroleum ether 60-80 / ethyl acetate 3:1 is 0.17 and 0.29. IR ($CHCl_3$): 3500 (OH), 3390 (NH), 1670 (δ-lactam), 690 (Ar).

2,3,4,6-tetra-O-benzyl-D-glucono-δ-lactam 13
Compound **7** (1.0 gram; 1.8 mmol) was dissolved in 25 ml acetonitrile and 6.5 ml formic acid. To this mixture, 360 mg sodium cyanoborohydride (2 mole eq.) was added and the reaction mixture was refluxed for two hours. The mixture was then cooled in ice and the reaction was quenched by adding aq. HCl-solution (0.1 M). After stirring for 15 minutes, the mixture was poured into a mixture of ethyl acetate / saturated aqueous $NaHCO_3$ solution (1:1, 100 ml). The water layer was separated and extracted with ethyl acetate; the combined organic fractions were then washed with brine and dried over Na_2SO_4. After concentration *in vacuo* the resulting white solid was crystallized from petroleum ether and ethyl acetate (R_f in petroleum ether / ethyl acetate 1:1 is 0.43). Yield 690 mg of white crystals (1.27 mmol; 71%). The same product could be obtained under the same conditions from the mixture of hydroxylactams **10**; in this case the yield was 79%. M.p. 100-102° C. $[\alpha]_D$ +105,5 (c 0,51; $CHCl_3$). IR ($CHCl_3$): 3385 (NH), 3000, 2920, 2880, 1672 (δ-lactam), 1490, 1450, 695 (Ar). ^1H NMR (C_6D_6): 3.11 (dd, 1H, C-6; J6-6 = 9.6 Hz; J5-6 = 6.4 Hz), 3.2-3.4 (m, 2H, C-5, C-6), 3.49 (dd, 1H, C-4; J4-5 = J4-3 = 8.3 Hz), 3.83 (dd, 1H, C-3; J4-3 = J3-2 = 8.3 Hz), 4.00 (d, 1H, C-2; J2-3 = 8.0 Hz), 4.12 (d, 1H, v; J = 12.1 Hz), 4.20 (d, 1H, $PhCH_2$; J = 12.1 Hz), 4.34 (d, 1H, $PhCH_2$; J = 11.5 Hz), 4.61 (d, 1H, $PhCH_2$; J = 11.4 Hz), 4.73 (d, 1H, $PhCH_2$; J = 11.5 Hz), 4.82 (d, 1H, $PhCH_2$; J = 11.5 Hz), 4.88 (d, 1H, $PhCH_2$; J = 11.5 Hz), 5.38 (d, 1H, $PhCH_2$; J = 11.5 Hz), 6.75 (bs, 1H, NH), 7.0-7.5 (m, 20H, ArH). MS (FAB): 538 (M+1). Analysis calcd for $C_{34}H_{35}NO_5$: C, 75.95; H, 6.56; N, 2.69. Found: C, 75.82; H, 6.63; N, 2.75.

2,3,4,6-tetra-O-benzyl-D-mannono-δ-lactam 14 and C-5 epimer 16
Ketoamide **8** (83 mg; 0.15 mmol) was allowed to react with 30 mg sodium cyanoborohydrate and 0.5 ml formic acid in 1.5 ml acetonitrile as described for compound **13**. A yellow syrup was obtained containing a mixture of two lactams. Flash chromatography with petroleum ether 60-80/ ethyl acetate 2:1 gave the lactams **14** and **16** in ratio of 8:5 (Rf 0.33 and 0.41), both as a yellow syrup. Yield 40 mg of **14** (0.074 mmol, 50%) and 24 mg of **16** (0.048 mmol, 32%). **14**: $[\alpha]_D$ -18.9 (c 0,28; $CHCl_3$). IR ($CHCl_3$): 3380 (NH), 1670 (δ-lactam), 690 (Ar). ^1H NMR ($CDCl_3$): 3.46 (dd, 1H, C-6; J5-6 = J6-6 = 9.9 Hz), 3.55-3.60 (m, 2H, C-6, C-5), 3.72 (dd, 1H, C-4; J4-3 = J4-5 = 5.0 Hz), 3.98 (dd, 1H, C-3; J4-3 = 5.2 Hz, J3-2 = 3.0 Hz), 4.21 (d, 1H, C-2; J2-3 = 2.9 Hz), 4.43-4.53 (m, 3H, $PhCH_2$), 4.60 (d, 1H, $PhCH_2$; J = 11.6 Hz), 4.63 (d, 1H, $PhCH_2$; J = 11.2 Hz), 4.73 (d,

1H, $PhCH_2$; J = 12.2 Hz), 5.08 (d, 1H, $PhCH_2$; J = 12.1 Hz), 6.28 (bs, 1H, NH), 7.18-7.47 (m, 20H, PhH). MS (FAB): 538 (M+1). $_{16}$:$[\alpha]_D$ -73.2 (c 0,40; $CHCl_3$). IR ($CHCl_3$): 3380 (NH), 1670 (δ-lactam), 690 (Ar). ^{1}H NMR ($CDCl_3$): 3.48 (dd, 1H, C-6; J5-6 = 4.4 Hz, J6-6 = 9.0 Hz), 3.57 (dd, 1H, C-6; J5-6 = J6-6 = 9.0 Hz), 3.68 (m, 1H, C-4), 3.99-4.04 (m, 2H, C-3, C-5), 4.23-4.32 (m, 3H, C-2, $PhCH_2$), 4.48 (d, 1H, $PhCH_2$, J = 11.7 Hz), 4.53 (d, 1H, $PhCH_2$, J = 11.7 Hz), 4.64 (d, 1H, $PhCH_2$, J = 12.1 Hz), 4.76 (d, 1H, $PhCH_2$, J = 12.4 Hz), 4.90 (d, 1H, $PhCH_2$, J = 12.2 Hz), 5.17 (d, 1H, $PhCH_2$, J = 12.4 Hz), 6.01 (bs, 1H, NH), 7.02-7.44 (m, 20H, ArH). APT ($CDCl_3$): 52.47 (C-5), 69.89 ((C-6), 72.82 ($PhCH_2$), 73.29 (2x $PhCH_2$), 73.45 (C-4), 73.87 ($PhCH_2$), 73.92 (C-3), 74.85 (C-2), 127.59, 127.70, 127.72, 127.75, 127.88, 127.97, 128.21, 128.23, 128.31, 128.32, 128.64, 136.85, 137.42, 137.99, 138.12 (Ph), 171.20 (C=O).

2,3,4,6-tetra-O-benzyl-D-galactono-δ-lactam **15**

The mixture of hydroxylactams **12** (403 mg; 0.73 mmol) was allowed to react with 160 mg sodium cyanoborohydride and 3 ml formic acid in 9 ml cyanonitrile as described for compound **13**. Flash chromatography with petroleum ether 60-80 / ethyl acetate 4:1 as eluent gave 285 mg of **15** as a yellow syrup (0.53 mmol; 73%). Rf in petroleum ether 60-80 / ethyl acetate 2:1 is 0.16. $[\alpha]_D$ +68.0 (c 0,38; $CHCl_3$) IR ($CHCl_3$): 3390 (NH), 1665 (δ-lactam), 690 (Ar). ^{1}H NMR ($CDCl_3$): 3.43 (dd, 1H, C-6; J5-6 = 3.1 Hz, J6-6 = 8.0 Hz). 3.52-3.61 (m, 2H, C-5, C-6), 3.83 (dd, 1H, C-3; J3-2 = 9.2 Hz, J3-4 = 1.4 Hz), 3.97 (bs, 1H, C-4), 4.34 (d, 1H, C-2; J2-3 = 9.1 Hz), 4.43 (d, 1H, $PhCH_2$; J = 11.8 Hz), 4.49 (d, 1H, $PhCH_2$; J = 11.6 Hz), 4.57 (d, 1H, $PhCH_2$; J = 11.5 Hz), 4.69 (d, 1H, $PhCH_2$; J = 11.9 Hz), 4.79 (d, 1H, $PhCH_2$; J = 12.0 Hz), 4.81 (d, 1H, $PhCH_2$; J = 11.3 Hz), 4.91 (d, 1H, $PhCH_2$; J = 11.5 Hz), 5.21 (d, 1H, $PhCH_2$; J = 11.3 Hz), 5.85 (bs, 1H, NH), 7.20-7.44 (m, 20H, Ar). APT ($CDCl_3$): 53,54 (C-5), 70.22 (C-6), 73.06 (C-4), 73.09, 73.53, 74.14 ($PhCH_2$), 77.41 (C-2), 80.66 (C-3), 127.58, 127.63, 127.73,127.78, 127.84, 127.89, 128.02, 128.28, 128.37, 128.44, 128.53, 137.42, 137.94, 138.16, 138.31 (Ph), 171.02 (C=O). MS (FAB): 538 (M+1).

2,3,4,6-tetra-O-benzyl-1,5-dideoxy-1,5-imino-D-glucitol **17**

To a solution of 100 mg of **13** (0.19 mmol) in 5 ml tetrahydrofuran 20 mg lithiumaluminumhydride (3 mole eq) was added. The reaction mixture was stirred for 3 hours at 70° C under nitrogen atmosphere. The mixture was then brought to room temperature and poured into a mixture of ether and ice water (1:1, 100 ml). After stirring for 15 minutes, 75 ml aquous sodium hydroxide (0.5 M) was added and the mixture was stirred for another 10 minutes. The water layer was then separated and extracted with ether; the organic fractions were collected and washed with brine and dried ($MgSO_4$). After concentration *in vacuo* the product was purified with flash chromatografy (eluent petroleumether 60-80 / ethylacetate 1:1; R_f is 0.36) to give a yellow syrup. Crystalliztation from ethyl acetate / petroleum ether 60-80 gave 61 mg of white crystals of **17** (1.12 mmol; 63%). $[\alpha]_D$ +29.5 (c 0,60; $CHCl_3$). M.p. 43-45° C (Lit[11] $[\alpha]_D$ +33.1 (c 0,60; $CHCl_3$). M.p. 46-47.5° C). IR ($CHCl_3$): 3340 (NH), 3000, 2960, 2920, 2880, 1950, 1870, 1820, 1490, 1450, 690 (Ar). ^{1}H NMR ($CDCl_3$,): 2.06 (s, 1H, NH), 2.49 (dd, 1H, C-1; J1-1 = 12.0 Hz; J1-2 = 10.0 Hz), 2.74 (ddd, 1H, C-5; J = 2.6, 6.1 and 9.0 Hz), 3.26 (dd, 1H, C-1; J1-1 = 12.2 Hz; J1-2 = 4.5 Hz), 3.37 (dd, 1H, C-4; J4-5 = 8.8 Hz; J4-3 = 9.6 Hz), 3.45-3.60 (m, 3H, C-2, C-3, C-6), 3.69 (dd, 1H, C-6; J6-6 = 9.0 Hz; J5-6 = 2.6 Hz), 4.40-4.55 (m, 3H, $PhCH_2$), 4.70 (s, 2H, $PhCH_2$), 4.85 (d, 1H, $PhCH_2$; J = 10.9 Hz), 4.88 (d, 1H, $PhCH_2$; J = 10.9 Hz),
5.00 (d, 1H, $PhCH_2$; J = 10.9 Hz), 7.20-7.35 (m, 20H, ArH).

D-glucono-δ-lactam **18**

Compound **13** (300 mg; 0.56 mmol) was dissolved in 10 ml methyl alcohol and 3 ml ethyl alcohol. To this solution, 60 mg palladium hydroxide on coal (20% w/w) was added, together with a few µl aqueous HCl solution (1M). This mixture was shaken for 48 hours under 50 Parr in a Parr apparatus. The mixture was then filtrated over hyflow and the filtrate was concentrated *in vacuo* . The product was dissolved in a small amount of water and crystallized with ethyl alcohol. Yield 56 mg white powder (0.32 mmol; 57%). M.p. 195-198° C. $[\alpha]_D$ +63.4 (c 0.51; H_2O) (Lit[7b] M.p. 204-205° C. $[\alpha]_D$ +57 (c 0.63; H_2O). IR (KBr): 3500-3000 (b; 3420, 3380, 3180; OH, NH), 1650-1640 (δ-lactam). ^{1}H NMR (D_2O): 3.34-3.38 (m, 1H) and 3.66-3.83 (m, 4H) and 3.97-4.01 (m, 1H): C-2, C-3, C-4, C-5, C-6. ^{13}C NMR C: 175.65 (C=O), 62.64 (C-6), 75.61, 72.94, 69.83, 59.25

(C-2,-C-3, C-4, C-5). MS (FAB): 178 (M+1). Analysis calculated for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.65; H, 6.19; N, 7.98.

D-manno-δ-lactam **19**

Lactam **14** (254 mg; 0.47 mmol) in 10 methyl alcohol and 3 ml ethyl alcohol was subjected to hydrogenolysis with 60 mg palladium hydroxide on coal (20% w/w) and hydrogen as described for **18**. Concentration *in vacuo* yielded 70 mg yellow syrup (0.39 mmol; 84%) which could not be crystallized. $[\alpha]_D$ +1.6 (c 0.38; H_2O). (Lit[8a] M.p. 169-170° C. $[\alpha]_D$ +1.6 (c 0.8; H_2O) ^1H NMR (D_2O): 3.40 (m, 1H), 3.73 (dd, 1H), 3.83 (m, 1H), 3.89 (dd, 1H), 3.89 (dd, 1H), 4.06 (dd, 1H), 4.37 (d, 1H).

D-isomanno-δ-lactam **20**

Lactam **16** (172 mg; 0.32 mmol) in 10 methyl alcohol and 3 ml ethyl alcohol was subjected to hydrogenolysis with 60 mg palladium hydroxide on coal (20% w/w) and hydrogen as described for **18**. Concentration *in vacuo* yielded 40 mg yellow syrup (0.22 mmol; 70%) which could not be crystallized. $[\alpha]_D$ -27.0 (c 0.50; H_2O). ^1H NMR (D_2O): 3.68-3.74 (m, 1H), 3.78-3.88 (m, 2H), 4.22-4.29 (m, 2H), 4.42 (d, 1H).

D-galactono-δ-lactam **21**

Lactam **15** (600 mg; 1.12 mmol) in 15 ml methyl alcohol and 6 ml ethyl alcohol was reduced under hydrogen with 100 mg palladium hydroxide on coal as described for **18**. Crystallization yielded 100 mg white crystals (0.56 mmol; 50%).mp 192-195°C. $[\alpha]_D$ +160 (c 0.26; H_2O). ^1H NMR (D_2O): 3.61-3.70 (m, 2H), 3.75-3.82 (m, 1H), 3.95 (d, 1H; J=2.4 and 10.0 Hz), 4.20-4.25 (m, 2H). APT (D_2O): 57.55, 63.59, 70.59, 71.99, 74.98, 176.34 (C=O). MS (FAB): 178 (M+1). Analysis calculated for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.55; H, 6.26; N, 7.91.

2,3,5-tri-O-benzyl-D-arabino-γ-lactone **22**[10b]

2,3,5-tri-O-benzyl-arabinofuranose (4.08 g; 9.70 mmol) was allowed to react with 12 ml dimethyl sulfoxide and 8 ml acetic anhydride for 12 hours under a nitrogen atmosphere. The reaction mixture was then poured into 200 ml water and stirred for 1 hour. The crude product pricipitated as a white solid which was filtrated and washed with water (2x). The product was used for the next steps without further purification. Yield 4.00 g of **22** (9.65 mmol; 99%). Rf in petroleum ether / ethyl acetate 3:2 is 0.54. $[\alpha]_D$ +8.3 (c 0,36; $CHCl_3$). IR ($CHCl_3$): 1785 (γ-lactone), 1490, 1450, 670 (Ar). ^1H NMR ($CDCl_3$): 3.60 (dd, 1H, C-5; J4-5 = 3.5 Hz, J5-5 = 11.6 Hz), 3.72 (dd, 1H, C-5; J4-5 = 2.0 Hz, J5-5 = 11.5 Hz), 4.31-4.38 (m, 3H, C-2, C-3, C-4), 4.51 (d, 1H, $PhCH_2$; J = 12.0 Hz), 4.54 (d, 1H, $PhCH_2$; J = 12.1 Hz), 4.57 (d, 1H, $PhCH_2$; J = 12.6 Hz), 4.65 (d, 1H, $PhCH_2$; J = 11.6 Hz), 4.78 (d, 1H, $PhCH_2$; J = 11.6 Hz), 5.08 (d, 1H, $PhCH_2$; J = 11.6 Hz), 7.22-7.43 (m, 15H, ArH).

2,3,5-tri-O-benzyl-D-arabinoamide **23**

Lactone **22** (900 mg; 2.15 mmol) was reacted with 20 ml $MeOH/NH_3$ (8M ammonia) as described for **4**. Yield 937 mg of a white solid of **23** (2.15 mmol, 99%). Rf in petroleum ether 60-80 / ethyl acetate 3:2 is 0.36. M.p. 111-112° C. IR ($CHCl_3$): 3505, 3395 (NH, OH), 1680 (amide), 690 (Ar), ^1H NMR ($CDCl_3$): 2.51 (d, 1H, OH; J = 7.2 Hz), 3,57 (dd, 1H, C-5; J4-5 = 4 .3 Hz, J5-5 = 9.6 Hz), 3.64 (dd, 1H, C-5; J4-5 = 3.0 Hz, J5-5 = 9.5 Hz), 3.94-4.00 (m, 1H, C-4), 4.02 (dd, 1H, C-3; J3-2 = 2.0 Hz, J3-4 = 8.8 Hz), 4.31 (d, 1H, C-2; J2-3 = 2.0 Hz), 4.41 (d, 1H, $PhCH_2$; J = 11.0 Hz), 4.46 (d, 1H, $PhCH_2$; J = 11.8 Hz), (d, 1H, $PhCH_2$; J = 11.8 Hz), 4.58 (d, 1H, $PhCH_2$; J = 11.0 Hz), 4.65 (s, 2H, $PhCH_2$), 5.58 (bs, 1H, NH), 6.74 (bs, 1H, NH), 7.18-7.37 (m, 15H, ArH). APT ($CDCl_3$): 69.27 (C-4), 70.57 (C-5), 73.40, 74.38, 74.59 ($PhCH_2$), 79.37 (C-3), 79.78 (C-2), 127.78, 127.89, 127.96, 128.28, 128.30, 128.48, 128.58, 136.98, 137.69, 137.74 (Ar), 174.96 (C=O). MS (FAB): 436 (M+1).

2,3,5-tri-O-benzyl-4-dehydro-4-oxo-D-arabinoamide 24

Amide **23** (300 mg; 0.69 mmol) was dissolved in 5 ml dichloromethane. 425 mg Dess Martin reagent[13] (1.5 eq.) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction was then quenched by pouring it into a mixture of 3 ml sodium bicarbonate and 7 ml sodium thiosulfate. After stirring for 30 minutes during which the mixture became clear the water layer was removed and washed with dichloromethane (2x). The organic fractions were collected and washed with brine and dried over magnesiumsulfate. Concentration *in vacuo* yielded 261 mg of a white solid of **24** (0.60 mmol; 88%). Rf in petroleum ether / ethyl acetate 1:1 is 0.15. M.p. 130-133° C. IR ($CHCl_3$): 3505, 3395 (NH), 1730 (C=O), 1685 (amide), 690)Ar). ^1H NMR ($CDCl_3$): 4.16 (d, 1H, C-5; J5-5 = 18.5 Hz), 4.29 d, 1H, C-5; J5-5 = 18.4 Hz), 4.41-4.58 (m, 8H, C-2, C-3, $PhCH_2$), 5.99 (bs, 1H, NH), 6.67 (bs, 1H, NH), 7.29-7.36 (m, 15H, ArH). APT ($CDCl_3$): 73.27 (C-5), 74.20, 74.55, 74.75 (3x $PhCH_2$), 80.21 (C-3), 83.75 (C-2), 127.97, 128.29, 128.40, 128.48, 128.53, 128.67, 136.14, 136.53, 137.08 (Ar), 172.32, 206.51 (C=O).

2,3,5-tri-O-benzyl-4-dehydro-4-hydroxy-D-arabino-γ-lactam and C-4 epimer 25

Compound **24** (260 mg; 0.60 mmol) was stirred in 15 ml of an 8 M ammonia solution in methyl alcohol for 4 hours. After evaporation and flash chromatography (eluent petroleum ether / ethyl acetate 1:1, Rf is 0.25) 246 mg of a white syrup was obtained which, from NMR-data, showed to be a 1:1 mixture of the hydroxylactams **25** (0.57 mmol; 94%). IR ($CHCl_3$): 3405 (NH, OH), 1710 (lactam), 690 (Ar).

2,3,5 tri-O-benzyl-D-arabino-γ-lactam 26

The mixture of hydroxylactams **25** (1.69 mg; 4.055 mmol) was allowed to react with 500 mg sodium cyanoborohydride (2 mol eq.) in 15 ml acetonitrile and 5 ml formic acid as described for compound **13**. Flash chromatography with as eluent petroleum ether / ethyl acetate 2:1 gave 1.15 mg of lactam **26** as a white solid (2.80 mmol; 69%, Rf is 0.13) along with 125 mg of the C-4 epimer (0.30 mmol; 7%, Rf is 0.07).M.p. 54.5-56°C. $[\alpha]_D$ -3.9 (c 0.77; $CHCl_3$). IR ($CHCl_3$): 3410 (NH), 1710 (lactam), 690 (Ar). ^1H NMR ($CDCl_3$): 3.32 (dd, 1H, C-5; J4-5 = 8.4 Hz, J5-5 = 9.3 Hz), 3.61 (dd, 1H, C-5; J4-5 = 3.5 Hz, J5-5 = 9.3 Hz), 3.68 (ddd, 1H, C-4; J4-5 = 3.5 and 8.3 Hz, J4-3 = 6.0 Hz), 3.89 (dd, 1H, C-3; J3-4 = J3-2 = 6.0 Hz), 4.22 (d, 1H, C-2; J2-3 = 6.2 Hz), 4.45-4.53 (m, 3H, $PhCH_2$), 4.61 (d, 1H, $PhCH_2$; J = 11.8 Hz), 4.80 4.61 (d, 1H, $PhCH_2$; J = 11.6 Hz), 5.11 4.61 (d, 1H, $PhCH_2$; J = 11.6 Hz), 5.94 (bs, 1H, NH), 7.22-7.42 (m, 15 H, ArH). APT ($CDCl_3$): 56.17 (C-4), 71.37 (C-5), 72.25, 72.56, 73.45 ($PhCH_2$), 80.72 (C-2), 81.09 (C-3), 127.65, 127.78, 127.85, 127.91, 127.95, 128.32, 128.43, 128.45, 128.52, 137.41, 137.43, 137.57 (Ar), 172.92 (C=O). MS (FAB): 418 (M+1).

2,3,5-tri-O-benzyl 1,4-dideoxy-1,4 imino-D-arabinitol 27

Lactam **26** (370 mg; 0.89 mmol), was dissolved in 15 ml THF. 95 mg lithium aluminiumhydride was added and the reaction mixture was stirred for 4 hours at 50° C under nitrogen atmosphere. The reaction mixture was then poured into a stirred mixture of 50 ml ice water and 50 ml diethyl ether. After stirring for 10 minutes 75 ml sodium hydroxide solution (0.5 M) was added and the mixture was stirred for another 10 minutes. The water layer was then removed and extracted with 25 ml of diethyl ether (2x); the combined organic fractions were washed with brine and water. Flash chromatography (petroleum ether / ethyl acetate 1:2, Rf is 0.14) yielded 307 mg light yellow syrup (0.76 mmol; 86%). $[\alpha]_D$ +3.5 (c 0.79; $CHCl_3$). IR ($CHCl_3$): 3400-3300 (NH), 690 (Ar). ^1H NMR ($CDCl_3$): 2.08 (bs, 1H, NH), 3.10 (d, 2H, C-1; J1-2 = 3.9 Hz), 3.24 (dd, 1H, C-4; J4-3 = 5.2 Hz, J4-5 = 10.3 Hz), 3.56 (dd, 1H, C-5; J4-5 = 5.6 Hz, J5-5 = 9.5 Hz), 3.62 (dd, 1H, C-5; J4-5 = 5.1 Hz, J5-5 = 9.5 Hz), 3.88 (dd, 1H, C-3; J3-2 = 1.9 Hz, J3-4 = 4.8 Hz), 4.02 (ddd, 1H, C-2; J2-3 = 1.9 Hz, J2-1 = 3.7 Hz), 4.51-4.58 (m, 6H, $PhCH_2$), 7.25-7.35 (m, 15H, ArH). APT ($CDCl_3$): 51.06 (C-1), 64.13 (C-4), 70.63 (C-5), 71.05, 71 86, 73.18 ($PhCH_2$), 84.51 (C-2), 85.72 (C-3), 127.56, 127.62, 127.67, 127.73, 128.34, 128.38, 138.13, 138.32 (Ar). MS (FAB): 403 (M+1).

D-arabino-γ-lactam **28**

A solution of 350 mg of **15** (0.84 mmol) in 15 ml methyl alcohol and 6 ml ethyl alcohol was reduced under hydrogen pressure with 100 mg palladium hydroxide on coal as described for **18**. After crystallization from methanol 49 mg of white crystals of **27** (0.33 mmol; 40%) were obtained. M.p. 130-133°C. $[\alpha]_D$ +14.7 (c 0.58; D_2O). ^1H NMR (D_2O): 3.45-3.50 (m, 1H, C-4), 3.64 (dd, 1H, C-5; J4-5 = 4.9 Hz, J5-5 = 12.2 Hz), 3.81 (dd, 1H, C-5; J4-5 = 2.8 Hz, J5-5 = 12.2 Hz), 4.03 (dd, 1H, C-3; J3-2 = J3-4 = 7.5 Hz), 4.33 (d, 1H, C-2; J2-3 = 8.0 Hz).

1,4-dideoxy-1,4-imino-D-arabinitol **29**

To a solution of 425 mg of **27** (1.05 mmol) in 15 ml of methyl alcohol was added 150 mg Palladium on coal (10% w/w) and a catalytic amount of aquous HCl (1 M). The reaction mixture was then stirred under hydrogen pressure for 16 hours. The mixture was passed over a column packed with hyflow and concentrated. The resulting yellow syrup was dissolved in 10 ml methyl alcohol and a few ml of 3M aquous HCl was added dropwise. After stirring for 30 minutes ether was added until crystals started to precipitate.The mixture was stored at 4°C overnight. The resulting white crystals were filtrated and washed with ether yielding 110 mg of **29** as it's HCl-salt (0.69 mmol; 66%). M.p. 113-115°C. $[\alpha]_D$ +27.27 (c 0.47; D_2O) (Lit[12] M.p. 111-113°C. $[\alpha]_D$ +36.7 (c 0.1.225; D_2O)). ^1H NMR (D_2O): 3.39 (dd, 1H, C-1; J1-1 = 12.5 Hz, J1-2 = 2.8 Hz), 3.60 (dd, 1H, C-1; J1-1 = 12.6 Hz, J1-2 = 4.7 Hz), 3.65 (dd, 1H, C-4; J4-5 = 4.2 and 8.4 Hz), 3.86 (dd, 1H, C-5; J4-5 = 8.3 Hz, J5-5 = 12.2 Hz), 3.98 (dd, 1H, C-5; J4-5 = 4.7 Hz, J5-5 = 12.2 Hz), 3.93 (t, 1H, C-3; J = 3.4 Hz), 4.36 (dt, 1H). APT (D_2O): 52.80, 61.71 (C-1 and C-5), 69.42, 77.06, 78.46 (C-2, C-3 and C-4).

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