A New Method for the Synthesis of 2,3-Aziridino-2,3-dideoxyhexonamides and Their Conversion into 3-Amino-2,3-dideoxyhexonic Acids

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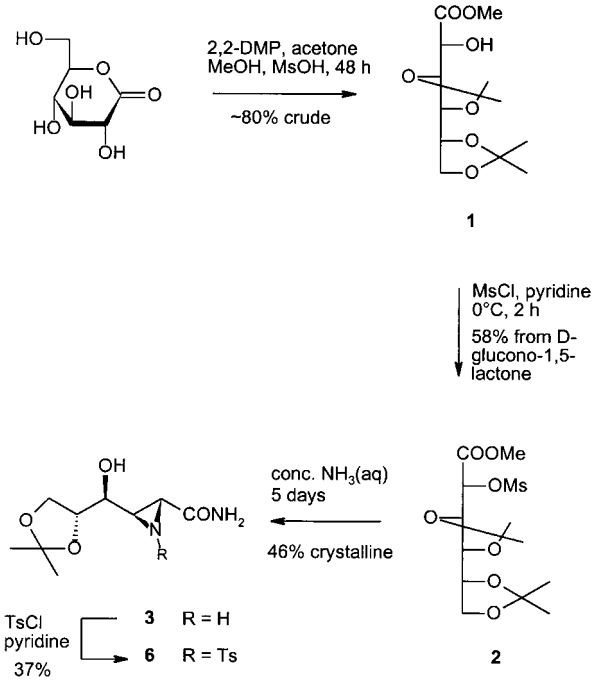
Abstract: Two new 2,3-aziridino-2,3-dideoxyhexonamides **3** and **11** were prepared by a three-step procedure from commercially available D-glucono-1,5-lactone and D-gulono-1,4-lactone, respectively. The lactones were converted into methyl 3,4:5,6-di-*O*-isopropylidene-2-*O*-mesyl esters **2** and **10**, which upon treatment with ammonia formed the title aziridino compounds. These were reductively cleaved by hydrazine to give 3-amino-2,3-dideoxyhexonic hydrazides **13** and **15**, which were easily converted into the corresponding lactone **14** and acid **16**, respectively.

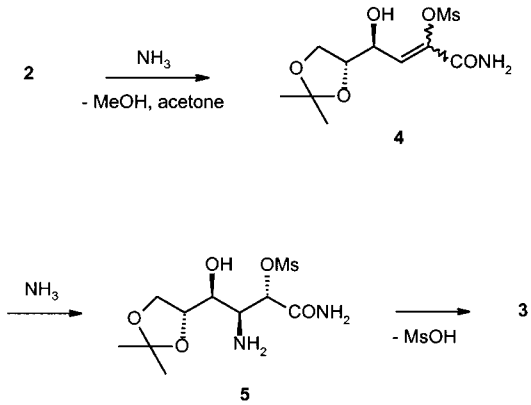
Key words: sugar lactones, aziridines, amino acids

Enantiopure aziridine-2-carboxylic acids are an important class of compounds as they can be used as intermediates in the synthesis of α- and β-amino acids. An aziridine ring can be opened by nucleophiles with complete stereochemical inversion.[1] Optically active aziridine-2-carboxylic acid derivatives have previously been prepared from starting materials such as oxiranes,[2] the naturally occurring hydroxy acids,[3] L-amino acids[4] and carbohydrates.[5,6] Asymmetric aziridination, with and without the use of chiral auxiliaries, has also been reported.[7–9] We describe here a novel and easy three-step procedure for the preparation of 2,3-aziridino-2,3-dideoxyhexonamides using readily available sugar lactones. The applicability of these new products is illustrated by a simple transformation into 3-amino-2,3-dideoxyhexonolactones. The latter may be reduced to aminodeoxy-hexoses, which constitute the sugar part of a large number of antibiotics.[10] The aziridinohexonamides allow a simultaneous generation of the C-3 amino and C-2 deoxy functions. In contrast, 3-aminodeoxyhexoses are usually prepared by introducing the C-3 amino function into mono- and dideoxyhexoses.[10]

It has been previously reported that the acid-catalyzed isopropylidenation of D-glucono-1,5-lactone with 2,2-dimethoxypropane (2,2-DMP) and methanol gives the diacetal methyl ester **1** in good yield.[11] Different derivatives of this ester have been synthesized by modification of the C-2 position (halogenation and deoxygenation,[12] *O*-acylation and *O*-alkylation[13,14]). In the present work, the 2-*O*-mesyl ester **2**[14] was treated with concentrated aqueous ammonia to give the 2,3-aziridino-2,3-dideoxyhexonamide **3** as the main product (Scheme 1). The reaction is believed to proceed via elimination[12,13] to **4** followed by addition of ammonia to give **5**, which subsequently yields the *trans*-aziridine **3** (Scheme 2). The addition of ammonia appeared to be diastereoselective as predicted from the work of Chittenden and Regeling,[12] but the ^{1}H NMR spectrum of the crude product showed several minor byproducts, none of which have been isolated and identified. The observed selectivity is in analogy with similar additions to α-bromoacrylates.[6] Compound **3** could be easily isolated in 46% yield by crystallization after treatment with a basic ion-exchange resin.



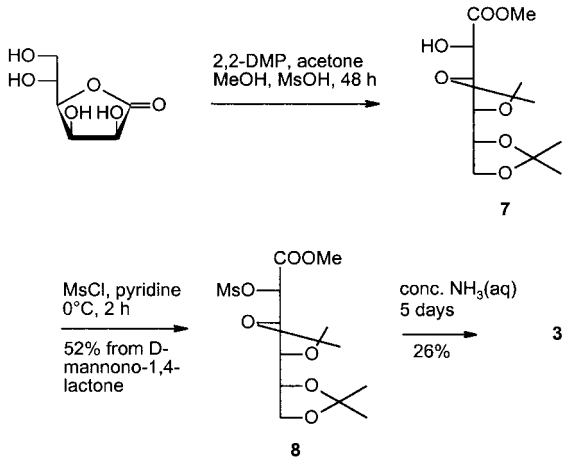
Scheme 1



Scheme 2

The structure of **3** was established by X-ray analysis of the *N*-tosylated derivative **6**, which also proved to be more suitable for NMR spectroscopic characterization. The unprotected aziridine **3** gave broad signals in both ^{1}H and ^{13}C NMR spectra due to slow exchange of the NH proton and/or slow inversion at the nitrogen atom. *N*-Tosylation is known to lower the energy barrier for inversion[15] and, in agreement with this, ^{1}H NMR spectrum of **6** showed sharp lines revealing the expected low value (4.3 Hz) of the $J_{2,3}$ coupling constant.[16]

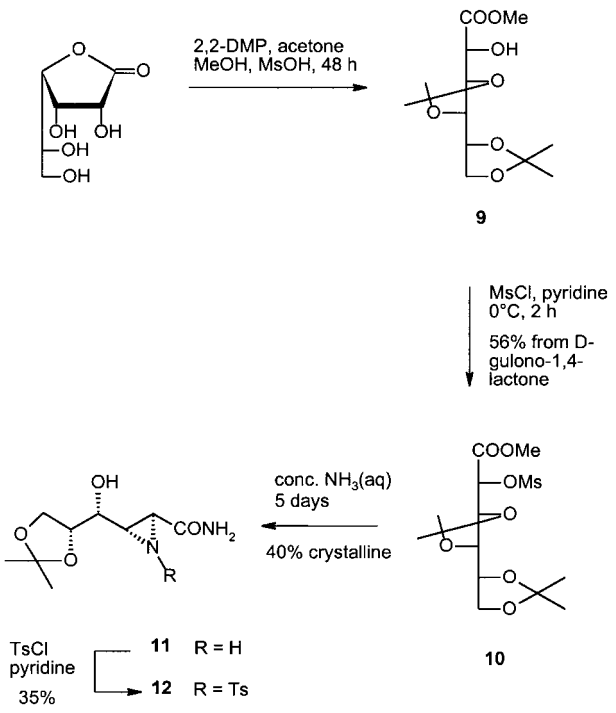
Starting with D-mannono-1,4-lactone, obtained from isoascorbic acid,[17] the crystalline diacetal methyl ester **8** was prepared analogously to **2** in 52% overall yield (Scheme 3). The assigned structure was established by comparison of the ^{1}H NMR data of **7** and **8**. As the only notable change, the doublet at $\delta = 4.35$ ($J_{2,3} = 3.0$ Hz) in **7** was moved downfield to $\delta = 5.35$ ($J_{2,3} = 2.2$ Hz) in **8** indicating *O*-mesylation at C-2. The *manno*-configurated compound **7** had previously been prepared from **1** by epimerization of the OH-group, but no physical data were reported.[13] Treatment of **8** with concentrated aqueous ammonia gave **3** in accordance with the suggested mechanism.



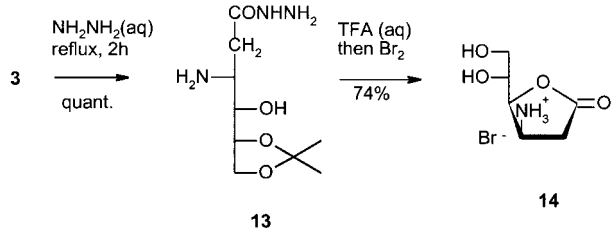
Scheme 3

As the original stereochemistry at C-2 and C-3 is assumed to be lost during the reaction, only C-4 or C-5 isomeric products could lead to other isomers. Using commercially available D-gulono-1,4-lactone and applying the same reaction conditions as described above, a similar regioselective di-*O*-isopropylidenation took place to give **9**. Mesylation of crude **9** gave the crystalline *gulo*-derivative **10** in 56% overall yield. Treatment of **10** with concentrated aqueous ammonia yielded the crystalline 2,3-aziridino-2,3-dideoxy hexonamide **11** in 40% yield (Scheme 4). Unidentified byproducts were also formed in this case. The *ido*-configuration was proven by X-ray analysis of the *N*-tosylate **12**.

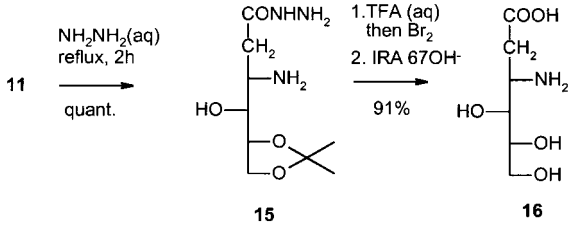
Reductive cleavage of aziridine-2-carboxylic acids provides a route to α- and β-amino acids. Hydrogenolysis can be used, but substitution patterns, catalyst and solvent effect the direction of the reduction. With *N*-tosylated aziridine-2-carboxylates high yields of both α-amino and β-amino esters have been obtained.[8,18] Recently a highly regioselective reduction with samarium(II) iodide was reported, leading exclusively to β-amino esters.[19] In the present work it was found that boiling **3** with aqueous hydrazine gave the 3-amino-2,3-dideoxyhydrazide **13** in quantitative yield. The reaction is believed to proceed via a ketene intermediate.[20] A similar cleavage of the aziridine ring has been observed for *N*-alkylated aziridines.[21] Treatment of the hydrazide **13** with bromine gave the crystalline 3-amino-2,3-dideoxylactone **14** as the hydrobromide in 74% yield (Scheme 5). Analogously, the hydrazide **15** could be obtained quantitatively from **11**, and subsequent cleavage of the hydrazide gave the acid **16** in 91% yield (Scheme 6).



Scheme 4



Scheme 5



Scheme 6

In summary, we have described a three-step synthesis of two 2,3-aziridino-2,3-dideoxyhexonamides with D-*gluco* and D-*ido* configuration. Although the yields are moderate, the method is convenient as the starting materials are readily available and the experimental procedures are simple (no chromatography). These diastereomerically pure aziridine-2-carboxyamides **3** and **11** proved to be useful precursors for 3-amino-2,3-dideoxyhexonic acids.

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter. NMR spectra were recorded on Bruker AC-250 or AM-500 instruments. $CHCl_3$ ($\delta = 7.27$ and 76.9) was used

as an internal reference for $CDCl_3$ solutions and dioxane (δ = 67.4) for ^{13}C NMR spectra measured in D_2O. H_2O (δ = 4.60) was used as internal reference for ^1H NMR spectra measured in D_2O solutions. Column chromatography was performed on silica gel using the flash technique. Microanalyses were performed by Research Institute for Ph armacy and Biochemistry, Prague, and Chemistry Department II, University of Copenhagen.

Methyl 3,4;5,6-Di-*O*-isopropylidene-2-*O*-mesyl-D-gluconate (2):
D-Glucono-1,5-lactone (10.6 g, 59.6 mmol) was stirred for 48 h at r.t. in a mixture of 2,2-dimethoxypropane (20 mL), anhyd acetone (6 mL), MeOH (2 mL) and $MeSO_3H$ (0.1 mL). The mixture was then neutralized with $NaHCO_3$, filtered and concentrated to give crude **1** (~17 g), which was dissolved in pyridine (40 mL) and cooled in an ice bath. $MeSO_2Cl$ (10.0 g, 89.4 mmol) was added and the mixture was stirred for 1 h at 0 °C and then 1 h at r.t. When the mixture was poured into a large volume of ice water (250 mL), the product precipitated as a white solid. Filtration and recrystallization from MeOH/H_2O gave **2** (12.7 g, 58%); mp 82–84°C. Further recrystallization of a sample from MeOH/H_2O gave a product with mp. 84–85°C (Lit.[12] mp 86–88°C); $[\alpha]_D$ +42.6 (*c* = 1.8, $CHCl_3$) (Lit.[12] $[\alpha]_D$ +19.4). The NMR data are in accordance with the literature.[14]

2,3-Aziridino-2,3-dideoxy-5,6-*O*-isopropylidene-D-gluconamide (3):
The methyl ester **2** (13 g, 35 mmol) was suspended in 25% aq ammonia (200 mL) and stirred for 5 d. The ammonia was then evaporated and the crude product was passed through a column of ion exchange resin (IRA 420 OH^-, 100 mL) in order to remove mesylate ions. The resin was washed with H_2O (500 mL) and the eluate concentrated to give about 6 g (80 %) of a crude syrup, which was coevaporated twice with EtOAc. The syrup could then be crystallized from EtOAc to give **3** (3.5 g, 46 %) as colorless crystals; mp 106–108 °C. Recrystallization from EtOAc gave a product with mp 110–111 °C. $[\alpha]_D$ –44. 1 (*c* = 1 .0, H_2O).
^{13}C NMR (D_2O): δ = 174.8 (C-1), 11 1.0 (isoprop-*C*), 77.8 (C-5), 72.3 (C-4), 66.2 (C-6), 39.4, 34.4 (C-2 and C-3), 26.2, 24.8 (isoprop- *C*H_3).
$C_9H_{16}N_2O_4$ (216.2): calc. C 49.99 H 7.46 N 12.95 ; found C 49.79 H 7.46 N 12.95.

2,3-Aziridino-2,3-dideoxy-5,6-*O*-isopropylidine-N-tosyl-D-gluconamide (6):
The aziridine **3** (1.6 g, 7.4 mmol) was dissolved in pyridine (6 mL) and cooled in an ice bath. *p*-Toluenesulfonyl chloride (1.6 g, 8.4 mmol) was added and the mixture was stirred for 2 h at 0 °C. Crystallization of the product took place upon addition of ice water (15 mL) to give **6** (1.0 g, 37%); mp 157–158 °C. No attempts were made to optimize the yield. Recrystallization from EtOAc did not alter the mp; $[\alpha]_D$ –27.3 (*c* = 1.3, $CHCl_3$).
^{13}C NMR ($CDCl_3$): δ = 167.5 (C-l), 145.2, 129.9, 127.3 (C_{arom}), 110.0 (isoprop-*C*), 76.6 (C-5), 71. 1 (C-4), 66.8 (C-6), 52.3, 44.2 (C-2 and C-3), 26.7, 25.0 (isoprop-*C*H_3), 21.5 (Ar-*C*H_3).
^1H NMR ($CDCl_3$): δ = 7.85 (d, *J* = 8.2 Hz, 2 H_{arom}), 7.40 (d, *J* = 8.2 Hz, 2 H_{arom}), 5.9–6.0 (2 br s, 2 H, $CONH_2$), 4.05–4.16 (m, 3 H, H-4, H-5, H-6a), 3.95 (br t, *J* = 8.0 Hz, 1 H, H-6b), 3.54 (d, *J* = 4.3 Hz, 1 H, H-2), 3.53 (br s, 1H, OH), 3.09 (dd, *J* = 4.3 ; 8.8 Hz, 1 H, H-3), 2.45 (s, 3H, Ar-*C*H_3), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).
$C_6H_{22}N_2O_6S$ (370.4): calc. C 51.88 H 5.99 N 7.56; found C 51.95 H 5.97 N 7.52.

Selected Crystal Structure Data for 6:[23]
$C_{16}H_{22}N_2O_6S$ = 370.42; crystal system orthorhombic; space group $P2_12_12_1$; Z = 4; cell parameters a = 6.760(4) Å, b = 12.248(4) Å, c = 21.732(4) Å; radiation (CuKα) λ = 1.5418 Å; 315 parameters for 2716 reflections ($I > 2\sigma(I)$); final R = 0.065.

Methyl 3,4;5,6-Di-*O*-isopropylidene-2-*O*-mesyl-D-mannonate (8):
D-Mannono-1,4-lactone (4.5 g, 25 mmol) was stirred for 48 h in a mixture of 2,2-dimethoxypropane (10 mL), anhyd acetone (2.5 mL), MeOH (1 mL) and a drop of $MeSO_3H$. The mixture was worked up as described above to give the crude methyl 3,4:5,6-di-*O*-isopropylidene-D-mannonate (**7**, ~ 5.8 g) as a syrup.

Compound **7:**
^{13}C NMR ($CDCl_3$): δ = 171.9 (C-1), 109.8 (2 C, isoprop-*C*), 82.0, 77.0, 76.9, 71.0 (C-2, C-3, C-4 and C-5), 67.6 (C-6), 52.3 (OCH_3), 26.8, 26.6, 26.2, 25.1 (isoprop-CH_3).
The product **7** was treated with $MeSO_2Cl$ (4.3 g, 38 mmol) in pyridine (15 mL) for 1 h at 0 °C and 1 h at r.t. When the mixture was poured into ice water (100 mL) the product precipitated immediately. Filtration and washing with MeOH/H_2O gave **8** (4.86 g, 52%); mp 67–68°C. Recrystallization from MeOH/H_2O gave colorless needles; mp 68–69°C; $[\alpha]_D$ –4.8 (*c* = 1.8, $CHCl_3$).

Compound **8:**
^{13}C NMR ($CDCl_3$): δ = 166.4 (C-1), 110.4, 110.0 (isoprop-*C*), 80.1, 76.8 (2 C), 76.6 (C-2, C-3, C-4 and C-5), 67.6 (C-6), 52.6 (OCH_3), 39.1 (OMs), 27.1, 26.6, 26.3, 25.2 (isoprop-*C*H_3).
^1H NMR ($CDCl_3$): δ = 5.37 (d, *J* = 2.2 Hz, 1 H, H-2), 4.42 (dd, *J* = 2.2; 7.0 Hz, 1 H, H-3), 4.14 (dd, *J* = 5.6; 8.5 Hz, 1 H, H-6a), 4.05 (dd, *J* = 7.0; 8.5 Hz, 1 H, H-4), 4.01 (m, 1 H, H-5), 3.96 (dd, *J* = 4.5; 8.5 Hz, 1 H, H-6b), 3.80 (s, 3 H, OCH_3), 3.19 (s, 3 H, OSO_2CH_3), 1.40 (s, 3 H, CH_3), 1.39 (s, 6 H, CH_3), 1.32 (s, 3 H, CH_3).
$C_{14}H_{24}O_9S$ (368.4): calc. C 45.64 H 6.57; found C 45.75 H 6.38.

Preparation of 3 from 8:
The methyl ester **8** (1.05 g, 2.9 mmol) was suspended in 25% aq ammonia (15 mL) and the mixture was stirred for 5 d and then worked up as described above. Crystallization from EtOAc afforded **3** (0.16 g, 26%); mp 106–108°C; $[\alpha]_D$ –42.8(*c* = 1.0, H_2O).

Methyl 3,4;5,6-Di-*O*-isopropylidene-2-*O*-mesyl-D-gulonate (10):
D-Gulono-1,4-lactone (10.9 g, 61.2 mmol) was stirred for 48 h in 2,2-dimethoxypropane (20 mL), anhyd acetone (6 mL), MeOH (2 mL) and $MeSO_3H$ (0. 1 mL) and worked up as described above to give crude methyl 3,4:5,6-di-*O*-isopropylidene-D-gulonate (**9**, ~17 g) as a syrup.

Compound **9:**
^3C NMR ($CDCl_3$): δ = 171.9 (C-1), 109.7, 109.2 (isoprop-*C*), 78.1, 76.5, 74.6, 70.9 (C-2, C-3, C-4 and C-5), 65.3 (C-6), 52.1 (OCH_3), 26.6 (2C), 25.6, 25.1 (isoprop- *C*H_3).
The product **9** was then mesylated with $MeSO_2Cl$ (10 g, 87.7 mmol) as described above. When poured into ice water (250 mL) a syrup was obtained. The H_2O was decanted and the syrup dissolved in a mixture of MeOH and H_2O (2:1) by gentle heating. The product then crystallized to give **10** (12.5 g, 56%); mp 73–75°C. Recrystallization from MeOH/H_2O gave a product with mp 78–79°C; $[\alpha]_D$ –8.7 (*c* = 2.0, $CHCl_3$).

Compound **10:**
^{13}C NMR ($CDCl_3$): δ = 166.8 (C-l), 110.6, 109.7 (isoprop-*C*), 76.4, 76.2, 75.6, 74.0 (C-2, C-3, C-4 and C-5), 65.5 (C-6), 52.8 (OCH_3), 39.0 (OSO_2CH_3), 26.9, 26.8, 25.9, 25.4 (isoprop-*C*H_3).
^1H NMR ($CDCl_3$): δ = 5.20 (d, *J* = 3.8 Hz, 1 H, H-2), 4.45 (dd, *J* = 3.8; 8.0 Hz, 1 H, H-3), 4.21 (dd, *J* = 2.9; 8.0 Hz, 1 H, H-4), 4.05 (m, 2 H, H-5 and H-6a), 3.89 (dd, *J* = 6.0; 6.5 Hz, 1 H, H-6b), 3.83 (s, 3 H, OCH_3), 3.14 (s, 3 H, OSO_2CH_3), 1.43 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3).
$C_{14}H_{24}O_9S$ (368.4): calc. C 45.64 H 6.57; found C 45.84 H 6.73.

2,3-Aziridino-2,3-dideoxy-5,6-*O*-isopropylidene-D-idonamide (11):
The methyl ester **10** (6.7 g, 18 mmol) was suspended in 25% aq ammonia (90 mL) and treated as described above. The major product crystallized on addition of EtOAc to give **11** (1.6 g, 40 %); mp 138–141 °C. Recrystallization from EtOH gave a product with mp 148–149 °C; $[\alpha]_D$ +18.4 (*c* = 1.0, H_2O).
$C_9H_{11}N_2O_4$ (216.2): calc. C 49.99 H 7.46 N 12.95 : found C 50.19 H 7.30 N 12.92.

2,3-Aziridino-2,3-dideoxy-5,6-*O*-isopropylidene-N-tosyl-D-idonamide (12):
The aziridine **11** (1.0 g, 4.6 mmol) was tosylated as described above. Crystallization of the product took place by addition of ice water to give **12** (0.60 g, 35%); mp 164–166 °C. Recrystallization from EtOAc

gave a product with mp 171 °C; $[\alpha]_D$ –1.8 (*c* = 1.0, $CHCl_3$). $[\alpha]_D$ –24.0 (*c* = 1.1, pyridine). No attempts were made to optimize the yield.
^{13}C NMR ($CDCl_3$): δ = 167.4 (C-1), 129.9, 127.5 (C_{arom}), 110.0 (isoprop-*C*), 76.4 (C-5), 69.0 (C-4), 65.3 (C-6), 52.1, 42.8 (C-2 and C-3), 26.0, 24.9 (isoprop-*C*H_3), 21.6 (Ar- *C*H_3).
^1H NMR ($CDCl_3$): δ = 7.88 (d, *J* = 8.2 Hz, 2 H_{arom}), 7.37 (d, *J* = 8.2 Hz, 2 H_{arom}), 5.85 and 5.58 (2 br s, 2 H, $CONH_2$), 4.28 (ddd, *J* = 4.0; 6.8, 7.0 Hz, 1 H, H-5), 4.13 (m, 1 H, H-4, shows dd with *J* = 4.0 and 9.0 Hz after exchange with D_2O), 4.10 (dd, *J* = 7.0; 8.5 Hz, 1 H, H-6a), 4.01 (dd, *J* = 6.8; 8.5 Hz, 1 H, H-6b), 3.47 (d, *J* = 4.1 Hz, 1 H, H-2), 3.23 (br d, *J* = 5.0 Hz, 1 H, OH, exchangeable with D_2O), 3.17 (dd, *J* = 4.1, 9.0 Hz, 1 H, H-3), 2.47 (s, 3 H, Ar-C*H*$_3$), 1.42 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3).
$C_{16}H_{22}NO_6S$ (370.4): calc. C 51.88 H 5.99 N 7.56; found C 51.94 H 6.09 N 7.54.

Selected Crystal Structure Data for 12:[22]
$C_{16}H_{22}N_2O_6S$ = 370.42; crystal system monoclinic; space group $P2_1$; Z = 2; cell parameters a = 5.918(3) Å, b = 26.801(2) A, c = 5.908(2) Å; radiation (MoKα) λ = 0.71073 Å; 233 parameters for 1297 reflections [I > 2σ(I)]; final R = 0.059.

3-Amino-2,3-dideoxy-D-*arabino*-hexono-1,4-lactone Hydrogen Bromide (14):
The aziridine **3** (2.0 g, 9.3 mmol) was dissolved in a mixture of H_2O (10 mL) and hydrazine hydrate (10 mL) and refluxed for 2 h. The solution was evaporated 4 times with H_2O in order to remove the hydrazine and then concentrated to give 3-amino-2,3-dideoxy-5,6-di-*O*-isopropylidene-D-*arabino*-hexonohydrazide (**13**; 2.1 g, 100%) as a partly crystalline solid; mp ~ 215°C (dec.).

Compound **13:**
^{13}C NMR (D_2O): δ = 176.8 (C-1), 110.0 (isoprop-*C*), 75.0 (C-5), 69.7 (C-4), 65.3 (C-6), 50. 1 (C-3), 35.5 (C-2), 24.9, 23.4 (isoprop- *C*H_3).
^1H NMR (D_2O): δ = 4.10 (m, 1 H, H-5), 4.06 (dd, *J* = 6.8; 8.5 Hz, 1 H, H-6a), 3.84 (dd, *J* = 5.0; 8.5 Hz, 1 H, H-6b), 3.63 (dd, *J* = 4.5; 6.5 Hz, 1 H, H-4), 3.48 (ddd, *J* = 4.5; 5.5; 8.0 Hz, 1 H, H-3), 2.49 (dd, *J* = 5.5; 17.0 Hz, 1 H, H-2a), 2.43 (dd, *J* = 8.0; 17.0 Hz, 1 H, H-2b), 1.24 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3).
The crude solid product **13** was dissolved in 10% aq CF_3CO_2H (10 mL) and stirred for 1 h at r.t. The mixture was then concentrated and the residue dissolved in H_2O (20 mL). Br_2 was added (dropwise) until no more N_2 evolved and the solution was taken to almost dryness. The remaining crude product crystallized upon addition of EtOH to give **14** (1.65 g, 74%); mp ~225°C (dec.). Recrystallization from 90% EtOH gave a product with mp 226–227°C (dec); $[\alpha]_D$ +16.5 (*c* = 1.0, H_2O).

Compound **14:**
^{13}C NMR (D_2O): δ = 176.9 (C-1), 80.4 (C-4), 69.4 (C-5), 62.8 (C-6), 50.5 (C-3), 35.1 (C-2).
^1H NMR (D_2O): δ = 4.69 (t, *J* = 6.2 Hz, 1 H, H-4), 4.27 (ddd, *J* = 0.7; 6.2; 8.0 Hz, 1 H, H-3), 3.99 (dt, *J* = 3.0, 6.2 Hz, 1 H, H-5), 3.72 (dt, *J* = 3.0; 12.5 Hz, 1 H, H-6a), 3.61 (dd, *J* = 3.0; 12.5 Hz, 1 H, H-6b), 3.17 (dd, *J* = 8.0; 18.5 Hz, 1 H, H-2a), 2.65 (dd, *J* = 0.7; 18.5 Hz, 1 H, H-2b).
$C_6H_{12}BrNO_4$ (242.1): calc. C 29.77 H 5.00 N 5.79 Br 33.01; found C 29.80 H 4.93 N 5.80 Br 33.70.

3-Amino-2,3-dideoxy-D-xylo-hexonic Acid (16):
The aziridine **11** (0.44 g) was refluxed for 2 h with a mixture of hydrazine hydrate (2 mL) and H_2O (2 mL) and then worked up as described above to give 3-amino-2,3-dideoxy-5,6-di-*O*-isopropylidene-D-*xylo*-hexonohydrazide (**15**; 0.47 g, 100%) as a colorless syrup.

Compound **15:**
^{13}C NMR (D_2O): δ = 173.2 (C-1), 110.9 (isoprop-*C*), 77.1 (C-5), 73.3 (C-4), 66.3 (C-6), 51.2 (C-3), 38.6 (C-2), 26.1, 25.0 (isoprop- *C*H_3).
^1H NMR (D_2O): δ = 4.12 (dt, *J* = 5.0; 6.9 Hz, 1 H, H-5), 3.92 (dd, *J* = 6.9; 8.2 Hz, 1 H, H-6a), 3.60 (dd, *J* = 6.9; 8.2 Hz, 1 H, H-6b), 3.28 (dd, *J* = 4.5; 5.0 Hz, 1 H, H-4), 3.00 (m, 1 H, H-3), 2.27 (dd, *J* = 5.3; 14.5 Hz, 1 H, H-2a), 2.10 (dd, *J* = 8.5; 14.5 Hz, 1 H, H-2b), 1.22 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3).

Compound **16:**
Hydrolysis with 10% aq CF_3CO_2H (4 mL) followed by treatment with Br_2 as described above gave a solution, which was neutralized with IRA-67 OH^- and concentrated to give the title compound **16** (0.33 g, 91%) as a syrup (containing some lactone). Crystallization from MeOH/H_2O gave colorless crystals, which started to decompose from ~180°C; $[\alpha]_D$ –24.5 (*c* = 0.8, H_2O).
^{13}C NMR (D_2O): δ = 178.1 (C-1), 72.5, 69.9 (C-4 and C-5), 63.4 (C-6), 52.7 (C-3), 36.9 (C-2).
^1H NMR (D_2O): δ = 3.78 (ddd, *J* = 2.0; 5.5; 6.2 Hz, 1 H, H-5), 3.75 (dd, *J* = 2.0; 6.0 Hz, 1 H, H-4), 3.59–3.65 (m, 3 H, H-6a, H-6b and H-3), 2.58 (dd, *J* = 5.2; 16.8 Hz, 1 H, H-2a), 2.48 (dd, *J* = 8.0; 16.8 Hz, 1 H, H-2b).
$C_6H_{13}NO_5$ (179.2): calc. C 40.22 H 7.31 N 7.82; found C 40.08 H 7.01 N 7.66.

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(22) Atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK, and are available on request. Requests should be accompanied by a full citation of this paper