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# Unusual ring contraction by substitution of 4-*O*-activated-pentono-1,5-lactams with cyanide. Stereospecific synthesis of 6-amino-1,4,5,6- tetradeoxy-1,4-imino-hexitols

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**Abstract**

Reaction of 4-*O*-sulfonylated 2,3-*O*-isopropylidene-D-*ribo*- or -D-*lyxo*-1,5-lactams with tetrabutylammonium cyanide gave 4-amino-5-*C*-cyano-4,5-dideoxy-2,3-*O*-isopropylidene-L-*lyxo*-**5** or -L-*ribo*-**15**-1,4-lactams, respectively. A stereospecific ring contraction with inversion at C-4 had taken place in each case. Reduction of the cyano-lactams with $LiAlH_4$ gave 6-amino-1,4,5,6-tetradeoxy-1,4-imino-L-*lyxo*-**6** or -L-*ribo*-**16**-hexitol, respectively. The 6-amino-1,4,5,6-tetradeoxy-1,4-imino-L-*ribo*-hexitol **16** was found to be a moderate inhibitor of α-L-fucosidase with a $K_i$ of 110 μM. 

## 1. Introduction

The success of iminosugars as glycosidase inhibitors has stimulated the interest in design and development of synthetic procedures by which new sugar analogues with nitrogen in the ring instead of oxygen can be obtained.[1] We became interested in studying the branching of an iminosugar at the 2- or 3-position to the nitrogen, partly because new carbon frameworks might thus be available, partly because introduction of a one-carbon unit would provide a simple method for carbon labelling in a glycosidase inhibitor. Having access to specific labelled glycosidase inhibitors is of importance, since in the process of selecting an inhibitor as a drug candidate, a metabolic study is necessary. The isotope of choice is dependent on the methods used in the study. Labelling of a compound with a carbon isotope ($^{14}C$ or $^{13}C$) from the available labelled precursor potassium cyanide requires a procedure whereby the one-carbon unit is introduced late in the synthesis. We have previously developed a method to introduce the branching at the 2-position with respect to the nitrogen, by addition of trimethylsilyl cyanide (TMSCN)

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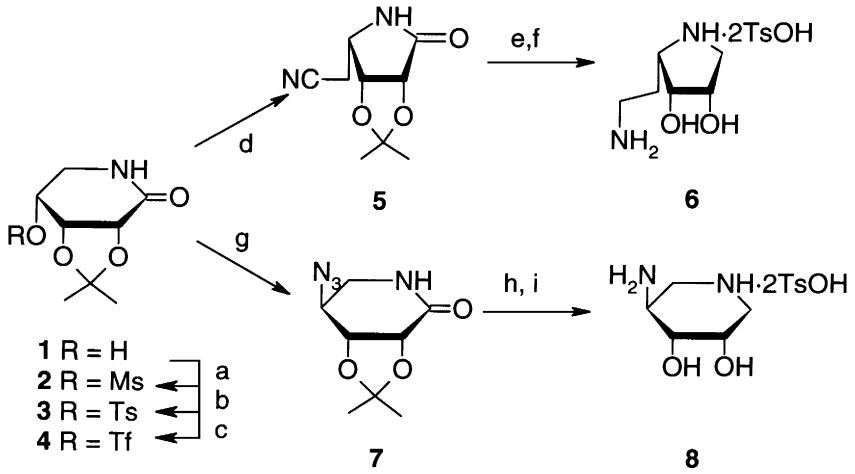
to (3*R*,4*R*)-dibenzoyloxy-1-pyrroline.[2] By this procedure $^{14}$C-5 1,4-dideoxy-1,4-imino-D-arabinitol was prepared using $^{14}$C labelled TMSCN. The TMS$^{14}$CN was prepared in situ from K$^{14}$CN.[2]

In this paper we present results related to the branching at the 3-position with respect to the nitrogen.

## 2. Results and discussion

A suitable precursor for the study was 5-amino-5-deoxy-2,3-*O*-isopropylidene-D-ribono-1,5-lactam **1** which is easily available from D-ribonolactone.[3] Activation of the OH-4 group, followed by substitution with cyanide and reduction of the lactam function, should result in a 3-cyano piperidine derivative. Thus, the free hydroxy group was activated by mesylation, tosylation or triflation to give the *O*-sulfonylated lactams **2**, **3** or **4**, respectively (Scheme 1), ready for nucleophilic substitution by a carbon nucleophile. To our surprise, however, reaction of each of the three lactams with tetrabutylammonium cyanide in DMF afforded in all cases the 4-amino-5-*C*-cyano-4,5-dideoxy-2,3-*O*-isopropylidene-L-lyxono-1,4-lactam **5** as a crystalline compound. The reaction proceeded in 65% yield when the mesylate **2** was used as the starting material, while the tosylate **3** only yielded 36% of **5**. Nevertheless, since the tosylated lactam **3** was more easily prepared (87%) this was chosen as the substrate for the practical preparation of **5**.




Scheme 1. (a) MsCl, pyridine, 0°C, 1 h (50% **2**). (b) TsCl, pyridine, 0°C, 1 h (87% **3**). (c) $Tf_2O$, pyridine, 0°C, 1 h (80% **4**). (d) $Bu_4NCN$, DMF, 100°C, 8 h (65% from **2**, 36% from **3**). (e) $LiAlH_4$, THF, 60°C, 4 h. (f) TsOH, $H_2O$, 50°C, 20 h. (g) $NaN_3$, DMF, rt, 3 h (from **4**). (h) LiAlH4, THF, rt, 22 h. (i) TsOH, MeOH, 50°C, 10 h

The structure of **5** was deduced from $^1$H and $^{13}$C NMR spectra. Thus, the $^{13}$C NMR spectrum showed the acetal carbon at 116.9 ppm compared to 109.7 ppm in **3**, indicating that the five-membered acetal is now fused to a five-membered ring.[4] This furthermore results in a downfield shift of C-2 to 80.2 ppm and C-3 to 78.5 ppm, both from ca. 73 ppm in the six-membered starting material **3**. The chemical shift of C-4, 53.7 ppm, suggested that the substituent was a nitrogen function, and the chemical shift of C-5, 20.8 ppm, indicated that the cyano group had been introduced at this carbon. The structure of **5** was confirmed by X-ray crystallography which furthermore shows that the ring contraction had occurred with inversion of configuration at C-4 (Fig. 1).

Having access to this interesting functionalised five-membered lactam **5** we investigated if the cyano function could be selectively reduced to an amine. However, hydrogenation in the presence of Pd on carbon was not successful, either under neutral or under acidic conditions. Besides the 6-amino-substituted 1,4-lactam, approximately 10% of, presumably, the corresponding seven-membered lactam

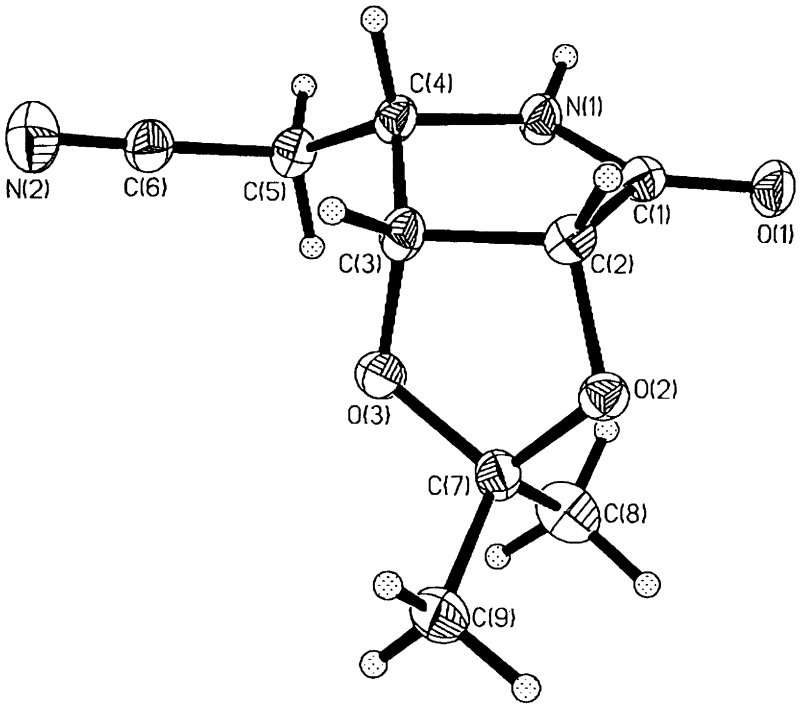



Fig. 1. View of 4-amino-5-*C*-cyano-4,5-dideoxy-2,3-*O*-isopropylidene-L-lyxono-1,4-lactam **5**. Thermal ellipsoids are drawn at the 50% probability level

was formed. Instead, compound **5** was treated with lithium aluminium hydride whereby both the cyano group as well as the lactam function were reduced. The resulting 6-amino-1,4,5,6-tetradeoxy-2,3-*O*-isopropylidene-1,4-imino-L-*lyxo*-hexitol was deprotected using 2.05 equivalents of *p*-TsOH in methanol, and the crystalline 6-amino-1,4,5,6-tetradeoxy-1,4-imino-L-*lyxo*-hexitol, ditosylate **6** was isolated (Scheme 1).

The unexpected ring contraction led us to investigate the substitution of the OH-4 activated pentonolactams with another nucleophile. When the triflate **4** was treated with sodium azide or tetrabutylammonium azide[5] in DMF, the isolated product was the expected 4-azido-1,5-lactam **7** (Scheme 1). The structure of **7** was confirmed by reduction of both the azide- and the lactam-functionality using lithium aluminium hydride. Deprotection by treatment with a slight excess of *p*-toluene sulfonic acid gave crystalline 4-amino-1,4,5-trideoxy-1,5-imino-L-lyxitol ditosylate **8**, having NMR spectra and the numerical value of the specific rotation identical to those of the enantiomeric compound.[6]

In order to test whether this ring contraction was specific for a five-membered lactam with *ribo* configuration the lactam having *lyxo* configuration was synthesised. Thus, potassium D-lyxonate **9**[7] was lactonised by treatment with conc. aq. HCl–methanol (ca. 1:9). After concentration the residue was treated with dimethoxypropane, acetone and methanesulfonic acid to give methyl 2,3:4,5-di-*O*-isopropylidene-D-lyxonate **10**. Selective cleavage of the 4,5-*O*-isopropylidene group with acetic acid:water (9:1) gave the 2,3-*O*-isopropylidene-D-lyxono-1,4-lactone **11**. Previous attempts to prepare this compound by treatment of D-lyxono-1,4-lactone with acetone under acidic conditions, gave a mixture of **11** and the 3,5-*O*-isopropylidene-1,4-lactone.[8] Mesylation of the OH-5 gave **12**, which by reaction with aqueous ammonia yielded the lactam **13**, according to our procedure for the L-enantiomer.[3] Tosylation of the OH-4 of lactam **13** proved unsastifactory and thus the mesylate **14** was synthesised. Reaction of **14** with tetrabutylammonium cyanide in DMF gave a 5-*C*-cyano-substituted 1,4-lactam, **15**, as indicated by $^{13}C$

NMR spectra. Thus, also in this case a ring contraction had occurred as discussed above for substitution reactions of the lactams **2**–**4** with *ribo* configuration. The structure of lactam **15** was established by X-ray crystallography, showing an inversion at C-4 compared to the starting material (Fig. 2).

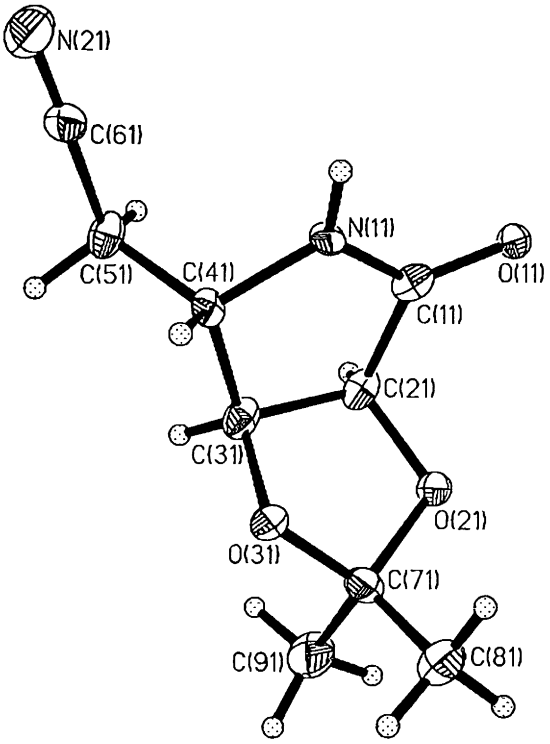
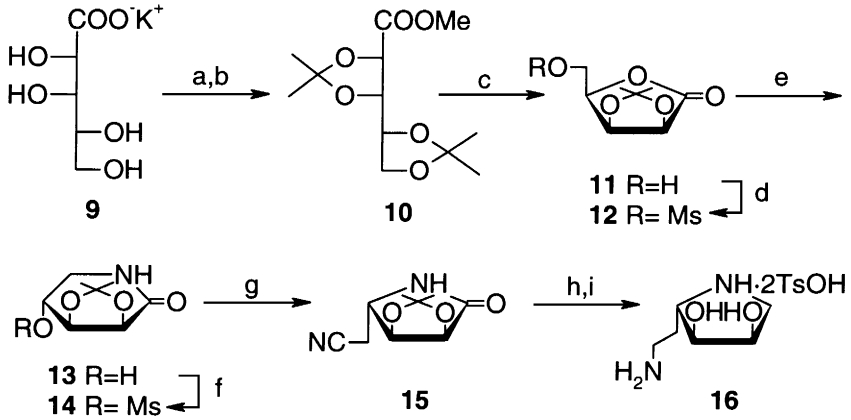


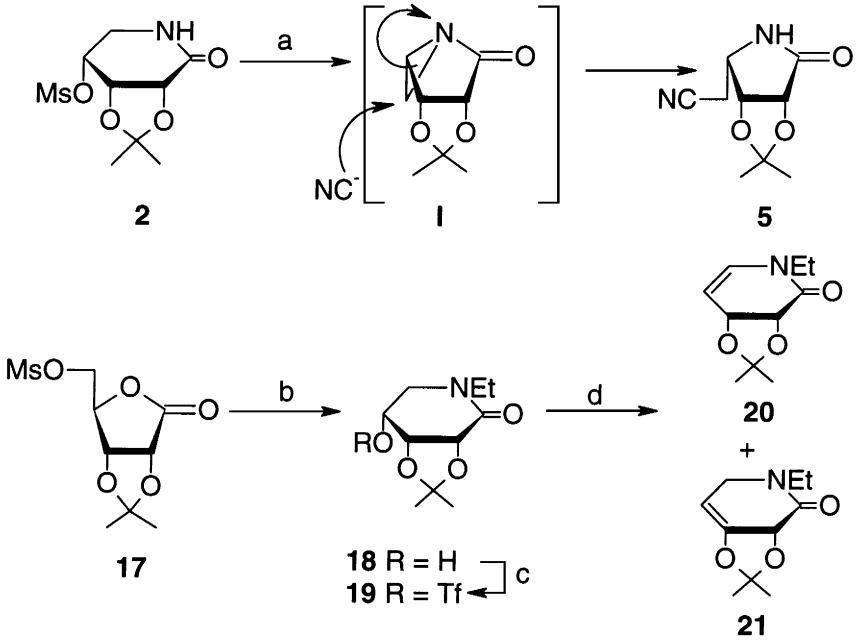

Fig. 2. View of 4-amino-5-*C*-cyano-4,5-dideoxy-2,3-*O*-isopropylidene-L-ribono-1,4-lactam **15**. Thermal ellipsoids are drawn at the 50% probability level

Reduction of **15** with lithium aluminium hydride gave the corresponding 6-amino-1,4,5,6-tetradeoxy-2,3-*O*-isopropylidene-1,4-imino-L-*ribo*-hexitol, which could be deprotected by treatment with excess *p*-TsOH to give 6-amino-1,4,5,6-tetradeoxy-1,4-imino-L-*ribo*-hexitol ditosylate **16** (Scheme 2).




Scheme 2. (a) Aq. HCl. (b) Dimethoxypropane, MsOH, rt, 20 h. (c) AcOH:$H_2O$ 90:10, 30°C, 16 h (45% from **9**). (d) MsCl, pyridine, 0°C 1 h (79%). (e) Aq. $NH_3$, rt, 5.5 h (85%). (f) MsCl, pyridine, 0°C, 2 h (59%). (g) $Bu_4NCN$, DMF, 100°C, 5 h (62%). (h) LiAlH4, THF, rt, 18 h. (i) TsOH, MeOH, 50°C, 4 h (43% from **15**)

Attempts to substitute a leaving group at C-4 in aldonolactams, having either *ribo* or *lyxo* configuration, with cyanide ion, resulted in products where the nucleophile was introduced at C-5 with simultaneous ring contraction and inversion of the configuration at C-4. A most likely explanation would be formation of an intermediate aziridine **I** by deprotonation of the NH group, followed by nucleophilic displacement of the mesyl group at C-4 (Scheme 3). Subsequent opening by cyanide ions at the less hindered primary position gave the 1,4-lactam. The reaction was very fast as the reaction of the triflate **4** with tetrabutylammonium cyanide was completed in less that 5 min at room temperature. Attempts to follow the substitution reaction of either the mesylated or tosylated lactam, **2** or **3,** by $^{13}C$ NMR spectroscopy gave no results. This might be due to low concentration of the possible aziridine intermediate **I**. If the mechanism proceeds via deprotonation of the nitrogen atom in the lactam function, the ring contraction should be blocked if an *N*-alkylated lactam is used as the substrate. In order to validate this hypothesis, synthesis of *N*-ethyl-5-amino-5-deoxy-2,3-*O*-isopropylidene-D-ribono-1,5-lactam **18** was initiated. Treatment of the lactone **17**[8] with aqueous ethylamine gave the lactam **18**. The reaction is analogous to the reaction of the mesylated lactone **11** with ammonia to give the lactam **13**, as discussed above. Conversion to the very reactive triflate **19** followed by reaction with tetrabutylammonium cyanide led to two unsaturated lactams, probably compounds **20** and **21**, in a ratio of 1:4 (Scheme 3). This result supports the mechanism suggested, as the deprotonation of the nitrogen should be a prerequisite for the ring contraction.




Scheme 3. (a) $Bu_4NCN$, DMF, 100°C, 8 h. (b) 70% aq. $EtNH_2$, rt, 6 days (100%). (c) $Tf_2O$, pyridine, 0°C, 30 min. (d) $Bu_4NCN$, DMF, rt, 28 h

Ring contractions[9] or enlargements[10] have been observed in similar substitution reactions of cyclic amines, where aziridine intermediates have been suggested as intermediates. Ring contractions in systems involving the less basic amide nitrogen have, to our knowledge, not been reported so far. Recently, however, a ring contraction of an *N*,*N*-dialkylated seven-membered cyclic urea, having two hydroxy groups, was reported. During its reaction with the fluorinating reagent (diethylamino)sulfur trifluoride (DAST) a ring contraction to a fluorinated six-membered piperidine derivative was observed.[11] The lactams investigated in the present study underwent ring contraction only, when treated with cyanide

and not with azide ions. The ring contraction must therefore be dependent on the basic and nucleophilic character of the nucleophile.

In conclusion, we have prepared C-5 cyano substituted aldono-1,4-lactams by stereospecific ring contraction of C-4 activated aldono-1,5-lactams. These compounds, **5** and **15**, are interesting chiral synthons for further chemical transformations. In this work 6-amino-1,4,5,6-tetradeoxy-1,4-imino-hexitols with L-*lyxo*- **6** and L-*ribo*-configuration **16** have been prepared.

The two amino-imines were tested as glycosidase inhibitors towards commercially available enzymes.[6] While the L-*lyxo*-derivative, **6**, did not show any activities the L-*ribo*-analogue, **16**, was a moderate inhibitor of α-L-fucosidase with a $K_i$ of 110 μM.

## 3. Experimental

NMR spectra were recorded on a Bruker AC-250 or a Bruker AM-500 instrument. Chemical shifts were measured in ppm and coupling constants ($J$) in hertz. For $^{13}C$ spectra and $^{1}H$ spectra recorded in $D_2O$, dioxane ($\delta$=67.4) and acetone ($\delta$=2.17) were used as internal references, respectively. In $CDCl_3$ ($\delta$=76.9), DMSO-$d_6$ ($\delta$=39.5), methanol-$d_4$ ($\delta$=49.0) and acetone-$d_6$ ($\delta$=29.8) the solvent signals were used as internal reference for $^{13}C$ spectra. For $^{1}H$ spectra in $CDCl_3$ ($\delta$=7.26) and acetone-$d_6$ ($\delta$=2.05) the solvent signals were used as internal reference unless otherwise stated. Assignments of signals were obtained from COSY or CH correlated spectra, if necessary. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Melting points are uncorrected. Evaporation was performed in vacuo on a rotary evaporator below 40°C. Column chromatography was performed on silica gel 60, Merck (mesh 230–400) using the flash technique. TLC was performed on aluminium sheets silica gel 60 $F_{254}$. Microanalyses were performed by Leo Microanalytical Laboratory, University of Copenhagen and Research Institute of Pharmacy and Biotechnology, Prague.

### 3.1. 5-Amino-5-deoxy-2,3-O-isopropylidene-4-O-methanesulfonyl-D-ribono-1,5-lactam **2**

5-Amino-5-deoxy-2,3-*O*-isopropylidene-D-ribono-1,5-lactam **1**[3] (9.51 g, 50.8 mmol) was dissolved in pyridine (28.5 ml) and cooled to 0°C. Methanesulfonyl chloride (5.53 ml, 71.1 mmol) was added during 40 min. The solution was stirred for another 30 min and then left at room temperature for 30 min. The reaction mixture was quenched with ice/$H_2O$ (100 g), concentrated to a syrup and extracted with boiling acetone (3×100 ml). The acetone extracts were concentrated, redissolved in $CH_2Cl_2$, filtered, and concentrated. The residue was purified by column (5×20 cm) chromatography eluting with EtOAc→EtOAc:EtOH 9:1. This gave the title compound as a crystalline residue (5.35 g, 40%); mp 166–167°C. Slightly impure fractions were concentrated to give an additional amount of **2** (1.40 g, 10%); mp 164–165.5°C. Recrystallisation from EtOAc furnished an analytical sample; mp 166–167°C; $[\alpha]_D^{20}$ +35.8 (*c* 1.1, acetone); $^{1}H$ NMR ($CDCl_3$): $\delta$ 6.77 (bs, NH), 5.02 (ddd, H-4, $J_{3,4}$=3.2 Hz, $J_{4,5}$=8.3 Hz, $J_{4,5'}$=3.9 Hz), 4.66 (ddd, H-3, $J_{2,3}$=6.8 Hz, $J_{3,5'}$=0.8 Hz), 4.54 (d, H-2), 3.76 (ddd, H-5, $J_{5,5'}$=12.5 Hz, $J_{5,NH}$=2.4 Hz), 3.45 (dddd, H-5′, $J_{5',NH}$=4.2 Hz), 3.12 (s, $CH_3SO_2$-), 1.53 (s, $CH_3$) and 1.43 (s, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 168.5 (C-1), 111.7 (acetal) 76.6, 76.6 (C-2, C-3), 71.5 (C-4), 40.5 (C-5), 38.8 ($CH_3SO_2$-), 26.3 ($CH_3$) and 24.9 ($CH_3$). Anal. calcd for $C_9H_{15}NO_6S$ (229.25): C, 40.75; H, 5.70; N, 5.28. Found: C, 40.63; H, 5.70; N, 5.09.

### 3.2. 5-Amino-5-deoxy-2,3-O-isopropylidene-4-O-p-toluenesulfonyl-D-ribono-1,5-lactam **3**

The 2,3-*O*-isopropylidene-D-ribono-1,5-lactam **1** (7.07 g, 37.8 mmol) was dissolved in pyridine (25 ml) and treated with *p*-toluenesulfonyl chloride (10.8 g, 56.7 mmol) as described above for the mesylation. By addition of ice/$H_2O$ (100 g) a colourless crystalline precipitate was formed, filtered off and washed with cold $H_2O$. Drying in vacuo gave **3** (11.18 g, 87%); mp. 166–170 °C; $[\alpha]_D^{20}$ +35.7 (*c* 1.1, acetone). Recrystallisation from MeOH furnished an analytical sample; mp 171.5–173°C; $[\alpha]_D^{20}$ +39.0 (*c* 1.0, acetone); $^1$H NMR (acetone-$d_6$): $\delta$ 7.87 (d, 2H, Ph), 7.50 (d, 2H, Ph), 6.92 (bs, NH), 4.98 (ddd, H-4, $J_{3,4}$=3.0 Hz, $J_{4,5}$=7.1 Hz, $J_{4,5'}$=4.0 Hz), 4.55 (ddd, H-3, $J_{2,3}$=6.8 Hz, $J_{3,5'}$=1.1 Hz), 4.43 (d, H-2), 3.57 (ddd, H-5, $J_{5,5'}$=12.1 Hz), 3.27 (ddd, H-5′), 2.47 (s, Ph-*CH*$_3$), 1.38 (s, $CH_3$) and 1.29 (s, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 166.9 (C-1), 145.2, 132.8, 130.2, 127.6 (aromatic), 109.7 (acetal), 73.5, 73.2, 72.9 (C-2, C-3 and C-4), 39.3 (C-5), 26.0 ($CH_3$), 24.7 ($CH_3$) and 21.1 (Ph-*CH*$_3$). Anal. calcd for $C_{15}H_{19}NO_6S$ (341.38): C, 52.78; H, 5.61; N, 4.10. Found: C, 52.82; H, 5.60; N, 4.17.

### 3.3. 5-Amino-5-deoxy-2,3-O-isopropylidene-4-O-trifluoromethanesulfonyl-D-ribono-1,5-lactam **4**

The 2,3-*O*-isopropylidene-D-ribono-1,5-lactam **1** (0.866 g, 4.63 mmol) was dissolved in pyridine (2.5 ml) and cooled to 0°C. Trifluoromethanesulfonic anhydride (1.00 ml, 6.02 mmol) was added slowly in a nitrogen atmosphere during 30 min. The mixture was stirred for an additional 30 min and left at room temperature for 20 min. Addition of $CH_2Cl_2$ (10 ml) and ice/$H_2O$ (10 g), followed by washing of the organic phase with 10% HCl (until acidic), water, aqueous $NaHCO_3$, drying ($Na_2SO_4$) and filtration, gave, after concentration, **4** as a pale yellow syrup (1.18 g, 80%). The syrup was pure according to a $^{13}$C NMR spectrum and was used directly for the synthesis of **7**. $^{13}$C NMR ($CDCl_3$): $\delta$ 168.8 (C-1), 117.3 (quartet, Tf), 111.4 (acetal) 78.4, 72.4, 72.3 (C-2, C-3, C-4), 40.2 (C-5), 25.3 ($CH_3$) and 24.1 ($CH_3$).

### 3.4. 4-Amino-5-C-cyano-4,5-dideoxy-2,3-O-isopropylidene-L-lyxono-1,4-lactam **5**

From **3**: The tosylated-D-ribono-1,5-lactam **3** (6.18 g, 18.1 mmol) was added to a solution of $Bu_4NCN$ in DMF (1.12 M, 24.3 ml, 27.2 mmol) and the mixture was kept at 100°C for 8 h. The solution was loaded on a column of mixed ion-exchange resin (Amberlite IR-120, $H^+$, 71.4 ml and Amberlite IRA-400, $HCO_3^-$, 123.4 ml) and eluted with $H_2O$ (400 ml). The eluate was concentrated, redissolved in $CH_2Cl_2$ (15 ml), placed on a column of silica (4×15 cm) and eluted with EtOAc to give the lactam **5** (1.28 g, 36%); mp 162–163°C; $[\alpha]_D^{20}$ −14.1 (*c* 1.0, MeOH); $^1$H NMR ($D_2O$): $\delta$ 4.93 (dd, H-3, $J_{2,3}$=5.8 Hz, $J_{3,4}$=4.9 Hz), 4.84 (d, H-2), 4.15 (ddd, H-4, $J_{4,.5}$=6.9 Hz, $J_{4,5'}$=5.0 Hz), 2.92 (dd, H-5, $J_{5,5'}$=17.3 Hz), 2.88 (dd, H-5′), 1.44 (s, $CH_3$) and 1.38 (s, $CH_3$); $^{13}$C NMR ($D_2O$, acetone $\delta$=33.01): $\delta$ 178.6 (C-1), 121.0 (CN), 116.9 (acetal), 80.5 (C-2), 78.5(C-3), 53.7 (C-4), 28.4 ($CH_3$), 27.7 ($CH_3$) and 20.8 (C-5). Anal. calcd for $C_9H_{12}N_2O_3$ (196.21): C, 55.09; H, 6.16; N, 14.28. Found: C, 54.91; H, 6.12; N, 14.05.

From **2**: The 4-*O*-mesylated-D-ribono-1,5-lactam **2** (2.87 g, 10.8 mmol) was added to a solution of $Bu_4NCN$ in DMF (1.31 M, 11.5 ml, 15.1 mmol) and the mixture was kept at 100°C for 8 h. The solution was poured on a column of mixed ion-exchange resin (Amberlite IR-120, $H^+$, 40 ml and Amberlite IRA-400, $HCO_3^-$, 70 ml) and eluted with $H_2O$ (400 ml). The eluate was concentrated, redissolved in boiling EtOAc (15 ml), placed on a column of silica (4×15 cm) and eluted with EtOAc to give the lactam **5** (1.43 g, 68%); mp 159–162°C.

### 3.5. 6-Amino-1,4,5,6-tetradeoxy-1,4-imino-L-lyxo-hexitol, ditosylate **6**

The 5-*C*-cyano-L-lyxono-1,4-lactam **5** (1.43 g, 7.29 mmol) was dissolved in dry tetrahydrofuran (40 ml) and slowly added to lithium aluminium hydride (2.75 g, 72.3 mmol) suspended in dry tetrahydrofuran (10 ml). The mixture was kept for 4 h at 60°C and then for 16 h at room temperature. $H_2O$ (5.68 ml, 310 mmol) was slowly added over 1 h followed by tetrahydrofuran (20 ml). The precipitate was filtered off, washed with tetrahydrofuran (50 ml) and the combined filtrates were concentrated to a residue, which was purified on a column of silica (3×15 cm) by elution with 2.5% $NH_3$ in MeOH. Concentration of the appropriate fractions gave the aminohexitol (0.801 g) as a colourless syrup. The syrup was dissolved in $H_2O$ (8 ml), *p*-toluenesulfonic acid monohydrate (1.73 g) was added and the mixture was kept at 50°C for 20 h. Concentration gave a crystalline residue. Recrystallisation from MeOH/$Et_2O$ gave **6** as colourless crystals (1.53 g, 43%); mp. 179–181°C; $[\alpha]_D^{20}$ +6.7 (*c* 1.0, $H_2O$). Further recrystallisation from MeOH/EtOH furnished an analytical sample; mp. 182–183°C; $[\alpha]_D^{20}$ +5.8 (*c* 1.1, $H_2O$); $^1$H NMR ($D_2O$, AcOH $\delta$=2.07): $\delta$ 7.68 (d, 2H, aromatic, *J*=8.1 Hz), 7.34 (d, 2H, aromatic, *J*=8.1 Hz), 4.48 (dt, H-2, $J_{1,2}$=7.8 Hz, $J_{1',2}$=7.6 Hz, $J_{2,3}$=4.0 Hz), 4.26 (t, H-3, $J_{3,4}$=3.8 Hz), 3.66 (ddd, H-4, $J_{4,5}$=8.1 Hz, $J_{4,5'}$=6.8 Hz), 3.53 (dd, H-1, $J_{1,1'}$=12.2 Hz), 3.19 (dd, H-1′), 3.12 (m, H-6, H-6′), 2.36 (s, Ph-$CH_3$), 2.29 (m, H-5) and 2.15 (m, H-5′). $^{13}$C NMR ($D_2O$, AcOH $\delta$=23.37): $\delta$ 145.4, 142.5, 132.4, 128.3 (aromatic carbon), 73.0 (C-2), 72.7 (C-3), 62.0 (C-4), 50.2 (C-1), 39.2 (C-6), 27.3 (C-5) and 23.4 (Ph-$CH_3$). Anal. calcd for $C_{20}H_{30}N_2O_8S_2$ (490.60): C, 49.07; H, 6.16; N, 5.73. Found: C, 48.96; H, 6.16; N, 5.71.

### 3.6. 5-Amino-4-azido-4,5-dideoxy-2,3-O-isopropylidene-L-lyxono-1,5-lactam **7**

5-Amino-5-deoxy-2,3-*O*-isopropylidene-4-*O*-trifluoromethanesulfonyl-D-ribono-1,5-lactam **4** (1.18 g, 3.7 mmol) was dissolved in DMF (5.0 ml) and sodium azide (2.4 g, 37.0 mmol) was added. The mixture was stirred for 3 h at room temperature under $N_2$, followed by addition of EtOAc (20 ml). Filtration and concentration gave a residue which was dissolved in EtOAc and purified by chromatography on a column of silica (3×15 cm) by elution with EtOAc:hexane 1:1→EtOAc:hexane 3:1. Pure fractions were concentrated to give **7** (0.37 g, 47%); $^1$H NMR ($CDCl_3$): $\delta$ 7.72 (bs, N*H*) 4.50 (d, H-2, $J_{2,3}$=7.0 Hz), 4.35 (dt, H-3, $J_{3,4}$=5.5 Hz, $J_{3,5'}$=0.5 Hz), 3.81 (ddd, H-4, $J_{4,5}$=3.4 Hz, $J_{4,5'}$=6.6 Hz), 3.53 (dt, H-5, $J_{5,5'}$=13.3 Hz, $J_{5,NH}$=3.2 Hz), 3.19 (dddd, H-5′, $J_{5',NH}$=0.5 Hz), 1.49 (s, $CH_3$) and 1.38 (s, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ 168.9 (C-1), 110.8 (acetal), 75.7, 72.9 (C-2, C-3), 58.3 (C-4), 40.4 (C-5), 26.6 ($CH_3$) and 24.6 ($CH_3$). ($C_8H_{12}N_4O_3$) *m/z* 197 (M−$CH_3$), 213 (M+$H^+$).

### 3.7. 4-Amino-1,4,5-trideoxy-1,5-imino-L-lyxitol, ditosylate **8**

The lactam **7** (0.32 g, 1.51 mmol) was dissolved in THF (10 ml) under $N_2$. $LiAlH_4$ was added slowly and stirring was continued for 22 h, then quenched by addition of $H_2O$ (0.5 ml), filtered and concentrated. Purification of the residue by column chromatography using MeOH as eluent gave a residue (75 mg) which was dissolved in $H_2O$, followed by addition of *p*-TsOH (170 mg) and kept at 50°C for 10 h. Concentration gave a crystalline residue which was recrystallised from MeOH twice to give **8** (248 mg, 5%) as colourless crystals; $[\alpha]_D^{20}$ +25.4 (*c* 1.0, $H_2O$) [enantiomer: $[\alpha]_D^{20}$ −24.4 (*c* 1.0, $H_2O$)[6]]; $^1$H NMR ($D_2O$): $\delta$ 7.62 (d, 2H, aromatic, *J*=8.0 Hz), 7.32 (d, 2H, aromatic, *J*=8.0 Hz), 4.24 (ddd, H-2, $J_{2,3}$=3.0 Hz, $J_{1,2}$=3.0 Hz, $J_{1',2}$=1.4 Hz), 3.87 (dd, H-3, $J_{3,4}$=10.2 Hz), 3.73 (ddd, H-4, $J_{4,5}$=4.7 Hz, $J_{4,5'}$=12.2 Hz), 3.69 (ddd, H-5, $J_{5,5'}$=12.2 Hz, $J_{1,5}$=2.0 Hz), 3.46 (ddd, H-1, $J_{1,1'}$=13.7 Hz), 3.22 (dd, H-1′) 3.13 (t, H-5′) and 2.34 (s, $CH_3$); $^{13}$C NMR ($D_2O$, acetone $\delta$=29.8): $\delta$ 141.8, 139.2, 129.0, 124.9 (aromatic), 68.3 (C-3), 64.8 (C-2), 47.8 (C-1), 46.0 (C-4), 42.9 (C-5) and 20.0 ($CH_3$).

### 3.8. 2,3-O-Isopropylidene-D-lyxono-1,4-lactone **11**

Potassium-D-lyxonate **9** (20.00 g, 97.9 mmol) was dissolved in MeOH (140 ml) and conc. aq. HCl (15 ml) and concentrated. Successive concentration with MeOH, toluene and MeOH gave a residue to which acetone (300 ml), 2,2-dimethoxypropane (50 ml, 408 mmol) and methanesulfonic acid (0.5 ml) were added, and the mixture was stirred for 20 h at room temperature. Neutralisation with $NaHCO_3$, filtration and concentration gave a syrupy residue (22.8 g), which was dissolved in $H_2O$ (150 ml) and extracted with $Et_2O$ (1×100 ml and 4×50 ml), dried ($Na_2SO_4$) and concentrated to give **10** (13.97 g) as a semi-crystalline residue. A mixture of acetic acid:$H_2O$ (9:1, 69.8 ml) was then added and the solution was stirred for 16.5 h at 28–29°C. Concentration gave a residue to which toluene was added with stirring to give a crystalline precipitate. The crystals were collected by filtration and dried in vacuo over KOH to give the lactone **11** (8.33 g, 45%); mp. 81–85°C. Further purification by dissolving the compound in acetone, filtration through activated carbon and recrystallisation from EtOAc furnished an analytical sample of **11**; mp 99–100°C; $[\alpha]_D^{20}$ +90.3 (*c* 1.0, acetone); $^1$H NMR ($D_2O$): $\delta$ 5.10 (d, H-2, $J_{2,3}$=5.6 Hz), 5.03 (dd, H-3, $J_{3,4}$=3.7 Hz), 4.76 (ddd, H-4, $J_{4,5}$=4.2 Hz, $J_{4,5'}$=8.0 Hz), 3.91 (dd, H-5, $J_{5,5'}$=12.5 Hz), 3.87 (dd, H-5′), 1.40 (s, $CH_3$) and 1.36 (s, $CH_3$); $^{13}$C NMR ($D_2O$): $\delta$ 177.9 (C-1), 115.5 (acetal), 81.8 (C-4), 77.2 (C-2), 77.0 (C-3), 60.5 (C-5), 26.6 and 25.6 (2×$CH_3$). Anal. calcd for $C_8H_{12}O_5$ (188.18): C, 51.06; H, 6.43. Found: C, 50.75; H, 6.43.

### 3.9. 2,3-O-Isopropylidene-5-O-methanesulfonyl-D-lyxono-1,4-lactone **12**

To the protected lyxono-1,4-lactone **11** (8.33 g, 44.3 mmol) in pyridine (25 ml) methanesulfonyl chloride (4.47 ml, 57.6 mmol) was added at 0°C in the course of 40 min. After stirring for 20 min at 0°C and 30 min at room temperature, ice/water (100 g) was added to give a crystalline precipitate. The product was collected by filtration, carefully washed with $H_2O$ (0°C) and dried in vacuo over KOH to give colourless crystals of **12** (9.34 g, 79%); mp 125–127°C. Recrystallisation from EtOAc furnished an analytical sample; mp 127.5–128.5°C; $[\alpha]_D^{20}$ −76.6 (*c* 1.0, MeOH); $^1$H NMR (acetone-$d_6$): $\delta$ 5.11 (d, H-2, $J_{2,3}$=6.3 Hz), 5.05 (dd, H-3, $J_{3,4}$=3.8 Hz), 4.95 (ddd, H-4, $J_{4,5}$=3.5 Hz, $J_{4,5'}$=8.2 Hz), 4.65 (dd, H-5, $J_{5,5'}$=11.5 Hz), 4.45 (H-5′), 3.19 (Ms), 1.42 (s, $CH_3$) and 1.36 (s, $CH_3$); $^{13}$C NMR (acetone-$d_6$): $\delta$ 173.9 (C-1), 114.6 (acetal C), 77.4 (C-4), 77.0 (C-2), 77.0 (C-3), 68.9 (C-5), 37.4 (Ms), 26.9 and 25.9 (2×$CH_3$). Anal. calcd for $C_9H_{14}O_7S$ (266.27): C, 40.60; H, 5.30. Found: C, 40.63; H, 5.28.

### 3.10. 5-Amino-5-deoxy-2,3-O-isopropylidene-D-lyxono-1,5-lactam **13**

The mesylated lyxono-1,4-lactone **12** (9.34 g, 35.1 mmol) was dissolved in aq. $NH_3$ (25%, 50 ml) and left for 5.5 h at room temperature in a sealed flask. Concentration and successive co-concentrations with MeOH, MeOH/toluene and EtOAc gave a residue which was extracted with boiling EtOAc (150 ml). The extract was cooled to 30°C, filtered and concentrated to give **13** (5.58 g, 85%) as colourless crystals; mp 95–122°C. According to a $^{13}$C NMR spectrum the lactam was sufficiently pure for further reactions. Purification by flash chromatography (EtOH:EtOAc 1:4), furnished an analytical sample, mp 125–126°C; $[\alpha]_D^{20}$ −6.7 (*c* 1.0, MeOH); $^1$H NMR ($D_2O$): $\delta$ 4.61 (d, H-2, $J_{2,3}$=6.8 Hz), 4.46 (ddd, H-3, $J_{3,4}$=5.3 Hz, $J_{3,5'}$=0.7 Hz), 4.02 (ddd, H-4, $J_{4,5}$=3.2 Hz, $J_{4,5'}$=6.0 Hz), 3.47 (dd, H-5, $J_{5,5'}$=13.5 Hz), 3.22 (dd, H-5′), 1.41 (s, $CH_3$) and 1.38 (s, $CH_3$); $^{13}$C NMR ($D_2O$, acetone $\delta$=29.8): $\delta$ 170.9 (C-1), 110.8 (acetal), 77.3 (C-3), 72.0 (C-2), 65.6 (C-4), 42.0 (C-5), 25.4 and 23.7 (2×$CH_3$). Anal. calcd for $C_8H_{13}NO_4$ (187.20): C, 51.33; H, 7.00; N, 7.48. Found: C, 51.16; H, 6.97; N, 7.48.

### 3.11. 5-Amino-5-deoxy-2,3-O-isopropylidene-4-O-methanesulfonyl-D-lyxono-1,5-lactam **14**

The protected D-lyxono-1,5-lactam **13** (4.55 g) was mesylated in pyridine (13.7 ml) with methanesulfonyl chloride (2.65 ml, 34.1 mmol) at 0°C as described above for the preparation of **2**. Ice/water (20 ml) was added and the solution was concentrated and co-concentrated with toluene to a residue. This was dissolved in $H_2O$ (20 ml) and extracted with EtOAc (4×20 ml). The organic phase was dried ($Na_2SO_4$), filtrated and concentrated to a syrup (5.49 g) which could be crystallised from EtOAc to give the mesylated lactam **14** as colourless crystals (3.77 g, 59%); mp 130.5–132.5°C. Recrystallisation from EtOAc furnished an analytical sample; mp 133–134°C; $[\alpha]_D^{20}$ −47.7 (*c* 1.0, acetone); $^1$H NMR (acetone-$d_6$ $\delta$=2.05): $\delta$ 7.07 (d, N*H*), 4.80 (m, H-4, $J_{2,4}$=1.2 Hz, $J_{3,4}$=4.0 Hz, $J_{4,5}$=2.7 Hz, $J_{4,5'}$=4.5 Hz), 4.63 (ddd, H-3, $J_{2,3}$=7.0 Hz, $J_{3,5'}$=1.4 Hz), 4.56 (dd, H-2), 3.67 (ddd, H-5, $J_{5,5'}$=13.7 Hz, $J_{5,NH}$=0.8 Hz), 3.50 (ddt, H-5′), 3.25 (s, Ms), 1.46 (s, $CH_3$) and 1.37 (s, $CH_3$); $^{13}$C NMR (acetone-$d_6$): $\delta$ 167.8 (C-1), 111.0 (acetal), 76.5, 76.2 and 74.3 (C-2, C-3 and C-4), 41.6 (C-5), 38.4 (Ms), 26.6 ($CH_3$) and 24.5 ($CH_3$). Anal. calcd for $C_9H_{15}NO_6S$ (265.29): C, 40.97; H, 5.72 N, 5.28. Found: C, 40.75; H, 5.70; N, 5.28.

### 3.12. 4-Amino-5-C-cyano-4,5-dideoxy-2,3-O-isopropylidene-L-ribono-1,4-lactam **15**

The mesylated D-lyxono-1,5-lactam **14** (6.78 g, 25.5 mmol) was added to a solution of $Bu_4NCN$ in DMF (1.31 M, 27.3 ml, 35.8 mmol) and the mixture was kept at 100°C for 5 h. The solution was poured on a column of mixed ion-exchange resin (Amberlite IR-120, $H^+$, 94.0 ml and Amberlite IRA-400, $HCO_3^-$, 162.5 ml) and eluted with $H_2O$ (400 ml). The eluate was concentrated and acetone (20 ml) was added to the residue which crystallised by cooling in dry ice/2-propanol. Filtration gave the title compound **15** (2.48 g, 50%); mp 199–201°C; $[\alpha]_D^{20}$ +47.6 (*c* 0.5 acetone); $^1$H NMR (acetone-$d_6$): $\delta$ 4.69 (s, H-2), 4.69 (d, H-3, $J_{3,4}$=1.6 Hz), 3.95 (ddd, H-4, $J_{4,5}$=5.0 Hz, $J_{4,5'}$=6.1 Hz), 3.94 (dd, H-5, $J_{5,5'}$=17.0 Hz), 3.89 (dd, H-5′), 1.39 (s, $CH_3$) and 1.35 (s, $CH_3$); $^{13}$C NMR (acetone-$d_6$): $\delta$ 172.5 (C-1), 117.1 (CN), 111.9 (acetal), 78.8 (C-2), 76.2 (C-3), 54.3 (C-4), 26.3 ($CH_3$), 24.9 ($CH_3$) and 22.8 (C-5). Anal. calcd for $C_9H_{12}N_2O_3$ (196.21): C, 55.09; H, 6.16; N, 14.28. Found C, 54.90; H, 6.12; N, 14.02.

The mother liquor was concentrated and crystallised from EtOAc (15 ml) to give a product having an mp 149–152°C. A $^{13}$C NMR spectrum showed that it was a mixture of the lactam **15** and the corresponding unprotected compound, 4-amino-5-*C*-cyano-4,5-dideoxy-L-ribono-1,5-lactam. Separation was performed by refluxing in acetone (10 ml) followed by filtration to give the 4-amino-5-*C*-cyano-4,5-dideoxy-L-ribono-1,5-lactam as a crystalline compound (0.34 g); mp 155–162°C. Concentration of the filtrate gave a residue which was recrystallised from $H_2O$ to give **15** as colourless crystals (0.19 g, 4%); mp 201–202°C; $[\alpha]_D^{20}$ +49.2 (*c* 0.6 acetone). The EtOAc from the precipitation of the lactam mixture was concentrated and purified on a column of silica (4×15 cm) by elution with EtOAc. This gave an additional amount of **15** (0.41 g, 8%; mp 202–203°C; $[\alpha]_D^{20}$ +49.9 (*c* 0.6, acetone)), bringing the total yield of **15** to 62%.

### 3.13. 6-Amino-1,4,5,6-tetradeoxy-1,4-imino-L-ribo-hexitol, ditosylate **16**

A solution of **15** (2.50 g, 12.7 mmol) in dry tetrahydrofuran (80 ml) was slowly added to lithium aluminium hydride (2.42 g, 55.9 mmol) suspended in dry tetrahydrofuran (10 ml). The mixture was stirred for 18 h at room temperature. Then $H_2O$ (4.27 ml, 237 mmol) was added with stirring in the course of 1 h, and stirring was continued for another 30 min. The precipitate was filtered off, washed with tetrahydrofuran (50 ml) and the combined filtrate was concentrated to a syrup. This was dissolved in $H_2O$ (20 ml) and *p*-toluenesulfonic acid monohydrate (4.00 g) was added and the mixture was kept at 50°C

for 4 h. Concentration gave a crystalline residue, which by recrystallisation from EtOH/$Et_2O$ gave **16** as colourless crystals (2.61 g, 42%); mp 151–155°C; $[\alpha]_D^{20}$ −21.6 (*c* 1.0, $H_2O$). Further recrystallisation from EtOH/$Et_2O$ furnished an analytical sample; mp. 163–164°C; $[\alpha]_D^{20}$ −22.4 (*c* 1.0, $H_2O$); $^1$H NMR ($D_2O$, AcOH $\delta$=2.07): $\delta$ 7.68 (d, 2H, aromatic, *J*=8.1 Hz), 7.33 (d, 2H, aromatic, *J*=8.1 Hz), 4.35 (dt, H-2, $J_{1,2}$=4.4 Hz, $J_{1',2}$=1.5 Hz, $J_{2,3}$=4.2 Hz), 4.12 (dd, H-3, $J_{3,4}$=9.1 Hz), 3.58 (dd, H-4), 3.55 (dd, H-1, $J_{1,1'}$=13.2 Hz), 3.36 (dd, H-1′), 3.21 (m, H-6, H-6′), 2.36 (s, Ph-$CH_3$), 2.22 (m, H-5, H-5′); $^{13}$C NMR ($D_2O$, AcOH $\delta$=23.37): $\delta$ 145.4, 142.6, 132.4, 128.4 (aromatic carbon), 78.0 (C-3), 72.0 (C-2), 62.5 (C-4), 52.7 (C-1), 39.4 (C-6), 30.7 (C-5) and 23.5 (Ph-$CH_3$). Anal calcd for $C_{20}H_{30}N_2O_8S_2$ (490.60): C, 48.93; H, 6.15; N, 5.70. Found: C, 48.96; H, 6.16; N, 5.71.

### *3.14.* N-*Ethyl-5-amino-5-deoxy-2,3*-O-*isopropylidene*-D-*ribono-1,5-lactam* ***18***

2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-D-ribono-1,4-lactone **17**[8] (4.0 g, 15.0 mmol) was dissolved in 70% aq. ethylamine (20 ml) and left for 144 h at room temperature in a sealed flask. Concentration and subsequent co-concentration with $H_2O$ and EtOAc gave a residue which was extracted with EtOAc (100 ml), filtered and concentrated to give **18** (3.46 g, 107%) as a slightly coloured syrup. The syrup was pure enough for further synthesis according to a $^{13}$C NMR spectrum. A small amount of **18** was chromatographed on a column of silica (3×15 cm) and eluted with EtOAc→EtOAc:EtOH 9:1. All fractions were analysed by HPLC (column: Hewlett–Packard Hypersil 5 μm 100×4.6 mm, eluent: 1% *i*-PrOH in EtOAc), and fractions containing the lactam **18** were pooled and concentrated to give an analytical sample; $[\alpha]_D^{20}$ +11.2 (*c* 1.5, acetone); $^1$H NMR (acetone-$d_6$): $\delta$ 4.54 (ddd, H-3, $J_{2,3}$=6.7 Hz, $J_{3,4}$=3.0 Hz, $J_{3,5'}$=1.1 Hz), 4.41 (d, H-2), 4.03 (m, H-4, $J_{4,5}$=9.3 Hz, $J_{4,5'}$=4.3 Hz), 3.54 (dd, H-5, $J_{5,5'}$=11.8 Hz), 3.48 (dq, $CH_3$-*CH*$_2$, $J_{CH2,CH3}$=7.2 Hz, $J_{CH2,CH2'}$=13.3 Hz), 3.24 (dq, $CH_2'$), 3.20 (ddd, H-5′), 2.87 (bs, O*H*), 1.37 (s, $CH_3$), 1.34 (s, $CH_3$) and 1.07 (t, *CH*$_3$-$CH_2$); $^{13}$C NMR (acetone-$d_6$): $\delta$ 166.6 (C-1), 110.5 (acetal), 76.8 (C-3), 75.6 (C-2), 66.0 (C-4), 47.7 (C-5), 42.4 (*CH*$_2$-$CH_3$), 26.8 ($CH_3$), 25.2 ($CH_3$) and 12.3 (*CH*$_3$-$CH_2$). $C_{10}H_{17}NO_4$(215.25) *m/z* 200 (M−$CH_3$), 215 (M).

### *3.15.* N-*Ethyl-5-amino-5-deoxy-2,3*-O-*isopropylidene-4*-O-*trifluoromethanesulfonyl*-D-*ribono-1,5-lactam* ***19***

Compound **18** (0.745g, 3.45 mmol) was dissolved in pyridine (5.0 ml), cooled to 0°C and treated with trifluoromethane-sulfonic anhydride (0.63 ml, 4.50 mmol) as described above for the preparation of **4** to give **19** as a pale yellow syrup (0.98 g, 81%). The syrup was pure according to a $^{13}$C NMR spectrum. $^{13}$C NMR ($CDCl_3$): $\delta$ 165.0 (C-1), 118.1 (quartet, Tf), 111.7 (acetal) 78.4, 73.2, 72.5 (C-2, C-3, C-4), 45.2 (C-5), 42.1 (*CH*$_2$-$CH_3$), 25.6 ($CH_3$), 24.3 ($CH_3$) and 11.6 ($CH_2$-*CH*$_3$).

### *3.16. Treatment of* N-*ethyl-5-amino-5-deoxy-2,3*-O-*isopropylidene-4*-O-*trifluoromethanesulfonyl*-D-*ribono-1,5-lactam* ***19*** *with tetrabutylammonium cyanide*

To the lactam **19** (0.868 g, 2.5 mmol) was added a solution of $Bu_4NCN$ in DMF (1.0 M, 3.75 ml, 3.75 mmol) and the mixture was allowed to stand for 28 h at room temperature. The solution was poured through a column of mixed ion-exchange resin (Amberlite IR-120, $H^+$, 10.0 ml and Amberlite IRA-400, $HCO_3^-$, 16.0 ml) which was washed with $H_2O$ (40 ml). The eluate was concentrated and the isomers were separated on a short column of silica (1.5–40 μm) using EtOAc as eluent. Fractions containing the compound with the highest $R_f$-value were collected to give a syrup (15 mg), probably of *N*-ethyl-5-amino-4,5-dideoxy-4-ene-2,3-*O*-isopropylidene-D-*erythro*-pentono-1,5-lactam **20**; $^1$H NMR ($CDCl_3$): $\delta$

6.17 (d, H-5, $J_{4,5}$=8.1 Hz), 5.21 (dd, H-4, $J_{3,4}$=4.6 Hz), 4.71 (dd, H-3, $J_{2,3}$=6.9 Hz), 4.51 (d, H-2), 3.56 (m, C$H_2$-CH$_3$), 1.18 (t, CH$_2$-C$H_3$, $J$=7.2 Hz).

Fractions containing the slower moving compound were concentrated to give a syrup (60 mg), probably of *N*-ethyl-5-amino-4-deoxy-3-ene-2,3-*O*-isopropylidene-D-*glycero*-pentono-1,5-lactam **21**; $^1$H NMR (CDCl$_3$): $\delta$ 4.86, 4.70 (m, H-2, m, H-4) 3.94 (ddd, H-5, $J_{5,5'}$=16.2 Hz), 3.64 (ddd, H-5′), 3.49 (m, C$H_2$-CH$_3$), 1.09 (t, CH$_2$-C$H_3$, $J$=7.2 Hz). $^{13}$C NMR (CDCl$_3$): $\delta$ 165.0 (C-1), 148.5 (C-3), 114.3 (acetal), 85.3 (C-4), 72.0 (C-2), 45.2 (C-5), 41.0 (*C*H$_2$-CH$_3$), 26.1 (CH$_3$), 24.5 (CH$_3$) and 12.3 (CH$_2$-*C*H$_3$).

### *3.17. Crystal structure determination for compound* ***5***[12]

Crystals were obtained by crystallisation from acetone. A colourless crystal of **5** with the dimensions 0.38×0.13×0.08 mm$^3$ was measured on a CAD-4F diffractometer using Cu$K\alpha$ radiation ($\lambda$=1.5418 Å). Crystal data: $C_9H_{12}N_2O_3$, M=196.21, orthorhombic space group $P2_12_12_1$, $a$=6.118(2) Å, $b$=9.714(4) Å, $c$=16.172(5) Å, $V$=961.1(6) Å$^3$, $Z$=4, $D$c=1.36 g/cm$^3$, F(000)=416, $\mu$(Cu$K\alpha$)=0.86 mm$^{-1}$. At 120 K in the range of 5.31°<$\theta$<73.93° 2248 reflections were measured of which 1954 were unique and 1693 ($R$)$_{(int)}$= 0.039, observed with $I$>2$\sigma$($I$). The structure was solved by direct methods and refined by least squares procedure within the SHELXL program system. The final residuals were $wR_{2(all)}$=0.1003 and $R_{1(obs)}$= 0.0406. The maximum and minimum peaks in the final electron density difference map were −0.20 and −0.14 $e$/Å$^3$, respectively. The absolute structure could not be determined reliably.

### *3.18. Crystal structure determination for compound* ***15***[12]

Crystals were obtained by crystallisation from acetone. A colourless crystal of **15** with the dimensions 0.28×0.07×0.06 mm$^3$ was measured on a CAD-4F diffractometer using Mo$K\alpha$ radiation ($\lambda$=0.71073 Å). Crystal data: $C_9H_{12}N_2O_3$, M=196.20, orthorhombic space group $P2_12_12_1$, $a$=11.134(7) Å, $b$=11.544(5) Å, $c$=15.595(8) Å, $V$=2004.4(18) Å$^3$, $Z$=8, $D$c=1.30 g/cm$^3$, F(000)=832, $\mu$(Mo$K\alpha$)=0.099 mm$^{-1}$. At 120 K in the range of 2.19°<$\theta$<24.93° 5583 reflections were measured of which 3479 were unique and 1625 ($R$)$_{(int)}$= 0.126, observed with $I$>2$\sigma$($I$). The structure was solved by direct methods and refined by least squares procedure within the SHELXL program system. The final residuals were $wR_{2(all)}$=0.1615 and $R_{1(obs)}$=0.0855. The maximum and minimum peaks in the final electron density difference map were −0.31 and 0.28 $e$/Å$^3$, respectively. The absolute structure could not be determined reliably.

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12. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-000000 (5), CCDC-000000 (15). Copies of the data can be obtained free of charge on application to CCDD, 12 Union Road, Cambridge CB2 1EZ, UK. (Fax: 44-1223/336-033; e-mail: deposit@chemcrys.cam.ac.uk).