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The Synthesis of a D-Glucose-like Piperidin-2-one: Isofagomine Lactam

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Benzyl 4-cyano-4-deoxy-α-D-arabinoside was converted into both its 2,3-di-*O*-acetyl and 2,3-di-*O*-(*tert*-butyldimethylsilyl) derivatives. The latter, by a process of hydrogenolysis, oxidation, and methanolysis, gave methyl 2,3-di-*O*-(*tert*-butyldimethylsilyl)-4-cyano-4-deoxy-D-arabinonate. Reduction of this methyl ester with borane dimethyl sulfide gave, after deprotection, isofagomine lactam.

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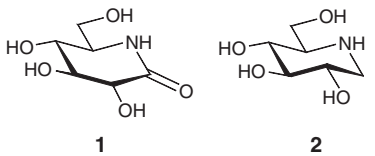
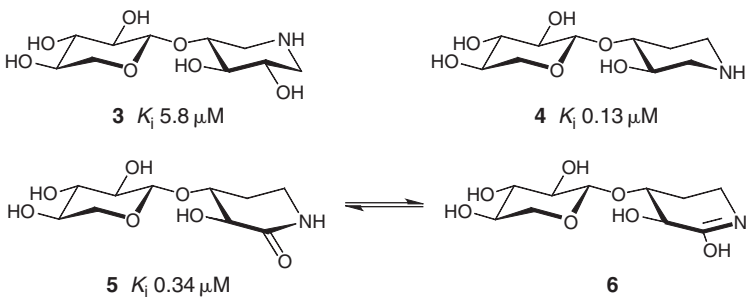
Introduction

Somewhat surprisingly, glycono-1,5-lactams are effective inhibitors of various glycoside hydrolases.[1–4] For example, the D-glucono lactam **1** (Scheme 1) shows good inhibition against almond β-glucosidase (K_i 37 μM[1] and 51 μM[3]). The reasons for these inhibitions are not clear but are generally ascribed to the (half-chair) shape of the molecules, purportedly mimicking the shape of a transition-state involved in the hydrolytic process.[3,4] Certainly, the glycono lactams are weaker inhibitors of glycosidases than are the related imino sugars, for example, 1-deoxynojirimycin **2**, where recent observations suggest that some of these basic amines bind as their conjugate acids to an inactive form of the hydrolase.[5]

The inhibitory potency of the glycono lactams increases markedly when the nitrogen atom and carbonyl moieties are placed in the *pseudo*-anomeric and C2 positions, respectively. Williams et al. have synthesized a number of potent xylobiose (imino sugar analogue) inhibitors of the *endo*-xylanase Cex from *Cellulomonas fimi*, including the D-xylosyl *xylo*-1-deoxynojrimycin **3**,[6] the D-xylosyl *xylo*-isofagomine **4**,[6] and the D-xylosyl *xylo*-isofagomine lactam **5**[7] (Scheme 2). Whilst not being quite as potent as the *xylo*-isofagomine **4**, the *xylo*-isofagomine lactam **5** shows remarkable inhibition and binds almost twenty times more tightly than the *xylo*-deoxynojirimycin **3**. This result stands in contrast to the inhibition of glycosidases observed for the D-glucono lactam **1**, which is a weaker inhibitor than 1-deoxynojirimycin **2**. Williams et al. postulated that the remarkable potency of **5** is a consequence of the lactam's binding in the active site as its (protonated) tautomer **6** (Scheme 2).[7] This tautomer approaches an ideal transition-state analogue, fulfilling several requirements. The protonated nitrogen can bind tightly to the catalytic amino acid carboxylate(s), the C=N bond flattens the ring to a conformation potentially more representative of the normal transition state, and, unlike an isofagomine derivative, a hydroxyl group at the *pseudo*-C2 position is available for additional stabilization of a transition-state-like intermediate. It has been shown that a hydroxyl group at C2 of a normal substrate provides strong



Scheme 1.



Scheme 2.

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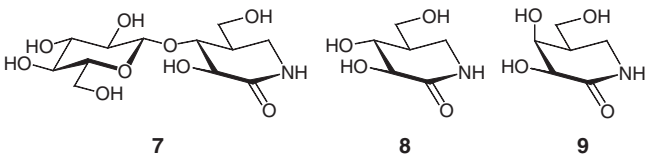
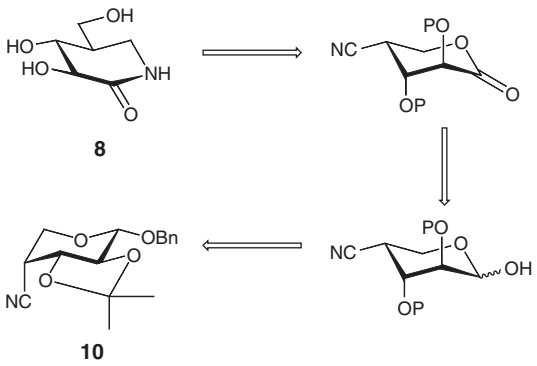
interactive forces to active-site residues (particularly of the catalytic nucleophile), in the order of 10–40 kJ mol^{-1}.[8–10]

X-ray crystallography, at a resolution of 2.0 Å, of the enzyme (Cex) inhibitor **5** complex was thought largely to confirm the hypothesis that the lactam **5** was indeed binding as its tautomer **6**.[7] However, more recent enzyme-inhibitor X-ray crystallographic studies, conducted at higher resolution (1.0 Å) and employing a homologous enzyme to Cex from *Cellulomonas fimi*, now refute this earlier assertion.[11] It appears that the observed inhibition is a result of the binding of the lactam **5** to an inactive form of the enzyme, where the protonation states of the nucleophile and acid/base residues are reversed.

Given the unexpected potency of the D-xylosyl *xylo*-isofagomine lactam **5** as an inhibitor of glycoside hydrolases, we wished to prepare the D-glucosyl isofagomine lactam **7** (Scheme 3). This paper reports our efforts towards just isofagomine lactam **8**, the necessary precursor for any synthesis of **7**.



Scheme 3.



Scheme 4. Retrosynthetic analysis. P is a protecting group.

Synthesis

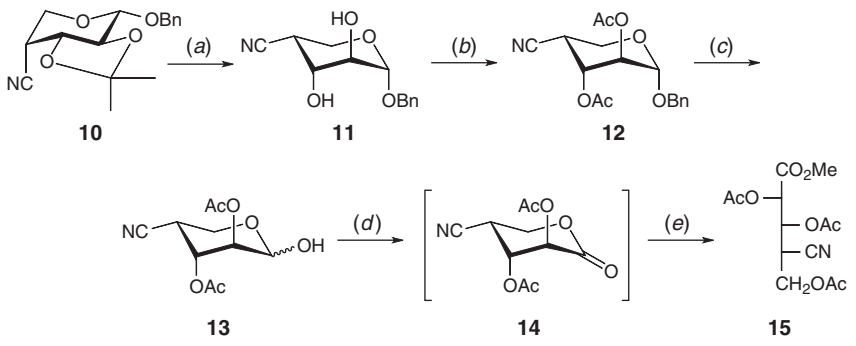
Apart from the synthetic work of Williams et al., the D-*galacto*-isofagomine lactam **9** has been prepared by Bols and co-workers.[12] We first announced a synthesis of isofagomine lactam **8** in 2002[13] and now give full details of this work; Bols and co-workers subsequently reported a separate synthesis of **8** in 2003.[14]

For our synthesis of the lactam **8**, we decided to apply the retrosynthetic analysis outlined in Scheme 4, with the nitrile **10** being an advanced intermediate in our synthesis of isofagomine itself.[15] However, we foresaw problems with the somewhat labile isopropylidene acetal in **10** and chose to replace it with more robust protecting groups.

The acetal **10** was carefully converted into the diol **11**, and thence the diacetate **12** (Scheme 5). Hydrogenolysis of the benzyl glycoside then furnished the hemiacetal **13**. The oxidation of **13**, utilizing the Swern procedure or pyridinium dichromate, appeared to proceed well (by TLC analysis) but isolation of the expected lactone **14** proved troublesome. Therefore, the hemiacetal was first oxidized and the crude product subjected to an acid-catalyzed methanolysis. Upon (re)acetylation of this crude material, the desired acyclic nitrile **15** was obtained in low yield. More disappointingly, the nitrile **15** was inert to the normal conditions of catalytic hydrogenation (PtO_2 in methanol).

Borane dimethyl sulfide reportedly reduces nitriles more rapidly than esters.[16,17] However, treatment of the nitrile **15** with the borane reagent gave an unrecognizable mess. Bearing in mind that the nitrile **15** also contained various ester moieties, and considering the unsatisfactory yield of **15**, we decided to change the protecting groups for the diol **11**, to silyl ethers.

The diol **11** was easily converted into the disilyl ether **16** (Scheme 6). Interestingly, analysis of the ^{1}H NMR spectrum of this disilyl ether showed one large value (10.8) for $J_{4,5}$, indicating that the molecule existed solely in a $^4C_1$ conformation. Such was probably not the case for the molecules **11**–**13** where there may be contributions from the other chair ($^1C_4$) conformation. This phenomenon has been observed previously with di- or poly-silylated pyranoses in which the sugars possess *adjacent* sterically encumbering silyloxy groups.[18–21]



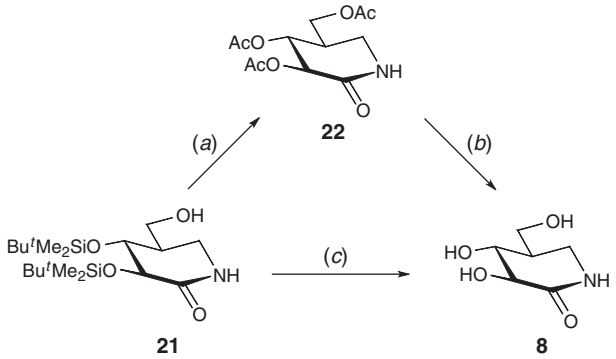
Scheme 5. (*a*) PPTS, MeOH, H_2O; (*b*) Ac_2O, pyridine, DMAP; (*c*) Pd/C, H_2, AcOH, H_2O, THF; (*d*) PDC, 4-Å sieves, CH_2Cl_2; (*e*) PTSA, MeOH, and then Ac_2O, pyridine, DMAP.

Hydrogenolysis of the disilyl ether **16** gave the hemiacetal **17**, and a subsequent Swern oxidation gave the lactone **18** in a modest yield. More satisfactory was a pyridinium dichromate oxidation of **17**, followed by transesterification of the crude lactone **18**, to give the acyclic methyl ester **19** in a pleasing yield of 80% over the two steps.

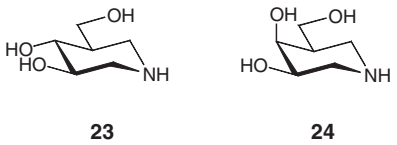
Next, the nitrile **19** was treated with borane dimethyl sulfide in tetrahydrofuran at reflux (Scheme 7). The 'borazine' intermediate was decomposed upon the addition of hydrochloric acid in methanol to give, presumably, the hydrogen chloride salt **20** of the amine. This crude material was then treated with base resin, hopefully to liberate the free amine that could then perform the desired intramolecular attack upon the methyl ester. The ^{1}H NMR spectrum of the crude material indicated the presence of several compounds, also difficult to separate by TLC, and, therefore, difficult to purify by flash chromatography. Fortuitously, upon trituration of this crude material with an ethyl acetate/petrol mixture, a single product crystallized that was found to be the desired lactam **21**. The lactam **21** was thus obtained in a modest yield of 34% from the nitrile **19**.

Finally, the lactam **21** was treated with 1% hydrochloric acid in ethanol (Scheme 8).[22] The crude product was acetylated under standard conditions, for ease of purification, to give the triacetate **22** of isofagomine lactam in 75% yield. Deacetylation of the triacetate gave the desired isofagomine lactam **8** in 89% yield. It was later found more convenient to purify the lactam **8** directly after removal of the silyl protecting groups. In this manner, the yield of isofagomine lactam **8** was 86% from the disilyl ether **21**.

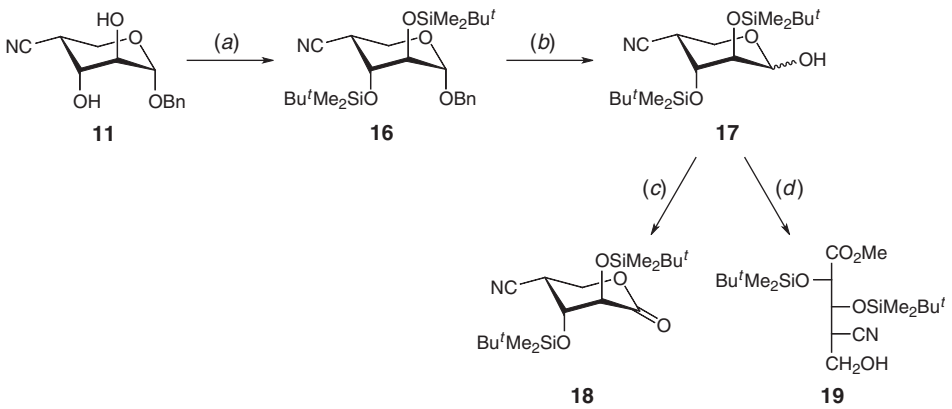
Our synthetic material matched well with the isofagomine lactam **8** produced by Bols and co-workers;[14] we were also able to locate the NH resonance for **8** in the ^{1}H NMR spectrum, and record a value for the optical rotation. Bols' inhibition studies revealed isofagomine lactam to be a poor inhibitor of almond β-glucosidase (K_i 29 μM)[14] relative to isofagomine **23** (K_i 0.11 μM; Scheme 9).[23] This disappointing result stands in contrast to the potent inhibition observed for the two xylobiose-derived analogues **4** and **5** (Scheme 2) for the xylanase (Cex) from *Cellulomonas fimi*,[6,7] and for



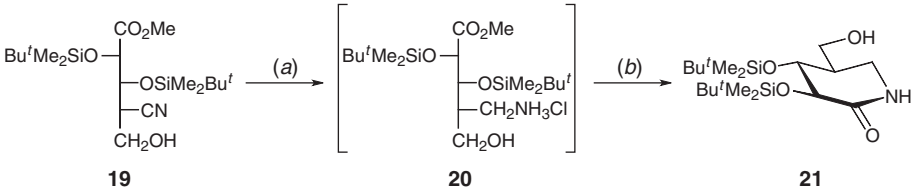
Scheme 8. (*a*) H_3O^+, EtOH, then Ac_2O pyridine; (*b*) NaOMe, MeOH; (*c*) H_3O^+, EtOH.



Scheme 9.



Scheme 6. (*a*) Bu^{t}Me$_2$SiCl, imidazole, DMF; (*b*) Pd/C, H_2, AcOH, H_2O, THF; (*c*) DMSO, $(COCl)_2$, CH_2Cl_2, and then Et_3N; (*d*) PDC, 4-Å sieves, CH_2Cl_2, and then PTSA, MeOH.



Scheme 7. (*a*) Me_2SBH_3, THF, and then H_3O^+, MeOH; (*b*) Amberlite IRA 400 (OH^-).

the two galactose-derived analogues **24** and **9** (Scheme 3) for the β-galactosidase from *Aspergillus oryzae*.[12,24]

Experimental

General experimental procedures have been given previously.[25]

*Benzyl 4-Cyano-4-deoxy-α-D-arabinoside **11***

Pyridinium *p*-toluenesulfonate (25 mg) was added to benzyl 4-cyano-4-deoxy-2,3-*O*-isopropylidene-α-D-arabinoside **10**[15] (1.51 g) in MeOH/H_2O (2 : 1, 30 mL) and the mixture concentrated to 20 mL by gentle distillation (1 atm, 5 h). The reaction mixture was treated with resin (Amberlite IRA 400, OH^-), filtered, and then concentrated (co-evaporating with toluene) to afford a colourless solid. Flash chromatography (EtOAc/petrol, 2 : 3 and then 4 : 1) of this solid gave the *diol* **11** (1.08 g, 83%) as a colourless solid. A small portion was recrystallized to give colourless micro-needles, mp 138–139°C (CH_2Cl_2/petrol), $[\alpha]_D$ +12.3° (MeOH) (Found: C 63.0, H 6.1, N 5.7. $C_{13}H_{15}NO_4$ requires C 62.6, H 6.1, N 5.7%). δ_H (500 MHz) 3.25 (dt, $J_{3,4}\approx J_{4,5}$ 3.9, $J_{4,5}$ 6.2, H4), 3.69 (dd, $J_{5,5}$ 12.1, H5), 3.76 (dd, $J_{1,2}$ 4.9, $J_{2,3}$ 6.8, H2), 3.90 (dd, H3), 4.17 (dd, H5), 4.51 (d, H1), 4.57, 4.87 (ABq, *J* 11.6, PhCH_2), 7.32–7.40 (m, Ph). δ_C (125.8 MHz) 32.74 (C4), 59.07 (C5), 68.95, 69.96 (C2, C3), 70.72 (PhCH_2), 100.26 (C1), 117.60 (CN), 128.28, 128.43, 128.70, 136.11 (Ph).

*Benzyl 2,3-Di-*O*-acetyl-4-cyano-4-deoxy-α-D-arabinoside **12***

The diol **11** (580 mg, 2.33 mmol), Ac_2O (1.75 mL, 18.6 mmol), and 4-dimethylaminopyridine (DMAP) (10 mg) were stirred overnight in pyridine (10 mL). MeOH (4 mL) was added and, after a further 30 min, the mixture was concentrated and then subjected to normal work-up (EtOAc) to give a pale yellow oil. Flash chromatography (EtOAc/petrol, 3 : 7 and then 2 : 3) of this oil gave the *diacetate* **12** (750 mg, 97%) as a colourless oil, $[\alpha]_D$ +52.8° (Found: C 61.6, H 5.7, N 4.0, *m*/*z* 334.1307. $C_{17}H_{19}NO_6$ requires C 61.2, H 5.7, N 4.2%, $[M+H]^+$ 334.1291). δ_H (500 MHz) 2.08, 2.09 (2s, 6H, CH_3), 3.39 (quintet, $J_{3,4}\approx J_{4,5}$ 3.8, $J_{4,5}$ 7.7, H4), 3.73 (dd, $J_{5,5}$ 11.7, H5), 4.26 (dd, H5), 4.53, 4.81 (ABq, *J* 12.0, PhCH_2), 4.65 (d, $J_{1,2}$ 3.7, H1), 5.03 (dd, $J_{2,3}$ 5.8, H3), 5.08 (dd, H2), 7.28–7.38 (m, Ph). δ_C (125.8 MHz) 20.57, 20.64 (2C, CH_3), 30.34 (C4), 57.85 (C5), 66.57, 66.71 (C2, C3), 69.95 (PhCH_2), 97.27 (C1), 116.15 (CN), 127.47, 127.92, 128.40, 136.72 (Ph), 168.84, 169.72 (2C, CH_3CO).

*2,3-Di-*O*-acetyl-4-cyano-4-deoxy-D-arabinose **13***

The diacetate **12** (570 mg), Pd/C (110 mg of 10%), and aqueous AcOH (0.2 mL of 9 M) were stirred vigorously in THF (20 mL) under an atmosphere of H_2 (1 atm, overnight). The mixture was filtered through Celite, washing with EtOAc, and the combined filtrate/washings were concentrated. Flash chromatography (EtOAc/petrol, 3 : 7 and then 3 : 2) of the residue gave the hemiacetal **13** (300 mg, 71%) as a colourless oil, $[\alpha]_D$ −176.5°. δ_C (125.8 MHz) 20.66, 20.70, 20.72, 20.74 (2C, CH_3), 32.42, 33.47 (C4), 58.33, 60.60 (C5), 65.59, 67.88, 68.98, 70.19 (C2, C3), 90.88, 95.35 (C1), 116.26, 116.73 (CN), 169.84, 169.88, 169.96, 170.32 (2C, CH_3CO).

*Methyl 2,3,5-Tri-*O*-acetyl-4-cyano-4-deoxy-D-arabinonate **15***

The hemiacetal **13** (170 mg, 0.51 mmol), pyridinium dichromate (960 mg, 2.6 mmol), and crushed molecular sieves (4 Å, 1.2 g) were stirred overnight in CH_2Cl_2 (15 mL). The mixture was filtered through Celite, washing with CH_2Cl_2, and the combined filtrate/washings were washed with H_2O (twice), dried ($MgSO_4$), filtered, and concentrated. The residue was taken up in MeOH (10 mL) and treated with *p*-toluenesulfonic acid (5 mg). After 2 h the mixture was neutralized with resin (Amberlite IRA 400, OH^-), filtered, and then concentrated. The residue was taken up in pyridine (2 mL) and treated with Ac_2O (250 μL, 2.6 mmol) for 2 h. MeOH (1 mL) was added and, after 30 min, the mixture was concentrated and then subjected to normal work-up (EtOAc). Flash chromatography (EtOAc/petrol, 4 : 7 and then 1 : 1) then gave the *triacetate* **15** (37 mg, 17%) as a colourless oil, $[\alpha]_D$ +33.2° (Found: C 49.7, H 5.7, N 4.2, *m*/*z* 316.1041. $C_{13}H_{17}NO_8$ requires C 49.5, H 5.4, N 4.4%, $[M+H]^+$ 316.1032). δ_H (500 MHz) 2.08, 2.11, 2.33 (9H, 3×s, CH_3), 3.40 (dt, $J_{3,4}$ 8.7, $J_{4,5}\approx J_{4,5}$ 4.9, H4), 3.74 (s, OCH_3), 4.22–4.28 (2H, m, H5), 5.38 (d, $J_{2,3}$ 2.3, H2), 5.61 (dd, H3). δ_C (125.8 MHz) 20.26, 20.31, 20.45 (3×C, CH_3), 32.77 (C4), 52.93 (OCH_3), 59.44 (C5), 67.52 (C3), 70.83 (C2), 115.82 (CN), 166.61, 169.09, 169.54, 170.05 (4C, C1, CH_3CO).

*Benzyl 2,3-Di-*O*-(*tert*-butyldimethylsilyl)-4-cyano-4-deoxy-α-D-arabinoside **16***

The diol **11** (650 mg, 2.6 mmol), Bu^{t}Me$_2$SiCl (1.96 g, 13.0 mmol), and imidazole (1.80 g, 26.0 mmol) were heated (100°C, 5 days) in DMF (10 mL). The mixture was concentrated and subjected to a normal work-up (EtOAc). Flash chromatography (EtOAc/petrol, 3 : 97 and then 1 : 9) gave the *disilyl ether* **16** (1.03 g, 83%) as a colourless solid. A small portion was recrystallized to give colourless prisms, mp 65–67°C (MeOH), $[\alpha]_D$ +78.8° (Found: C 62.9, H 8.8, N 2.8, *m*/*z* 478.2795. $C_{25}H_{43}NO_4Si_2$ requires C 62.8, H 9.1, N 2.9%, $[M+H]^+$ 478.2809). δ_H (500 MHz) 0.01, 0.04, 0.10, 0.16 (12H, 4×s, $SiCH_3$), 0.86, 0.88 (18H, s, CCH_3), 3.27 (ddd, $J_{3,4}$ 2.6, $J_{4,5}$ 4.0, 10.8, H4), 3.59–3.64 (m, 2H), 3.92–3.95 (m, 1H), 4.27 (t, $J_{5,5}$ 10.8, H5), 4.45, 4.71 (ABq, *J* 11.9, PhCH_2), 4.53 (br s, H1), 7.26–7.35 (m, Ph). δ_C (125.8 MHz) −5.01, −4.99, −4.89, −4.44 (4×C, $SiCH_3$), 17.86, 18.00 (2×C, *C*CH_3), 25.60, 25.63 (6×C, C*C*H_3), 30.98 (C4), 55.44 (C5), 68.90, 69.01 (C2,3), 69.62 (PhCH_2), 99.06 (C1), 118.56 (CN), 127.68, 128.14, 128.25, 137.39 (Ph).

*2,3-Di-*O*-(*tert*-butyldimethylsilyl)-4-cyano-4-deoxy-D-arabinose **17***

The benzyl glycoside **16** (370 mg), Pd/C (140 mg of 10%), and AcOH (100 μL) were stirred vigorously in THF (15 mL) under an atmosphere of H_2 (1 atm, 3 days). The mixture was filtered through Celite, washing with EtOAc, and the combined filtrate/washings were concentrated. Flash chromatography (EtOAc/petrol, 1 : 24 and then 1 : 10) of the residue gave the *hemiacetal* **17** (280 mg, 94%) as an oil, $[\alpha]_D$ −9.1° (Found: C 56.0, H 9.5, N 3.5, *m*/*z* 388.2365. $C_{18}H_{37}NO_4Si_2$ requires C 55.8, H 9.6, N 3.6%, $[M+H]^+$ 388.2339). δ_C (75.5 MHz) −4.97, −4.92, −4.89, −4.83, −4.57, −4.53 (4×C, $SiCH_3$), 17.93 (2×C, *C*CH_3), 25.62, 25.65 (6×C, C*C*H_3), 29.54, 30.48 (C4), 54.31, 60.65 (C5), 67.21, 69.83, 70.10, 70.35 (C2, C3), 91.42, 94.51 (C1), 117.92, 118.03 (CN).

*2,3-Di-*O*-(*tert*-butyldimethylsilyl)-4-cyano-4-deoxy-D-arabinono-1,5-lactone **18***

DMSO (25 μL, 0.35 mmol) was added dropwise to $(COCl)_2$ (30 μL, 0.32 mmol) in CH_2Cl_2 (4 mL) at −78°C. After 3 min, the hemiacetal **17** (50 mg, 0.13 mmol) in CH_2Cl_2 (4 mL) was added dropwise and the mixture stirred (30 min, −78°C). Et_3N (200 μL) was added and the mixture was allowed to warm to room temperature. The mixture was washed with H_2O (twice), and brine, and then dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (EtOAc/petrol, 3 : 97 and then 3 : 22) of the residue gave the *lactone* **18** (24 mg, 48%) as a colourless solid. A small portion was recrystallized to give needles, mp 64–67°C (petrol), $[\alpha]_D$ −47.3° (Found: C 56.4, H 9.0, N 3.4, *m*/*z* 386.2174. $C_{18}H_{35}NO_4Si_2$ requires C 56.1, H 9.1, N 3.6%, $[M+H]^+$ 386.2183). δ_H (300 MHz) 0.13, 0.15, 0.16, 0.22 (12H, 3×s, $SiCH_3$), 0.89, 0.92 (18H, s, CCH_3), 3.59 (ddd, $J_{3,4}$ 1.9, $J_{4,5}$ 5.9, 11.2, H4), 4.04 (d, $J_{2,3}$ 3.8, H2), 4.16 (dd, H3), 4.49 (dd, $J_{5,5}$ 11.0, H5), 4.62 (t, H5). δ_C (75.5 MHz) −5.36, −5.07, −4.90, −4.78 (4×C, $SiCH_3$), 17.91, 17.99 (2×C, *C*CH_3), 25.52 (6×C, C*C*H_3), 28.29 (C4), 64.30 (C5), 70.54, 70.75 (C2, C3), 116.75 (CN), 166.83 (C1).

*Methyl 2,3-Di-*O*-(*tert*-butyldimethylsilyl)-4-cyano-4-deoxy-D-arabinonate **19***

The hemiacetal **17** (260 mg, 0.55 mmol), pyridinium dichromate (1.0 g, 2.8 mmol), and crushed molecular sieves (4 Å, 1.2 g) were stirred in CH_2Cl_2 (15 mL) for 30 h. The mixture was filtered through Celite, washing with CH_2Cl_2, and the combined filtrate/washings were washed

with H_2O (twice), and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was taken up in MeOH (15 mL) and treated with *p*-toluenesulfonic acid (5 mg). After 24 h the mixture was neutralized with resin (Amberlite IRA 400, OH^-), filtered, and then concentrated. Flash chromatography (EtOAc/petrol, 1 : 19 and then 3 : 17) of the residue gave the *methyl ester* **19** (230 mg, 80%) as a colourless oil, $[\alpha]_D$ +15.0° (Found: C 54.7, H 9.1, N 3.2, *m/z* 418.2429. $C_{19}H_{39}NO_5Si_2$ requires C 54.6, H 9.4, N 3.3%, $[M+H]^+$ 418.2445). δ_H (500 MHz) 0.06, 0.10, 0.13 (12H, 3×s, $SiCH_3$), 0.88, 0.93 (18H, s, CCH_3), 2.42 (br s, OH), 3.17 (dt, $J_{3,4}$ 7.4, $J_{4,5}\approx J_{4,5}$ 4.8, H4), 3.47 (s, OCH_3), 3.85 (dd, $J_{5,5}$ 11.4, H5), 3.92 (dd, H5), 4.31 (dd, $J_{2,3}$ 3.4, H3), 4.38 (d, H2). δ_C (125.8 MHz) −5.31, −5.06, −4.86, −4.82 (4×C, $SiCH_3$), 17.97, 18.21 (2×C, CCH_3), 25.56, 25.65 (6×C, CCH_3), 37.60 (C4), 51.96 (OCH_3), 59.46 (C5), 71.59, 73.78 (C2, C3), 119.31 (CN), 171.46 (C1).

*(3*S*,4*R*,5*R*)-3,4-Di-(*tert*-butyldimethylsilyloxy)-5-(hydroxymethyl)piperidin-2-one* ***21***

The nitrile **19** (150 mg, 0.36 mmol) and Me_2SBH_3 (70 μL, 0.72 mmol) were heated under reflux in THF (5 mL) for 1.5 h. The mixture was allowed to cool, and was then brought to pH 5 by the cautious addition of hydrochloric acid in MeOH (0.1 M) and stirred (30 min). The mixture was neutralized with resin (Amberlite IRA 400, OH^-), filtered, and then concentrated. The residue was subjected to normal work-up (EtOAc) to afford an oil that crystallized. Recrystallization gave the lactam **21** (50 mg, 36%) as colourless micro-needles, mp 202–210°C (EtOAc/petrol), $[\alpha]_D$ −26.8°. δ_H (500 MHz) 0.090, 0.097, 0.18, 0.20 (4×s, 12H, $SiCH_3$), 0.88, 0.91 (2×s, 18H, CCH_3), 2.12 (m, H5), 2.24 (br s, OH), 3.28 (dt, $J_{5,6}\approx J_{6,NH}$ 3.4, $J_{6,6}$ 12.0, H6), 3.65 (ddd, *J* 1.7, 5.5, H6), 3.77–3.81 (2H, m), 3.85–3.87 (1H, m), 3.99 (1H, t, $J\approx J$ 3.0), 5.49–5.54 (m, NH). δ_C (125.8 MHz) −5.29, −4.94, −4.75, −4.70 (4×C, $SiCH_3$), 17.93, 18.12 (2×C, CCH_3), 25.67, 25.72 (6×C, CCH_3), 39.78 (C6), 41.09 (C5), 61.88 (CH_2O), 72.36, 72.91 (C3, C4), 170.03 (C2). *m/z* (FAB) 390.2505 ($C_{18}H_{40}NO_4Si_2$ $[M+H]^+$ requires 390.2496).

*(3*S*,4*R*,5*R*)-3,4-Diacetoxy-5-(acetoxymethyl)piperidin-2-one* ***22***

The lactam **21** (45 mg, 0.12 mmol) in hydrochloric acid (10 M)/EtOH (1 : 99, 2 mL) was kept overnight. The mixture was concentrated (co-evaporating with toluene), and then taken up in pyridine (2 mL) and treated with Ac_2O (200 μL, 2.2 mmol) for 2 h. MeOH (0.5 mL) was added and, after a further 30 min, the mixture was concentrated. Flash chromatography (EtOAc/petrol, 4 : 1 followed by $MeOH/CHCl_3$, 1 : 19) of the residue gave the triacetate **22** (25 mg, 75%) as a colourless glass, $[\alpha]_D$ +6.2°. δ_H (600 MHz) 2.06, 2.09, 2.13 (3×s, 9H, CH_3), 2.42–2.44 (m, H5), 3.31–3.36 (m, H6), 3.43 (ddd, *J* 3.6, 5.0, 12.3, H6), 4.09 (1H, dd, $J_{5,H}$ 3.5, $J_{H,H}$ 11.6, CH_2O), 4.19 (1H, dd, $J_{5,H}$ 6.4, CH_2O), 5.08 (d, $J_{3,4}$ 9.1, H3), 5.37 (dd, $J_{4,5}$ 10.7, H4), 6.09–6.14 (m, NH). δ_C (150.9 MHz) 20.61, 20.68 (3×C, CH_3), 38.07 (C5), 41.07 (C6), 61.30 (CH_2O), 69.21, 72.37 (C3, C4), 167.19, 169.81, 170.23, 170.55 (4×C, C=O). *m/z* (FAB) 288.1069 ($C_{12}H_{18}NO_7$ $[M+H]^+$ requires 288.1083).

*(3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)piperidin-2-one (Isofagomine Lactam)* ***8***

Method 1: The disilyl ether **21** (14 mg) in hydrochloric acid (10 M)/EtOH (1 : 99, 2 mL) was heated to 50°C for 1.5 h. The mixture was concentrated (co-evaporating with toluene). Flash chromatography (EtOAc/MeOH/H_2O, 15 : 2 : 1 and then 7 : 2 : 1) of the residue gave the lactam **8** (5.0 mg, 86%) as a colourless, amorphous solid, $[\alpha]_D$ +11.0° (MeOH). δ_H (600 MHz, D_2O) 2.12–2.18 (m, H5), 3.16 (ddd, $J_{6,NH}$ 0.8, $J_{5,6}$ 10.3, $J_{6,6}$ 12.8, H6), 3.40 (dd, $J_{5,6}$ 5.8, H6), 3.67–3.72 (2H, m, H4, CH_2O), 3.82 (1H, dd, $J_{5,H}$ 3.8, $J_{H,H}$ 11.5, CH_2O), 4.03 (dd, $J_{3,NH}$ 0.8, $J_{3,4}$ 9.3, H3), 8.45 (s, NH).[14] δ_C (150.9 MHz, D_2O) 41.15 (C5), 41.24 (C6), 60.89 (CH_2O), 71.24 (C4), 73.39 (C3), 174.25 (C2).[14] *m/z* (EI) 161.0694 ($C_6H_{11}NO_4$ $[M]^{+\bullet}$ requires 161.0688).

Method 2: A small piece of Na was added to the triacetate **22** (10 mg) in dry MeOH (3 mL). After 2 h the mixture was neutralized with resin (Amberlite IR-120, H^+), filtered, and then concentrated. Flash chromatography (EtOAc/MeOH/H_2O, 15 : 2 : 1 and then 7 : 2 : 1) of the residue gave the lactam **8** (5.0 mg, 89%) as a colourless, amorphous solid, consistent, by ^1H (500 MHz) and ^{13}C (125.8 MHz) NMR spectroscopy, with the material prepared above.

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