Efficient Synthesis of Isofagomine and Noeuromycin

Jens Andersch and Mikael Bols*[a]

Abstract: Starting from D-arabinose the synthesis of the very strong glycosidase inhibitors isofagomine (**2**) and noeuromycin (**3**) was achieved in six and seven steps, respectively. Keystep in the reaction sequence is the application of an efficient C-4 oxidation method to benzyl α-D-*arabino*-pyranoside. Subsequent Henry reaction of the obtained aldoketose with nitromethane provided the required branched carbohydrate precursors, which gave access to **2** and **3** in 17–21% overall yield.

Keywords: azasugars · glycosidases · Henry reaction · inhibitors · oxidation

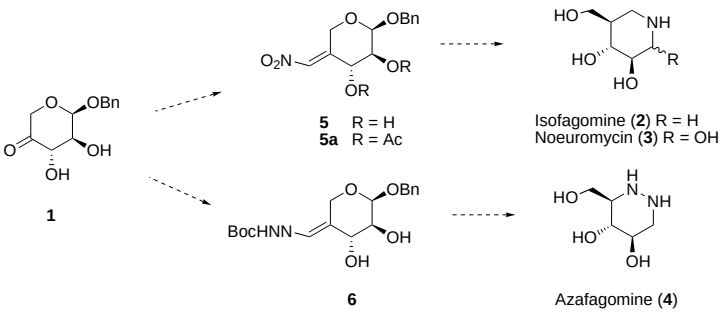
Introduction

Since the beginning of azasugar synthesis in the early 1960s—pioneered by Hans Paulsen—and the first isolation of a glucose mimic azasugar from natural sources in 1966[1] (deoxynojirimycin from *Streptomyces roseochromogenes* R-468) a new boom in azasugar chemistry has arisen during the last decade due to the extraordinary physiological properties of sugar mimics in which the ring oxygen or anomeric carbon is replaced by a nitrogen atom. These compounds bind many orders in magnitude stronger to glycosidases than their corresponding natural substrates. They act as competitive glycosidase inhibitors and influence many biochemical processes essential for organisms. The α-glucosidase inhibitors acarbose and miglitol are in use as oral medicaments for the management of non-insulin-dependend diabetes mellitus. The treatment of other diseases such as cancer or viral infections are under current investigation.

With view to the mechanism of the hydrolyses of D-glucosides we designed isofagomine (**2**) as a analogue of the D-glucosyl carbocation.[2] Isofagomine (**2**) is a selective and very strong inhibitor of β-glucosidase ($K_i = 0.11$ μM, sweet almond, pH 6.8, 37 °C).[2, 3] The synthesis of **2** is relatively difficult, because of the lack of a suitably branched carbohydrate precursor, which limits the application of **2** as a biochemical tool and for pharmaceutical investigations. Synthetic approaches starting from natural pool compounds have the advantage of a defined stereochemistry giving enantiomerically pure **2**. Disadvantage is the complex protecting group strategy which is usually necessary for polyhydroxy compounds. Thus, in our original synthesis, isofagomine (**2**) was obtained from levoglucosan in ten steps.[2, 4] Other approaches from D-lyxose[5] or from D-tartaric acid[6] as well as from arecoline[7] (leading to racemic **2**) are also both material and time consuming. A more suitable syntheses has been reported giving **2** in seven steps from (*R*)-2,3-*O*-cyclohexylidene glyceraldehyde.[8] A synthesis of **2** from ethyl nicotinate in eight steps giving 41% overall yield has also been reported.[9]

Recently, we have found that the 2-hydroxyanalogue of isofagomine (**2**), noeuromycin (**3**), is an extremely potent inhibitor being 2 to 1000 times more potent than **2**.[11] The noeuromycin synthesis is, however, even longer than those of **2**.

Our new retrosynthetic analysis of several D-glucose resembling azasugars have led us to propose a short reaction pathway to the inhibitors **2**–**4** all of them derived from the same carbohydrate building block **1** which is available from D-arabinose in two steps.[10] The simple derivatives **5** and **6** should eventually give **2**–**4** upon diastereoselective reductive cyclisation (Scheme 1). We describe in this paper the results of the use of this pathway for an improved synthesis of isofagomin (**2**) and noeuromycin (**3**) derived D-arabinose in six and seven steps, respectively.



Scheme 1. Strategy for an efficient synthesis of various powerful glucosidase inhibitors via benzyl β-D-*threo*-pentopyranosid-4-ulose derivatives (**5** and **6**).

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Results and Discussion

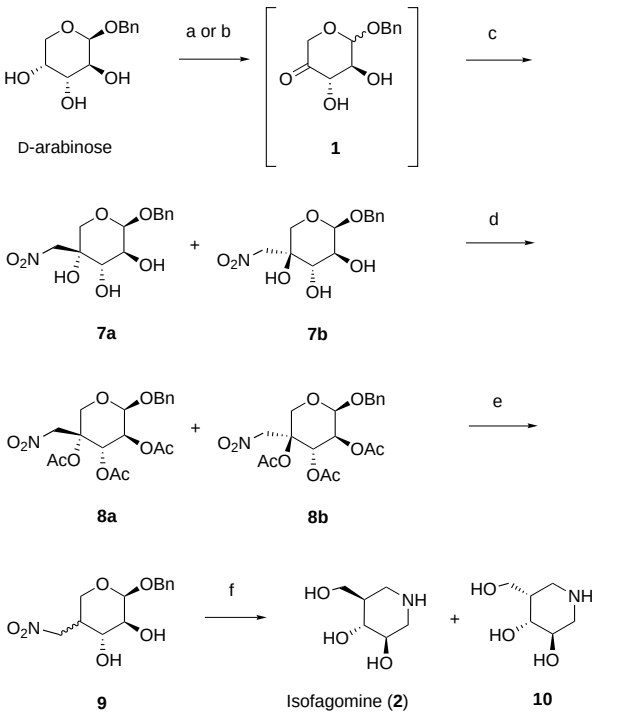
Benzyl β-D-*arabino*-pyranoside was synthesised in 85% yield analogous to our procedure reported for the corresponding β-L-derivative.[12] Following a procedure of Heyns et al. the selective C-4 oxidation of the glycoside with the Adams catalyst with oxygen in water led to isolation of ketone **1** in up to 30% yield. This was separated from the unreacted starting material by recrystallisation from water.[13] The application of Tsuda's method for the regioselective mono-oxidation of non-protected glycosides with Br_2 and $(Bu_3Sn)_2O$ in $CHCl_3$[14] to benzyl β-D-*arabino*-pyranoside gave **1** in 80–95% yield. Ketone **1** was obtained as a complex isomeric mixture of hemiketals. The high reactivity of the carbonyl group led to the formation of dimerised hemiketals analogues to the reported hemiketals derived from methyl α-L-*arabino*-pyranoside.[14] The analytical characterisation of **1** is furthermore complicated due to a small amount of the corresponding α-anomer, which is formed by anomerisation under the strongly acidic reaction conditions.

Nevertheless, the subsequent Henry reaction of **1** gave the nitromethane adduct benzyl 4-deoxy-4-*C*-nitromethylene-β-D-*arabino*-pyranoside (**7a**) in 36–43% yield (see Scheme 2), which precipitated as white needles from the reaction mixture. Purification of the residual filtrate by flash chromatography gave the epimer benzyl 4-deoxy-4-*C*-nitromethylene-β-D-*xylo*-pyranoside (**7b**) in 12–25% yield. Several other nitromethane adducts were detected in the filtrate by mass spectroscopy. In the following reactions both epimers **7a** and **7b** could be used. However, to prevent side reactions from other by-products, **7a** and **7b** were separated and purified before use. Especially, in the final catalytic hydrogenation rearranged and over-oxidized compounds would decrease the yield by intermolecular reductive aminations or by separation problems.

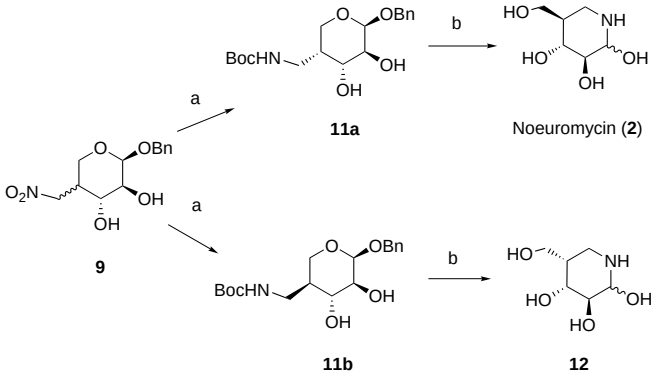
Subsequent reactions could thus be carried out on either pure **7a**, **7b** or the mixture of epimers. Acetylation of **7a** and **7b** with acetic anhydride and 4-toluene sulfonic acid provided the very base sensitive compounds **8a** and **8b**. Heating of **8a** and **8b** in acetic acid to 115 °C or pouring the acetylation mixture directly on a flash column provided benzyl 4-deoxy-4-*C*-nitromethylene-β-D-*arabino*-pyranoside (**5a**) in up to 88% yield. Due to the sterical influence of the C-3 *O*-acetyl group reductive elimination of **8a** or reduction of **5a** with $NaBH_4$ or K-Selectride gave mixtures of the 4*R* and 4*S* epimers of benzyl 4-deoxy-4-*C*-nitromethylene-β-D-*arabino*-pyranoside (**9**) in which the desired isofagomine/noeuromycin precursor (4*S*)-**9** was slightly favored (< 2:1).

Catalytic hydrogenation of a diluted solution of **9** in methanol or hydrogenation of a concentrated solution of **9** in the presence of an acid over 10% palladium on charcoal at atmospheric pressure and room temperature gave a mixture of easy separable isofagomine (**2**) and its 5-*epi*-isomer **10** in 85–90% yield (< 2:1, **2**:**10**, Scheme 2). Pure **2** could be isolated by chromatography, using a method previously described,[5] in 53% yield.

However, when the catalytic hydrogenation of **9** is performed under slightly basic conditions, the nitro group of **9** is reduced selectively without debenzylation of the anomeric center. The high selectivity of the hydrogenation allowed us to protect the amino intermediate with *tert*-butyloxycarbonyl dicarbonate which led to benzyl 4-*C*-*tert*-butyloxycarbonyl-aminomethylene-4-deoxy-β-D-*arabino*-pyranoside (**11a**) and benzyl 4-*C*-*tert*-butyloxycarbonylaminomethylene-4-deoxy-β-D-*xylo*-pyranoside (**11b**). These two derivatives could be separated by flash chromatography, which gave **11a** in 44% yield and **11b** in 41% yield, respectively. Subsequent catalytic hydrogenation of **11a** in methanol over 10% palladium on charcoal at atmospheric pressure and room temperature, followed by treatment of the residue with 0.2 N hydrochloric acid gave almost quantitatively noeuromycine (**3**). The same procedure applied to **11b** gave **12** (Scheme 3).



Scheme 2. Synthesis of isofagomine: a) Pt, O_2, H_2O (< 30%); b) $(Bu)_3$-$Sn)_2O$, $CHCl_3$, Br_2 (80–95%); c) CH_3NO_2, NEt_3 (55–65%); d) Ac_2O, pTSA (82%); e) $NaBH_4$, EtOH, then NaOMe (96%); f) H_2, Pd/C, MeOH, then separation (85–90%, **2**:**10** < 2:1).



Scheme 3. Synthesis of noeuromycine. a) H_2, Pd/C, NEt_3, MeOH, then Boc_2O, NEt_3, then separation (78%, **11a**:**11b** < 2:1); b) H_2, Pd/C, EtOH, then HCl, H_2O (98%).

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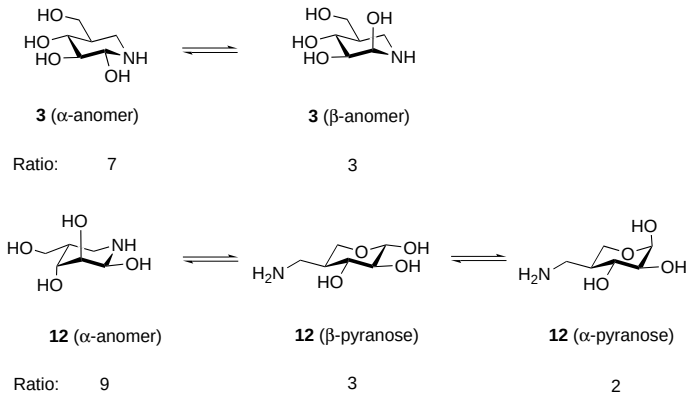
The configuration and conformation of all compounds were assigned on the basis of their ^{1}H and ^{13}C NMR spectroscopic data. It is noteworthy that in contrast to the hydrochloride of **3**, which in water mainly exists in the piperidine form with the 2-hydroxy group dominantly in equatorial position (> 7:3 α:β), the hydrochloride of **12** exists in equilibrium with its pyranose form with an exocyclic aminomethylene group in the ratio aminol:β-pyranose:α-pyranose 9:3:2. This can for instance be seen from the presence of signals at $\delta = 92$ and 96 in the ^{13}C NMR spectrum representing C-1 of the α- and β-anomer. The presence of pyranose forms is probably caused by the unfavorable 1,3-diaxial interaction that will occur in the piperidine form of **12**, which forces the compound to adopt hemiacetals (Scheme 4).



Scheme 4. Tautomeric forms of **3** and **12**.

In conclusion, we have established a very efficient route to isofagomine (**2**) From D-arabinose **2** was obtained in six steps in 21 % overall yield. This is definitely the shortest route to this compound so far, though it may be less efficient than the synthesis from nicotinic ester, which used eight steps to obtain a overall 41 % yield.[9] The new synthesis of noeuromycin (**3**), which is seven steps and 17 % overall yield, is definitely a vast improvement over the previous 13-step synthesis.[11]

Experimental Section

General: See ref. [15].

Oxidation of benzyl β-D-*arabino*-pyranoside with Br_2 (largest scale applied, 2 g scale easier to handle): A stirred suspension of benzyl β-D-*arabino*-pyranoside (8.10 g, 34 mmol, recrystallised from 94 % EtOH and dried in vacuum) molecular sieves (30 g, 3 Å), and $(Bu_3Sn)_2O$ (40.2 g, 68 mmol) in dry $CHCl_3$ (180 mL) was heated under reflux for 3.5 h. Then the mixture was cooled to 0 °C. Bromine was added (about 3.5 mL, 68 mmol) dropwise within 5 min until the color of the reaction mixture had a persistant faint yellow color. The mixture was stirred further for 3 min. Then the whole mixture was immediately poured onto a column filled with flash gel (0.04 – 0.063 mm, 20 cm, ∅ 5 cm) and $CHCl_3$. The column had a solvent reservoir of 1.0 L above the silica gel. First the reaction mixture was quickly decanted onto the column, then pressure was applied to the column until the liquid phase was absorbed, followed by quick pouring of the residual molecular sieves onto the column and subsequent washing. Afterwards the column was washed carefully with $CHCl_3$ until the tin compounds were eluted (R_f > 0.9, ethyl acetate/toluene 1:1). Then the washing solvent was changed to ethyl acetate and the products eluted until small amounts of unreacted starting material appeared ($R_f = 0.31$, $CHCl_3$/MeOH 8:1). All fractions containing the product ($R_f < 0.8$, ethyl acetate/toluene 1:1 and $R_f > 0.31$, $CHCl_3$/MeOH 8:1) were collected, evaporated and dried in vacuum for 6 h to give **1** as a colorless syrup (7.27 g, 91 %). When the reaction time was extended a yellow syrup of **1** was obtained, which has a lower quality, because of increasing amounts of β-**1** and other by-products. In that case the yield of the following reaction drops and purification of **6a** by column chromatography is necessary. For characterisation of **1** see ref.[14].

Henry reaction of 1: NEt_3 (0.46 g, 4.7 mmol) was added at 0 °C to a stirred suspension of **1** (1.12 g, 4.7 mmol) in dry CH_3NO_2 (30 mL). A clear yellowish solution was formed which after 1 h was allowed to warm to room temperature. The solution was then stirred at room temperature for 12 h during which time the white product (**7a**) precipitated. The precipitate was filtered off and washed with ethyl acetate (about 2 mL). The filtrate was concentrated and the new precipitate thus obtained was collected. The filtrate was evaporated, and the residue was pruified by chromatography (pentane/ethyl acetate 3:1 to 1:1 to 1:2 to 0:1). The precipitate (0.58 g) and fractions of **7a** (0.03 g) were recrystallized from *i*PrOH/$CHCl_3$ giving benzyl 4-deoxy-4-*C*-nitromethylene-β-D-*arabino*-pyranoside (**7a**) as colorless needles (0.60 g, 43 %). M.p. 190 – 192 °C; $R_f = 0.57$ ($CHCl_3$/MeOH 8:1); $[\alpha]_D = -157^\circ$ ($c = 1.0$ in MeOH); ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.38 – 7.15 (m, 5H, Ph), 5.14 (m, 1H, 4-OH), 5.04 (d, 1H, $J = 6.2$ Hz, OH), 4.79 (d, 1H, $J = 6.4$ Hz, OH), 4.68 (d, 1H, $J = 3.4$ Hz, 1-H), 4.63 (m, 2H), 4.37 (d, 1H, $J = 12.4$ Hz), 3.73 (d, 1H, $J = 11.6$ Hz), 3.55 (m, 2H), 3.40 (m, 2H); ^{1}H NMR (200 MHz, [D$_6$]acetone/D_2O): $\delta = 7.39 – 7.21$ (m, 5H, Ph), 4.90 (d, 1H, $J = 3.4$ Hz, 1-H), 4.82 – 4.65 (m, 3H, CH_2Ph, CH_2NO_2), 4.52 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 3.95 (d, 1H, $J = 12.0$ Hz, 5-H$_b$), 3.80 (dd, 1H, J = 9.2, 3.4 Hz, 2-H), 3.75 (d, 1H, $J = 12.4$ Hz, 5-H$_a$), 3.72 (d, 1H, $J = 9.6$ Hz, 3-H); ^{13}C NMR ([D$_6$]acetone): $\delta = 137.4$, 127.5, 127.0, 126.7 (6C, Ph), 98.0 (1-C), 78.9 (CH_2NO_2), 72.1, 69.5, 69.2 (2-, 3-, 4-C), 68.4 (CH_2Ph), 63.0 (5-C); EI-MS: calcd for $C_{13}H_{17}NO_7Na^+$: 322.0903, found 322.0909. Recrystallization of the fractions with $R_f = 0.64$ ($CHCl_3$/MeOH 8:1) from *i*PrOH/$CHCl_3$ gave benzyl 4-deoxy-4-*C*-nitromethylene-β-D-*xylo*-pyranoside (**7b**) as colorless needles (0.17 g, 12 %). M.p. 124 – 125 °C; $[\alpha]_D = -293^\circ$ ($c = 1.0$ in MeOH); ^{1}H NMR (200 MHz, [D$_6$]acetone/D_2O): $\delta = 7.39 – 7.21$ (m, 5H, Ph), 4.88 (d, 1H, $J = 3.4$ Hz, 1-H), 4.84 – 4.69 (m, 3H, CH_2Ph, CH_2NO_2), 4.55 (d, 1H, $J = 12.0$ Hz), 3.93 (d, 1H, $J = 9.2$ Hz, 3-H), 3.83 (d, 1H, J = 11.7 Hz, 5-H$_b$), 3.67 (d, 1H, $J = 11.7$ Hz, 5-H$_a$), 3.45 (dd, 1H, $J = 9.2$, 3.4 Hz, 2-H); ^{13}C NMR ([D$_6$]acetone): $\delta = 137.2$, 127.6, 127.1, 126.8 (6C, Ph), 97.5 (1-C), 75.7, 73.6, 71.8, 69.8 (2-, 3-, 4-C, CH_2NO_2), 68.6 (CH_2Ph), 61.3 (5-C); ESI-MS: calcd for $C_{13}H_{17}NO_7Na^+$: 322.0903, found 322.0909.

Benzyl 2,3,4-tri-*O*-acetyl-4-deoxy-4-*C*-nitromethylene-β-D-*arabino*-pyranoside (8a): *p*-TsOH · H_2O (285 mg, 1.5 mmol) was added at 0 °C to a stirred suspension of **7a** (448 mg, 1.5 mmol) in Ac_2O (20 mL). After formation of a clear solution, the mixture was allowed to warm to room temperature and was stirred over night. The solution was pored onto ice/water (50 mL) and stirred until Ac_2O was completely hydrolyzed. Then the water mixture was extracted with CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was successively washed with water, saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$ and finally evaporated. The residue was purified by chromatography (pentane/ethyl acetate 5:1) to give **8a** as a colorless syrup (520 mg, 82 %). The procedure could also be performed on **8b** or a mixture of **8a** and **8b** with essentially identical results. $R_f = 0.18$ (pentane/ethyl acetate 5:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.40 – 7.23$ (m, 5H, Ph), 5.59 (dd, 1H, J = 11.2, 1.6 Hz, 3-H), 5.14 – 5.04 (m, 2H), 5.02 (m, 1H), 4.79 (m, 2H), 4.50 (m, 2H, 5-H$_{a,b}$), 3.90 (d, 1H, $J = 12.8$ Hz, 2-H), 2.20 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO); ^{13}C NMR ([D$_6$]acetone): $\delta = 170.6$, 170.3, 169.9 (3 × CH_3CO), 136.7, 128.7, 128.4, 128.1 (6C, Ph), 95.1 (1-C), 79.6 (CH_2NO_2), 74.6, 70.1, 69.6, 69.2 (CH_2Ph, 2-, 3-, 4-C), 59.5 (5-C), 22.0, 20.8, 20.5 (3CH_3CO); ESI-MS: calcd for $C_{19}H_{23}NO_{10}Na^+$: 448.1220, found 448.1218.

Benzyl 2,3-di-*O*-acetyl-4-deoxy-4-*C*-nitromethylene-β-D-*arabino*-pyranoside (5a)

Method 1: A solution of **8a** (520 mg, 1.22 mmol) in Ac_2O (4 mL) was poured unto a silica gel 60 column. Heat development was observed. Chromatography with pentane/ethyl acetate 5:1, gave **5a** as yellowish syrup (393 mg, 88 %).

Method 2: A solution of **8a** (120 mg, 0.28 mmol) in HOAc (5 mL) was heated under reflux for 2 h. The solvent was evaporated and the residue chromatographed with pentane/ethyl acetate 5:1, providing **5a** (58 mg,

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57%). $R_f = 0.27$ (pentane/ethyl acetate 5:1); $[\alpha]_D = -116^\circ$ ($c = 1.0$ in MeOH); UV: $\lambda = 331$ (2.89), 228 (4.19); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35-7.26$ (m, 5H, Ph), 5.98 (dd, 1H, $J = 10.4$, 1.6 Hz, 3-H), 5.19 (d, 1H, $J = 15.0$ Hz, 6-H_b), 5.06 (d, 1H, $J = 3.4$ Hz, 1-H), 4.87 (dd, 1H, $J = 10.4$, 3.4 Hz, 2-H), 4.53 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.36 (d, 1H, $J = 15.0$ Hz, 6-H_a), 2.08 (s, 3H, CH_3CO), 1.97 (s, 3H, CH_3CO); ^{13}C NMR ($CDCl_3$): $\delta =$ 170.1, 169.4 (2CH_3*C*O), 143.7 (CH_2NO_2), 136.7 (C, Ph), 134.5 (4-C), 128.8, 128.5, 128.1 (5C, Ph), 95.0 (1-C), 78.9 (CH_2NO_2), 72.3, 70.3 (2-, 3-C), 67.5 (CH_2Ph), 56.9 (5-C), 20.8, 20.7 (2 × *C*H_3CO); ESI-MS: calcd for $C_{17}H_{19}NO_8Na^+$: 388.1008, found 388.1000.

Benzyl (4*R*,4*S*)-4-deoxy-4-*C*-nitromethylene-*β*-D-*arabino*-pyranoside (9): $NaBH_4$ (53 mg, 1.40 mmol) in EtOH (5 mL) was slowly added at 0 °C within 15 min to a stirred solution of **8a** and **8b** (0.50 g, 1.17 mmol) in EtOH (15 mL). The solution was then allowed to warm to room temperature and stirred further for 40 min. Afterwards the solvent was evaporated and the residue dissolved in dry methanol (15 mL). A freshly prepared solution of NaOMe in MeOH (0.5 mL, 0.2 N) was added. After completion of the deprotection (according to tlc after 30 min), ion exchange resin Amberlite IR 120 H^+ (about 3 mL, carefully washed before with H_2O then with Et_2O) was added. The mixture was stirred until pH ≈ 6 (about 30 min) to remove cations. The resin was filtered off, and the filtrate evaporated to give **9** ($R_f = 0.66$, $CHCl_3$/MeOH 8:1) as colorless syrup (0.32 g, 96%). Column chromatography of the (4*R*,4*S*)-isomeric mixture with pentane/ethyl acetate 1:1, provided a pure sample of (4*R*)-**9** which structure was assigned unequivocally by giving pure **10** after catalytic hydrogenation. (4*R*)-**9**: $R_f = 0.43$ (toluene/ethyl acetate 1:1); ^{1}H NMR (400 MHz, [D_6]acetone): $\delta = 7.45-7.23$ (m, 5H, Ph), 4.93 (d, 1H, $J = 3.2$ Hz, 1-H), 4.84 (dd, 1H, $J = 13.2$, 4.9 Hz), 4.75 (d, 1H, $J = 12.4$ Hz), 4.53 (m, 2H), 4.27 (d, 1H, $J = 4.8$ Hz), 3.80–3.65 (m, 4H), 3.48 (m, 1H, 2-H), 2.45 (m, 1H, 4-H); ^{13}C NMR ([D_6]acetone): $\delta = 137.4$, 127.5, 127.0, 126.7 (6C, Ph), 98.2 (1-C), 73.5, 73.2, 68.6, 68.3 (CH_2Ph, 2-, 3-, 4-C, CH_2NO_2), 59.3 (5-C), 41.3 (4-C); ESI-MS: calcd for $C_{13}H_{17}NO_6Na^+$: 306.0953, found 306.0954.

Isofagomine (2) and 5-*epi*-isofagomine (10): A solution of **9** (354 mg, 1.25 mmol, (4*R*:4*S*) ≈ 4:3) derived from a mixture of **7a**:**7b** (about 3:1) in methanol (200 mL) was hydrogenated over Pd/C (10%) under normal pressure at room temperature (about 16 h) until TLC indicated only two spots of **2** ($R_f = 0.38$, *i*PrOH/H_2O/NH_4OH 7:2:1) and **10** ($R_f = 0.26$) and the spot of benzyl (4*R*,4*S*)-4-*C*-aminomethylene-4-deoxy-*β*-D-*arabino*-pyranoside at $R_f = 0.55$ completely disappeared (ninhydrin). The catalyst was filtered off, the solvent evaporated and the residue chromatographed with *i*PrOH/H_2O/NH_4OH_C providing **2** (98 mg, 53%) and **10** (77 mg, 42%) as colorless solids. Addition of HCl (2.0 mL, 0.2 N) and subsequent evaporation provided the corresponding hydrochlorids of **2** and **10**, which had identical analytical data to those reported in refs. [4], [5], and [16].

Benzyl 4-*C*-*tert*-butyloxycarbonylaminomethylene-4-deoxy-*β*-D-*arabino*-pyranoside (11a) and **benzyl 4-*C*-*tert*-butyloxycarbonylaminomethylene-4-deoxy-*β*-D-*xylo*-pyranoside (11b)**: A solution of **9** (140 mg, 0.49 mmol) in dry MeOH (10 mL) and NEt_3 (0.01 mL) was hydrogenated over Pd/C (10%, 30 mg) at atmospheric pressure and room temperature for about 2 h. The catalyst was filtered off, the filtrate evaporated and the residue dissolved in a mixture of $CHCl_3$ (20 mL) and NEt_3 (1.0 mL). To the solution Boc_2O (248 mg, 0.59 mmol) was added, and the solution stirred for 2 h at room temperature. Afterwards the solvent was evaporated and the residue was purified by chromatography (pentane/ethyl acetate 1:1) providing **11a** (76 mg, 44%) and **11b** (71 mg, 41%) as white solids. **11a**: $R_f = 0.23$ (toluene/ethyl acetate 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.40-7.20$ (m, 5H, Ph), 4.81 (m, 3H, 1-H, CH_2Ph, OH), 4.48 (d, 1H, $J = 11.4$ Hz, CH_2Ph), 3.89 (m, 1H, 2-H), 3.65 (m, 3H), 3.52 (dd, 1H, $J = 11.4$, 8.0 Hz), 3.30 (m, 1H), 3.00 (m, 1H), 2.21 (br d, 1H, $J = 5.2$ Hz, NH), 2.15 (m, 1H, 4-H), 1.37 (s, 9H, *t*Bu); ^{1}H NMR (400 MHz, [D_6]acetone/D_2O 1:1): $\delta = 7.40-7.20$ (m, 5H, Ph), 5.18 (d, 1H, $J = 11.7$ Hz, 1-H), 5.02 (d, 1H, $J = 11.7$ Hz, CH_2Ph), 4.86 (d, 1H, $J = 11.7$ Hz, CH_2Ph), 4.31 (dd, 1H, $J = 8.0$, 4.8 Hz), 3.99 (dd, 1H, $J = 11.8$, 3.2 Hz, 2-H), 3.92 (m, 1H), 3.84 (dd, 1H, $J = 11.6$, 5.2 Hz), 3.57 (dd, 1H, $J = 14.0$, 4.8 Hz), 3.54 (dd, 1H, $J = 14.0$, 9.6 Hz), 2.47 (m, 1H, 4-H), 1.42 (s, 9H, *t*Bu); ^{13}C NMR ([D_6]acetone): $\delta = 157.4$ (NH-COO), 137.3, 128.7, 128.3, 128.2 (6C, Ph), 97.8 (1-C), 80.2 ((CH_3)$_3$*C*), 70.4, 70.1, 68.7 (2-, 3-C, CH_2Ph), 62.3 (5-C), 39.3 (NH-CH_2), 37.7 (4-C), 28.5 ((CH_3)$_3$C); ESI-MS: calcd for $C_{18}H_{27}NO_6Na^+$: 376.1736, found 376.1734. **11b**: $R_f = 0.15$ (toluene/ethyl acetate 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.40-7.20$ (m, 5H, Ph), 4.92 (br d, 1H, OH), 4.88 (d, 1H, $J = 3.2$ Hz, 1-H), 4.69 (d, 1H, $J =$ 11.8 Hz, CH_2Ph), 4.42 (d, 1H, $J = 11.8$ Hz, CH_2Ph), 3.65–3.25 (m, 6H), 2.98 (m, 1H), 2.32 (br d, 1H, $J = 7.8$ Hz, NH), 1.78 (m, 1H, 4-H), 1.38 (s, 9H, *t*Bu); ^{13}C NMR ([D_6]acetone): $\delta = 157.0$ (NH-COO), 137.3, 128.7, 128.1 (6C, Ph), 98.0 (1-C), 80.0 ((CH_3)$_3$*C*), 73.7, 71.4, 69.4 (2-, 3-C, CH_2Ph), 61.4 (5-C), 43.6 (4-C), 39.2 (NH-CH_2), 28.6 ((CH_3)$_3$C); ESI-MS: calcd for $C_{18}H_{27}NO_6Na^+$: 376.1736, found 376.1734.

Noeuromycin (3): A solution of **11a** (42 mg, 0.12 mmol) in dry EtOH (100 mL) was hydrogenated over Pd/C (10%) under atmospheric pressure at room temperature for about 16 h. Afterwards the catalyst was filtered off, the solvent evaporated and HCl (1.5 mL, 0.2 N) was added to the residue. After heating to 40 °C for 5 min the solvent was evaporated to give hydrochloride **3** as a pale yellow solid (23 mg, 98%), which has identical analytical data reported in ref. [11].

5-*epi*-Noeuromycin (12): A solution of **11b** (49 mg, 0.136 mmol) in EtOH (100 mL) was hydrogenated over Pd/C (10%) under atmospheric pressure at room temperature for about 16 h. Afterwards the catalyst was filtered off and the solvent evaporated. HCl (1.5 mL, 0.2 N) was added to the residue. After heating the mixture to 40 °C for 5 min the solvent was evaporated to give hydrochloride **12** as a pale yellow solid (27 mg, 98%). ^{1}H NMR (200 MHz, D_2O): $\delta = 5.20$ (d, $J = 3.6$ Hz, *β*-pyranose), 4.98 (m, *α*-anomer), 4.50 (d, $J = 7.8$ Hz, *α*-pyranose), 4.10 (m), 4.02–3.90 (m), 3.80–3.50 (m), 3.45–3.09 (m), 3.08 (d, $J = 12.8$ Hz), 3.00–2.80 (m), 2.70 (m), 2.34 (m, main isomer), 2.05 (m); ^{13}C NMR (D_2O): main isomer: $\delta = 77.2$ (2-C), 68.6, 66.8 (3-, 4-C), 59.3 (6′-C), 39.8 (5-, 6-C), 39.4; minor isomers: $\delta = 96.2$, 92.1, 91.3, 74.9, 73.7, 72.0, 70.2, 68.6, 68.2, 66.8, 59.7, 59.2, 46.1, 38.3, 37.4.

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