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Transformation of the 7-isopropylidene group in 5-dethia-5-oxacephams

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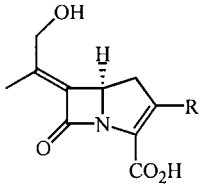
Abstract—[2+2]Cycloaddition of CSI to 5-*O*-protected-3-*O*-allenyl-1,2-*O*-isopropylidene-α-D-xylofuranoses **8** and **9** gave respective β-lactams **10**–**13** having an *exo*-propylidene group, in moderate stereoselectivity. Compounds **10**, **11** and tetracyclic cephams **14**, **15** obtained from **10** and **11** or **12** and **13**, were used as substrates for a variety of transformations leading to the introduction of isopropyl, hydroxyisopropyl, oxygen and nitrogen functions, α to the β-lactam carbonyl group. These reactions proceeded in high stereoselectivity with control of the absolute configuration of the cephams formed.

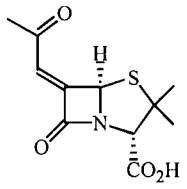
1. Introduction

Studies on β-lactam antibiotics have shown that the carbon atom next to the carbonyl group, that is C-6 of penams and C-7 of cephams, can be substituted by a variety of groups without loss of high biological activity.[1] The [2+2]cycloaddition of chlorosulfonyl isocyanate to nucleophilic olefins is one of the most common methods of the β-lactam ring formation. Regiospecific formation of the azetidin-2-one ring by this method requires an activation of the double bond of the olefin by an electron-donating substituent at one terminal only.[2] This significantly reduces the possibility of a direct functionalization of the azetidin-2-one ring by suitable preparation of the starting olefin.

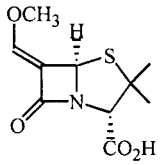


Asparenomycins **1**

R = SCH_2CH_2NHAc, $SOCH_2CH_2NHAc$, SCH=CHNHAc, SOCH=CHNHAc



Ro 15-1903 **2**



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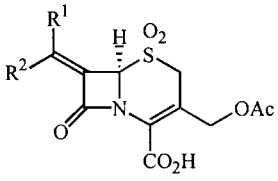

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R^1, R^2 = H, Halogen, Aryl, CO_2t-Bu, CHO, $COCH_3$, *t*-Bu

Chart 1.

Keywords: cephams; carbohydrates; stereocontrol.

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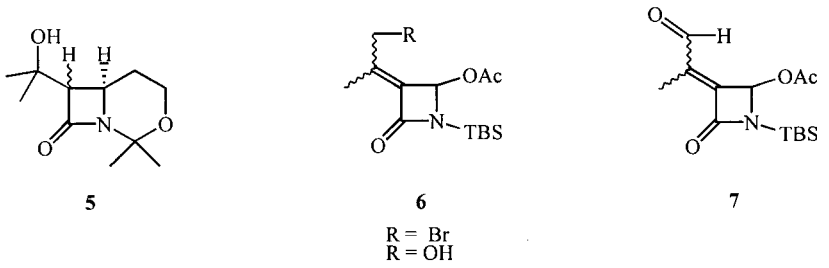
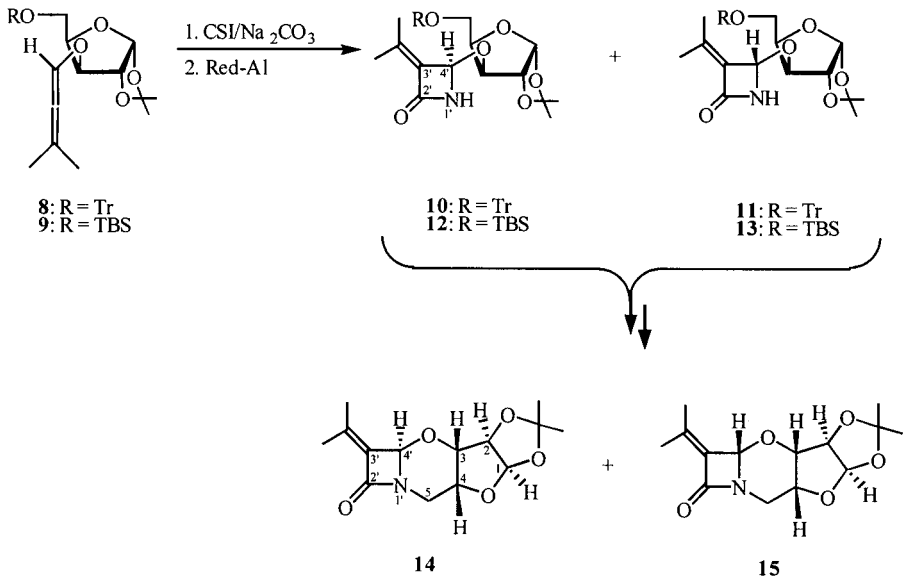


5 **6** **7**

R = Br
R = OH

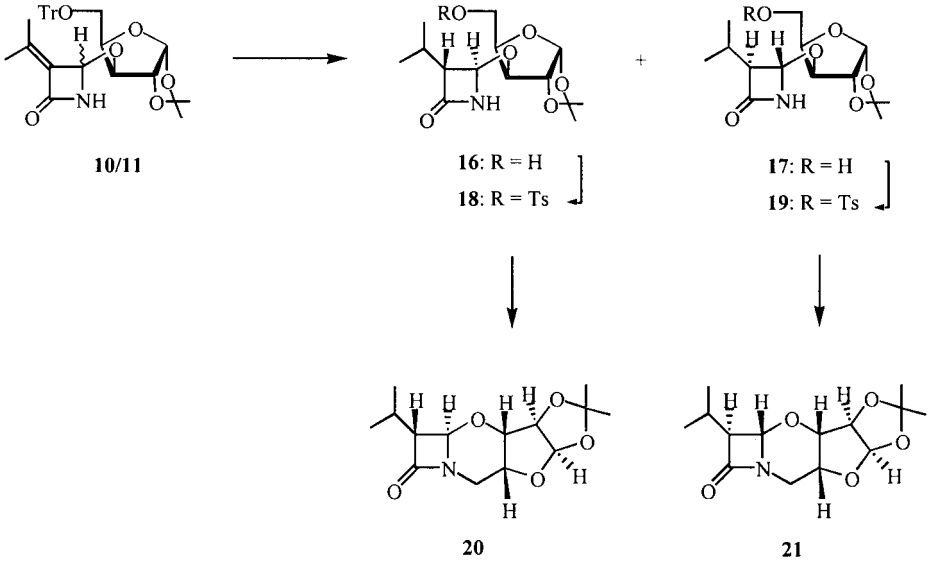
Chart 2.



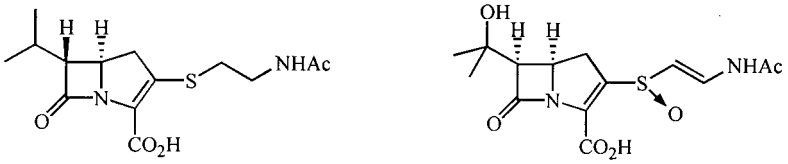
Scheme 1.

Buynak and coworkers[3–8] have introduced an attractive entry to 3-alkylidene azetidin-2-ones, based on [2+2]-cycloaddition of CSI to allenyl derivatives. The value of this strategy is that the *exo*-double bond not only exists in a number of antibiotics and β-lactamase inhibitors such as asparenomycins **1**,[9] alkylidenepenicillins **2**,[10] **3**,[11] and alkylidenecephalosporins **4**[12] (Chart 1), but also that it can be transformed into isopropyl,[3] hydroxyisopropyl **5**,[8] bromo-**6**,[3] hydroxy- **6**,[3] and oxo-isopropylidene **7**[3] residues (Chart 2).

It was of interest to explore application of Buynak's

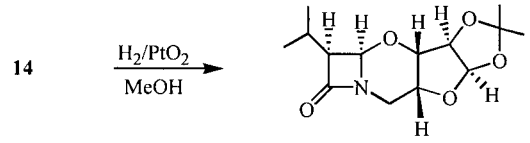


Scheme 2.



PS-6 **22** carpetimycin A **23**

Chart 3.



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Scheme 3.

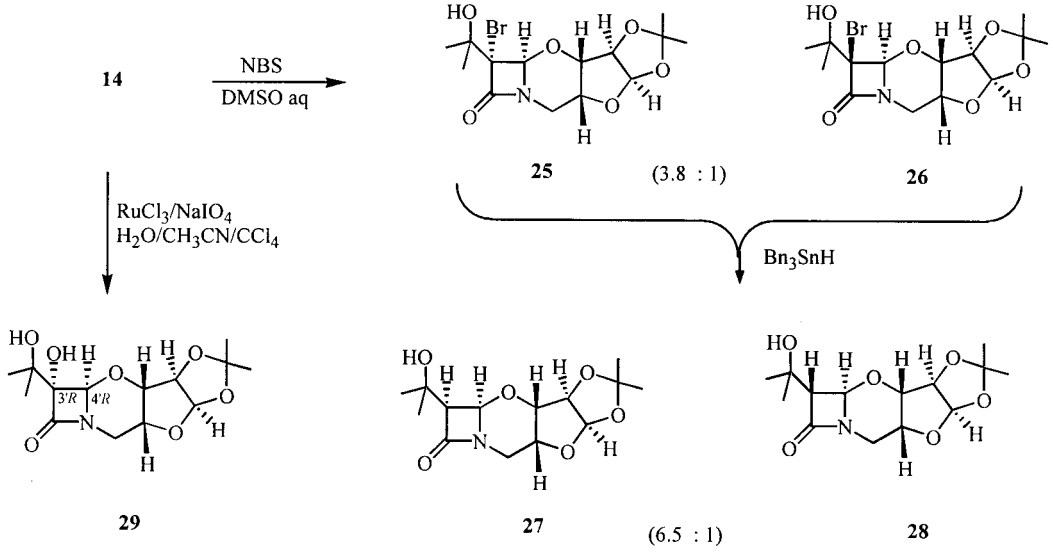
methodology[3–8] to 7-substituted-5-oxacephams and to demonstrate that the isopropylidene substituent can be used to introduce oxygen and nitrogen functionality at the C-7 carbon atom.

Recently, we have reported on stereoselective [2+2]-cycloadditions of CSI to the alkoxyallenes **8** and **9** derived from 1,2-*O*-isopropylidene-α-D-xylofuranose.[13] Cycloadducts **10**, **11** and **12**, **13**, thus obtained, were deprotected at C-5 of the sugar to give respective mixtures of the same diastereomers. Subsequent tosylation and the intramolecular alkylation of the β-lactam nitrogen atom afforded compounds **14** and **15** having the 5-oxacepham skeleton with the 7-*exo*-double bond suitable for further transformations (Scheme 1). (For the sake of simplicity, in numbering of tetracyclic cephams the reader is referred to combine sugar and azetidinone nomenclature.) It should be pointed out that, in comparison with Buynak's[3–8] compounds, introduction of an oxygen funcion to the C-4 of the azetidin-2-one ring makes our 5-oxacephams more sensitive to the β-elimination reaction.

The present paper reports on the transformation of the *exo*-double bond into alkyl, keto, hydroxy, and amino functions with control of the configuration at the C-7 stereogenic center of the cepham skeleton.

2. Results and discussion

The sodium in liquid ammonia reduction of the epimeric **10/11** mixture led to corresponding *trans* substituted azetidin-2-ones **16** and **17**. Compounds **16** and **17** were separated and, independently, subjected to intramolecular alkylation under the standard reaction sequence[14] to afford cephams **20** and **21**, respectively (Scheme 2). The configuration of both compounds was assigned by ^{1}H NMR. The coupling constant $J_{3',4'}$ below resolution (i.e. <1 Hz) testified to the *trans* substitution of the four-membered ring in both compounds. NOEs, measured for compound **21**, showed a spin–spin interaction between H-3 (δ 4.15 ppm) and H-4′ (δ 4.62 ppm) protons. Irradiation of the H-3 signal caused enhancement of the H-4′ signal by 6.0% and conversely, the signal due to H-3 was enhanced by 6.0% when H-4′ was irradiated. Compound **20** has the same isopropyl substituent α to the β-lactam carbonyl group and the configuration around the four-membered ring to that of PS-6 antibiotic **22**[15] (Chart 3). Further transformations were performed on cephams **14** and **15**, obtained and separated into pure epimers by the procedure described previously.[13]



25 (3.8 : 1) **26**

29 **27** (6.5 : 1) **28**

Scheme 4.

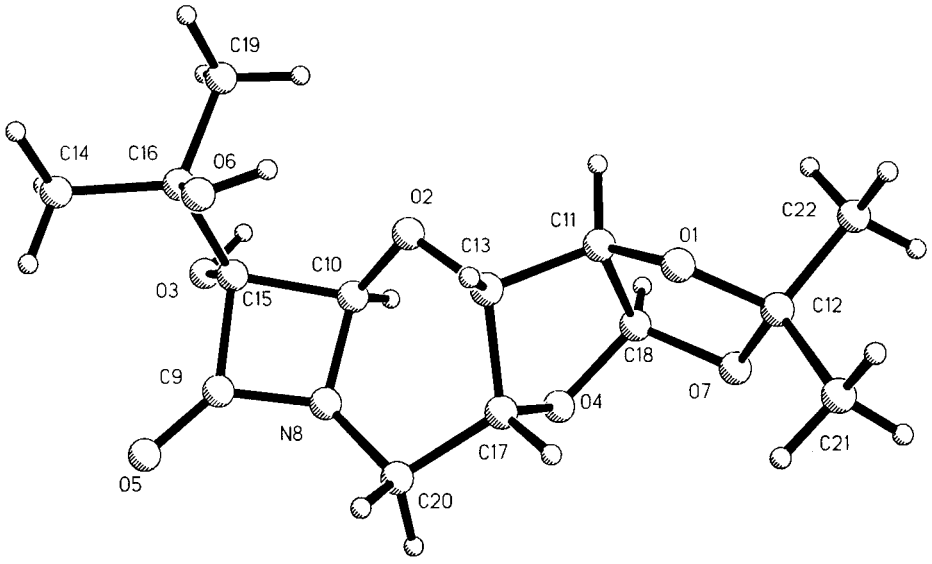


Figure 1. Molecular structure of the compound **29** with the crystallographic numbering scheme.

Hydrogenation of the double bond in **14** led to compound **24** having *cis* hydrogen atoms at C(3′) and C(4′), the alternative configuration to that afforded by the Na/NH_3 reduction of the double bond in **10** and **11** (Scheme 3).

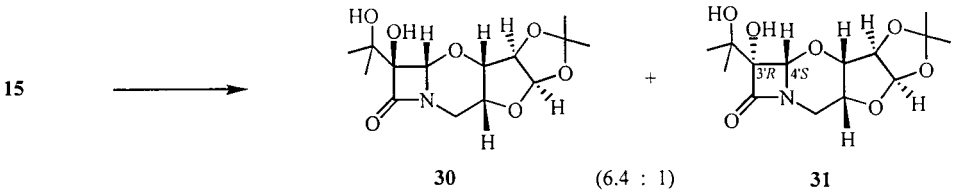
Treatment of **14** with NBS in wet DMSO,[16] according to the procedure of Buynak and Rao,[8] provided bromohydrins **25** and **26** in the ratio of about 3.8:1, respectively. The configuration of **25** and **26** was assigned by the assumption that Br^+ would approach the double bond for the least hindered side. Tributyltin hydride reduction of the mixture **25/26** yielded a mixture of α-hydroxyisopropyl β-lactams **27** and **28** in the ratio of *ca.* 6.5:1 (Scheme 4). A relatively high stereoselectivity of debromination followed from previous observations.[8,17] Tin hydride attacks the radical, obtained from both bromohydrins (**25/26**), *anti* to the C(4′) oxygen atom to produce the predominantly *cis* disubstituted compound **27**. The major product was easily isolated from the post-reaction mixture by crystallization from ethyl acetate/hexane solution. This two-step reaction sequence led to the construction of the side chain of carpetimycin A **23**.[18]

Ozonolysis of the double bond in both compounds **14** and **15** (−65°C, CH_2Cl_2 or AcOEt) led to the formation of polar products which were not investigated further since they did not show any carbonyl absorptions in IR spectra. Decomposition of the azetidin-2-one ring during the ozonolysis of α-ethylidene-azetidin-2-ones has been reported previously.[19]

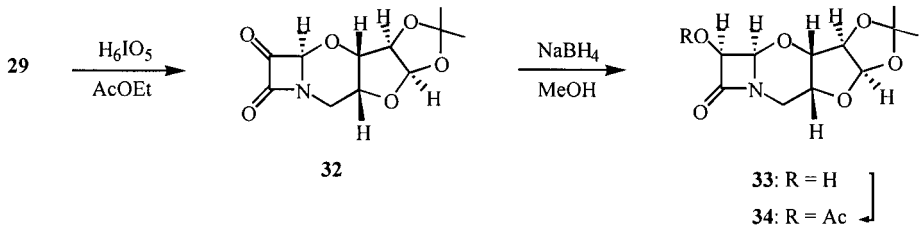
In order to cleave the double bond in **14** and **15** a two-step reaction sequence was applied. Oxidation of the cepham **14** with $RuCl_3/NaIO_4$ in $H_2O/CH_3CN/CCl_4$ mixture[20] in the presence of $CaCO_3$, for 5 min, afforded diol **29** in 85% yield (Scheme 4). The structure and configuration of **29** was demonstrated by X-ray crystallography (Fig. 1, cf. Experimental).

cis-Hydroxylation of the cepham **15**, under the same conditions,[20] gave a mixture of diols **30** and **31** in a ratio of *ca.* 6.4:1, respectively. Configuration of the major product **30** was tentatively assigned by an assumption that RuO_4 approaches preferentially the double bond *anti* to the oxygen atom at C-4′ of the azetidin-2′-one ring (Scheme 5).

Glycolic cleavage of the diol **29** using the standard conditions ($NaIO_4$ in H_2O/THF or Bu_4NIO_4 in boiling CH_2Cl_2) failed to give α-keto β-lactam due to the slow oxidation process. Application of $Pb(OAc)_4$ in CH_2Cl_2 was also unsuccessful, causing decomposition of the substrate. The cleavage, providing **32** was performed using H_6IO_5 in AcOEt.[21] Owing to its stability, compound **32** was used for further steps without purification. It should be pointed out that α-keto β-lactams are known to be very useful intermediates owing to the chemically very active[22] keto function. Reduction of **32** with $NaBH_4$ in methanol gave the alcohol **33** having *cis* oxygen atoms at the β-lactam ring (Scheme 6). We failed to transform the ketone **32** into the corresponding oxime due to decomposition of the substrate under the standard reaction conditions.



Scheme 5.



Scheme 6.

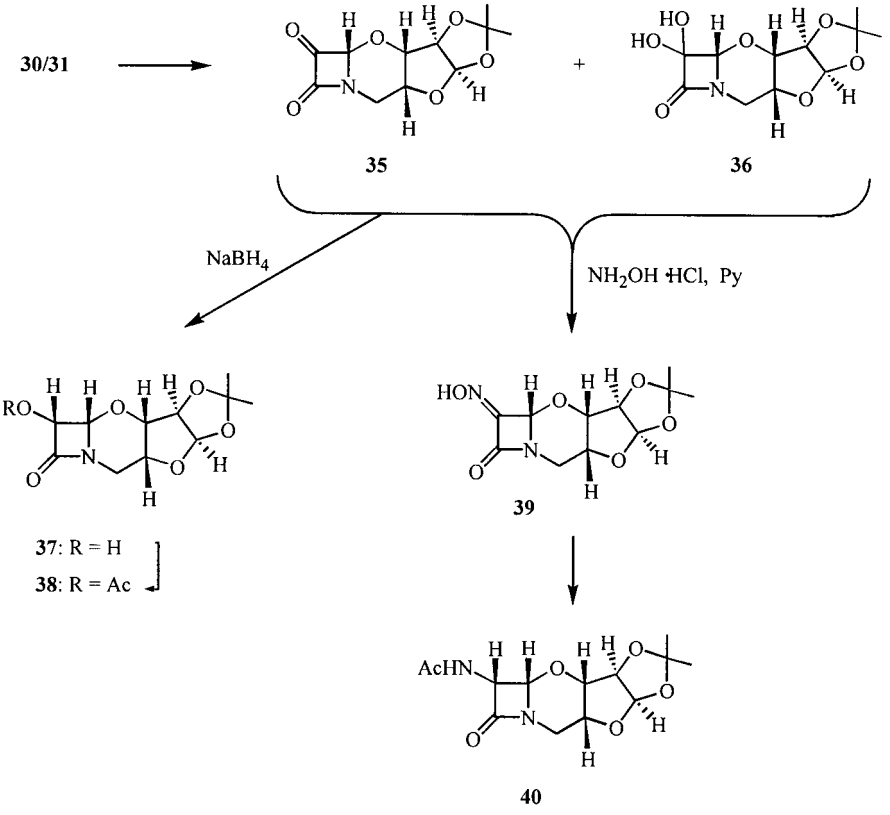
Glycolic cleavage of the mixture **30** and **31**, under the conditions used for **29**, afforded an unstable mixture of the α-keto β-lactam **35** and the hydrate **36**. The crude mixture of **35/36** was reduced with $NaBH_4$ to the alcohol **37** (Scheme 7). The mixture **35/36** treated with $NH_2OH{\cdot}HCl$ in pyridyne to yield a mixture of oximes **39**, which reduced with hydrogen over PtO_2 in the presence of Ac_2O/AcONa, to give the *N*-acetyl compound **40** in 65% yield (Scheme 7).

In summary, we have demonstrated that the [2+2]cycloadducts of CSI to 3-*O*-allenyl-α-D-xylofuranoses **10/11** are versatile intermediates for the preparation of a wide range of 7-substituted-5-oxacephams. Recently, we have shown that the tetracyclic oxacepham skeleton can be transformed into a bicyclic 5-oxacephem system.[24] Except the cycloaddition reaction that proceeds with a moderate stereoselectivity,[13] the other reactions offer high stereoselectivities and may provide substituents at C-7 existing in many active β-lactam antibiotics. Functionalization of the 4-alkoxyazetidin-2-one ring via the 3-isopropylidene residue offers certain advantages over the corresponding functionalization of the unsubstituted CH_2 group,[23] particularly that the latter usually proceeds via a carbanion stage which may cause a β-elimination of the 4-alkoxy fragment.

3. Experimental

3.1. General

Melting points were determined on a Kofler hot-stage apparatus with microscope. ^{1}H NMR spectra were obtained on Brucker Avance 500 and Varian Gemini AC-200 spectrometers for solution in acetone-d_6 or $CDCl_3$ with tetramethylsilane as an internal standard and are expressed as δ values. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 2000 spectrophotometer. Mass spectra were determined with an AMD 604 Inectra GmbH spectrometer. Optical rotations were measured using a JASCO P 3010 polarimeter at ambient temperature. Column chromatography was performed on Merck silica gel (230–400



Scheme 7.

mesh). All solvents were dried and purified by standard techniques.

3.1.1. (4′*R*) and (4′*S*) 1,2-*O*-Isopropylidene-3-*O*-[3′-(1-methylethylidene)-azetidin-2′-on-4′-yl]-5-*O*-trityl-α-D-xylofuranose (10 and 11). The mixture of stereoisomers **10/11** was obtained according to the known procedure (60%).[13]

3.1.2. (3′*R*,4′*R*) and (3′*S*,4′*S*) 3-*O*-(3′-Isopropyl-azetidin-2′-on-4′-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (16 and 17). To a solution of sodium (0.21 g, 9.23 mmol) in liquid ammonia (40 mL) the mixture of **10/11** (0.5 g, 0.92 mmol) in dry THF (2 mL) was added dropwise. The mixture was stirred at −60°C for 25 min. Subsequently, ammonium chloride (0.5 g) was added and ammonia was allowed to evaporate. The post-reaction mixture was treated with water (10 mL) and extracted with AcOEt (3×15 mL). The residue was separated by column chromatography on silica gel, using hexane/ethyl acetate 3.5:6.5 v/v as an eluent, to give the title compounds **16** (0.134 g, 48%) and **17** (0.067 g, 24%).

16: Oil; $[\alpha]_D^{22}=-5.3$ (*c* 0.25, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3606, 3398, 1774 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.55 (br s, 1H, NH), 5.95 (d, 1H, *J* 4.0 Hz, H-1), 4.96 (d, 1H, *J* 1.5 Hz, H-4′), 4.56 (d, 1H, *J*4.0 Hz, H-2), 4.31–4.35 (m, 1H, H-4), 4.06 (d, 1H, *J* 3.5 Hz, H-3), 3.74–3.78 (1m, 1H, H-5a), 3.89–3.93 (m, 1H, H-5b), 2.89 (dd, 1H, *J* 1.5, 8.5 Hz, H-3′), 1.90–2.10 (m, 1H, —C*H*Me_2), 1.33, 1.50 (2s, 6H, isoprop.), 1.09 (d, 3H, *J* 6.5 Hz, Me), 1.03 (d, 3H, *J* 6.5 Hz, Me); HRMS (EI) *m/z*: $(M—CH_3)^+$ found: 286.1275. $C_{13}H_{20}O_6N$ requires 286.1291.

17: Oil; $[\alpha]_D^{22}=-29.2$ (*c* 0.35, CH_2Cl_2); ν_{max} (film) 3605, 3399, 1773 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.70 (br s, 1H, NH), 5.95 (d, 1H, *J* 3.5 Hz, H-1), 4.84 (d, 1H, *J* 0.5 Hz, H-4′), 4.44 (d, 1H, *J*3.5 Hz, H-2), 4.19-4.23 (m, 1H, H-4), 3.9 (d, 1H, *J* 3.0 Hz, H-3), 3.83 (dd, 1H, *J* 4.5, 10.5 Hz, H-5b), 3.71 (dd, 1H, *J* 5.5, 10.5 Hz, H-5a), 2.81 (d, 1H, *J* 8.0 Hz, H-3′), 2.02 (br s, 1H, —OH), 1.89–1.96 (m, 1H, —C*H*Me_2), 1.24, 1.42 (2s, 6H, isoprop.), 0.99 (d, 3H, *J* 6.5 Hz, Me), 0.95 (d, 3H, *J* 6.5 Hz, Me); HRMS (LSIMS) *m/z*: $(M+Na)^+$ found 324.1407. $C_{14}H_{23}O_6NNa$ requires 324.1423.

3.1.3. (3′*R*,4′*R*) 3-*O*-(3′-Isopropyl-azetidin-2′-on-4′-yl)-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose (18). Compound **18** was obtained from **16** by the tosylation procedure (tosyl chloride, pyridine, 12 h; 85%). Colorless crystals; mp 131–133°C; [Found: C, 55.54; H, 6.67; N, 2.81. $C_{21}H_{29}O_8NS$ (455.54) requires C, 55.37; H, 6.42; N, 3.07%]; $[\alpha]_D^{22}=-17.9$ (*c* 1.08, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3397, 1776 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.31–7.85 (2m, 4H, tosyl), 6.33 (br s, 1H, NH), 5.87 (d, 1H, *J* 3.5 Hz, H-1), 4.97 (d, 1H, *J* 1.0 Hz, H-4′), 4.51 (d, 1H, *J*3.5 Hz, H-2), 4.37 (ddd, 1H, *J* 3.5, 5.0, 8.0 Hz, H-4), 4.24 (dd, 1H, *J* 8.0, 9.5 Hz, H-5b), 4.11 (dd, 1H, *J* 5.0, 9.5 Hz, H-5a), 4.08 (d, 1H, *J*3.5 Hz, H-3), 2.85 (dd, 1H, *J* 1.0, 9.0 Hz, H-3′), 2.46 (s, 3H, tosyl), 1.94–2.04 (m, 1H, —C*H*Me_2), 1.30, 1.46 (2s, 6H, isoprop.), 1.08 (d, 3H, *J* 6.5 Hz, Me), 1.02 (d, 3H, *J* 6.5 Hz, Me); HRMS (EI) *m/z*: M^+ found 455.1583. $C_{21}H_{29}O_8NS$ requires 455.1614.

3.1.4. (3′*S*,4′*S*) 3-*O*-(3′-Isopropyl-azetidin-2′-on-4′-yl)-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose (19). Compound **19** was obtained from **17** by the tosylation procedure (tosyl chloride, pyridine, 12 h; 78%). Oil; [Found: C, 55.46; H, 6.70; N, 2.98. $C_{21}H_{29}O_8NS$ (455.54) requires C, 55.37; H, 6.42; N, 3.07%]; $[\alpha]_D^{22}=-29.2$ (*c* 0.21, CH_2Cl_2); ν_{max} (film) 3327, 1770 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.31–7.85 (2m, 4H, tosyl), 6.43 (br s, 1H, NH), 5.86 (d, 1H, *J* 3.5, Hz, H-1), 4.89 (d, 1H, *J* 1.0 Hz, H-4′), 4.48 (d, 1H, *J*3.5 Hz, H-2), 4.39 (ddd, 1H, *J* 3.0, 5.0, 8.0 Hz, H-4), 4.24 (dd, 1H, *J* 8.0, 9.5 Hz, H-5b), 4.11 (dd, 1H, *J* 5.0, 9.5 Hz, H-5a), 4.04 (d, 1H, *J*3.0 Hz, H-3), 2.79 (dd, 1H, *J* 1.0, 8.0 Hz, H-3′), 2.46 (s, 3H, tosyl), 1.95–2.05 (m, 1H, —C*H*Me_2), 1.31, 1.46 (2s, 6H, isoprop.), 1.08 (d, 3H, *J* 6.5 Hz, Me), 1.03 (d, 3H, *J* 6.5 Hz, Me); HRMS (EI) *m/z*: M^+ found 455.1608. $C_{21}H_{29}O_8NS$ requires 455.1614.

3.1.5. (3′*R*,4′*R*) 5-Deoxy-3-*O*:5-*C*-(3′-isopropyl-azetidin-2′-on-1′,4′-di-yl)-1,2-*O*-isopropyli-dene-α-D-xylofuranose (20). Compound **20** was obtained from **18** according to the procedure described for **14/15**[13] (86%). Colorless crystals; mp 106–109.5°C; [Found: C, 59.70; H, 7.74; N, 4.73. $C_{14}H_{21}O_5N$ (283.33) requires C, 59.35; H, 7.47; N, 4.94%]; $[\alpha]_D^{22}=+118.6$ (0.31, CH_2Cl_2); ν_{max} (CH_2Cl_2) 1762 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.97 (d, 1H, *J* 3.5 Hz, H-1), 4.73 (s, 1H, H-4′), 4.61 (d, 1H, *J* 3.5 Hz, H-2), 4.40–4.42 (m, 1H, H-4), 4.29 (d, 1H, *J* 3.0 Hz, H-3), 3.80 (dd, 1H, *J* 4.5, 14.0 Hz, H-5b), 3.51 (dd, 1H, *J* 1.5, 14.0 Hz, H-5a), 2.78 (d, 1H, *J* 8.0 Hz, H-3′), 1.33, 1.49 (2s, 6H, isoprop.), 1.96–2.03 (m, 1H, —C*H*Me_2), 1.05 (d, 3H, *J* 6.5 Hz, Me), 0.95 (d, 3H, *J* 6.5 Hz, Me); HRMS (EI) *m/z*: M^+ found 283.1442. $C_{14}H_{21}O_5N$ requires 283.1420.

3.1.6. (3′*S*,4′*S*) 5-Deoxy-3-*O*:5-*C*-(3′-isopropyl-azetidin-2′-on-1′,4′-di-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (21). Compound **21** was obtained from **19** according to the procedure described for **14/15**[13] (80%). Colorless crystals; mp 99–105°C; [Found: C, 59.51; H, 7.62; N, 4.91. $C_{14}H_{21}O_5N$ (283.33) requires C, 59.35; H, 7.47; N, 4.94%]; $[\alpha]_D^{22}=-25.5$ (*c* 0.18, CH_2Cl_2); ν_{max} (film) 1754 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.88 (d, 1H, *J* 3.5 Hz, H-1), 4.62 (s, 1H, H-4′), 4.49 (d, 1H, *J* 3.5 Hz, H-2), 4.08 (d, 1H, *J* 15.0 Hz, H-5b), 4.03–4.05 (m, 1H, H-4), 3.23 (dd, 1H, *J* 4.0, 15.0 Hz, H-5a), 2.84 (d, 1H, *J* 8.0 Hz, H-3′), 1.96–2.03 (m, 1H, —C*H*Me_2), 1.31, 1.49 (2s, 6H, isoprop.), 1.06 (d, 3H, *J* 6.5 Hz, Me), 1.00 (d, 3H, *J* 6.5 Hz, Me); HRMS (EI) *m/z*: M^+ found 283.1438. $C_{14}H_{21}O_5N$ requires 283.1420.

3.1.7. (3′*S*,4′*R*) 5-Deoxy-3-*O*:5-*C*-(3′-isopropyl-azetidin-2′-on-1′,4′-di-yl)-1,2-*O*-isopropyli-dene-α-D-xylofuranose (24). The mixture of **14** (0.03 g, 0.11 mmol) and PtO_2 (0.015 g) in MeOH (10 mL) was shaken on a Parr hydrogenator at 30 psi for 10 h. The solution was then concentrated and purified by flash chromatography (30% ethyl acetate/hexane) to yield 0.019 g (63%) of the title compound **24** as an oil; $[\alpha]_D^{22}=+59.6$ (0.53, CH_2Cl_2); ν_{max} (film) 1757 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.97 (d, 1H, *J* 4.0 Hz, H-1), 4.98 (d, 1H, *J* 3.5 Hz, H-4′), 4.62 (d, 1H, *J* 4.0 Hz, H-2), 4.43 (ddd, 1H, *J* 1.5, 3.0, 4.5 Hz, H-4), 4.30 (d, 1H, *J* 3.0 Hz, H-3), 3.80 (dd, 1H, *J* 4.5, 14.0 Hz, H-5b), 3.51 (dt, 1H, *J* 1.5, 14.0 Hz, H-5a), 2.88 (ddd, 1H, *J* 1.5, 3.5,

11.5 Hz, H-3′), 2.08–2.16 (m, 1H, —C*H*Me$_2$), 1.33, 1.49 (2s, 6H, isoprop.), 1.12 (d, 3H, *J* 6.5 Hz, Me), 0.93 (d, 3H, *J* 6.5 Hz, Me); HRMS (EI) *m/z*: M^+ found 283.1424. $C_{14}H_{21}O_5N$ requires 283.1420.

3.1.8. (3′*R*,4′*R*) and (3′*S*,4′*R*) 5-Deoxy-1,2-*O*-isopropylidene-3-*O*:5-*C*-[3′-bromo-3′-(1-hydroxy-1-methyl-ethyl)-azetidin-2′-on-1′,4′-di-yl)-α-D-xylofuranose (25 and 26). *N*-Bromosuccinimide (0.095 g, 0.53 mmol) was added to a solution of **14** (0.1 g, 0.35 mmol) and H_2O (0.26 mL, 1.42 mmol) in DMSO (1.5 mL). The resulting solution was stirred at room temperature for 6 h and then poured into a two-phase system water/ether. The aqueous phase was extracted with ether, and the combined ether layers were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (30% ethyl acetate/hexane) yielded 0.074 g (57%) of bromohydrins **25** and **26** in a ratio *ca*. 3.8:1, respectively. [Found: C, 44.60; H, 5.58; N, 3.76. $C_{14}H_{20}O_6NBr$ (378.23) requires C, 44.46; H, 5.33; N, 3.70%]; ν_{max} (CH_2Cl_2) 3476, 1779 cm^{-1}; 25 (major isomer): δ_H (500 MHz, $CDCl_3$) selective signals taken from the spectrum of the mixture: δ 4.67 (d, 1H, *J*4.0 Hz, H-2), 5.13 (s, 1H, H-4′), 5.98 (d, 1H, *J*4.0 Hz, H-1).

26 (minor isomer): δ_H (500 MHz, $CDCl_3$) selective signals taken from the spectrum of the mixture: 6.01 (d, 1H, *J*4.0 Hz, H-1), 5.29 (s, 1H, H-4′), 4.68 (d, 1H, *J*4.0 Hz, H-2); HRMS (EI) *m/z*: $(M—CH_3)^+$ found 362.0257. $C_{13}H_{17}O_6NBr$ requires 362.0239.

3.1.9. (3′*S*,4′*R*) and (3′*R*,4′*R*) 5-Deoxy-3-*O*:5-*C*-[3′-(1-hydroxy-1-methyl-ethyl)-azetidin-2′-on-1′,4′-di-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (27 and 28). A solution of tributyltin hydride (0.85 mL, 0.317 mmol) and AIBN (0.0065 g, 0.04 mmol) in toluene (1 mL) was added to a hot (100°C) solution of bromohydrins **25/26** (0.06 g, 0.16 mmol) in toluene (3 mL). The reaction was allowed to stir at this temperature for 20 min, then the solvent was removed, and the product was purified by flash chromatography, using CH_2Cl_2/ethyl acetate/hexane 1:5:4 v/v as an eluent, to give the title compounds **27/28** in a ratio *ca*. 6.5:1 (0.043 g, 91%); ν_{max} ($CHCl_3$) 3509, 1755 cm^{-1}; **28**: δ_H (500 MHz, $CDCl_3$) selective signals taken from the spectrum of the mixture **27/28**: 4.92 (d, 1H, *J* 0.5 Hz, H-4′), 4.63 (d, 1H, *J* 4.0 Hz, H-2), 4.30 (d, 1H, *J* 3.0 Hz, H-3), 3.82 (dd, 1H, *J*4.5 and 14.0 Hz, H-5b), 3.56 (dd, 1H, *J* 2.0 and 14.0 Hz, H-5a), 3.01 (br s, 1H, —OH); HRMS (EI) *m/z*: $(M—CH_3)^+$ found 284.1141. $C_{13}H_{18}O_6N$ requires 284.1134.

After crystallization from AcOEt/hexane mixture, pure compound **27** was obtained. Colorless crystals; mp 146.5–152°C; [Found: C, 55.96; H, 7.22; N, 4.57. $C_{14}H_{21}O_6N$ (299.33) requires C, 56.18; H, 7.07; N, 4.68%]; $[\alpha]_D^{22}$= +66.8 (0.63, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3543, 1768 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.98 (d, 1H, *J* 4.0 Hz, H-1), 5.12 (d, 1H, *J* 3.5 Hz, H-4′), 4.67 (d, 1H, *J* 4.0 Hz, H-2), 4.45–4.47 (m, 1H, H-4), 4.42 (d, 1H, *J* 3.0 Hz, H-3), 3.80 (dd, 1H, *J*4.0, 13.5 Hz, H-5b), 3.59 (br d, 1H, *J* 13.5 Hz, H-5a), 3.24–3.26 (m, 1H, H-3′), 2.95 (br s, 1H, —OH), 1.41 (s, 3H, Me), 1.34 (s, 3H, Me), 1.33, 1.50 (2s, 6H, isoprop.); HRMS (EI) *m/z*: $(M—CH_3)^+$ found 284.1126. $C_{13}H_{18}O_6N$ requires 284.1134.

3.1.10. (3′*R*,4′*R*) 5-Deoxy-3-*O*:5-*C*-[3′-hydroxy-3′-(1-hydroxy-1-methyl-ethyl)-azetidin-2′-on-1′,4′-di-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (29). Into a well-stirred mixture of H_2O (7.5 mL), CH_3CN (5 mL) and CCl_4 (5 mL) were added $NaIO_4$ (0.375 g, 1.76 mmol), $CaCO_3$ (0.07 g, 0.70 mmol) and $RuCl_3 \cdot xH_2O$ (0.003 g, 0.015 mmol). The resulting mixture was cooled to 0°C and the solution of **14** (0.1 g, 0.355 mol) in CCl_4 (0.5 mL) was added dropwise. Stirring was continued at 0°C for 5 min; subsequently the reaction was quenched by the addition of *i*-propanol (1 mL). The precipitate was filtered on Celite and washed with ethyl acetate (2×10 mL). The combined filtrates were dried ($MgSO_4$) and the solvent was evaporated. Purification on silica gel, using hexane/ethyl acetate 4:6 v/v as an eluent gave the title compound **29** (0.1 g, 85%). Colorless crystals; mp 198–203°C; [Found: C, 53.29; H, 6.78; N, 4.48. $C_{14}H_{21}O_7N$ (315.33) requires C, 53.33; H, 6.71; N, 4.44%]; $[\alpha]_D^{22}$=+126.7 (0.4, CH_2Cl_2); ν_{max} (film) 3407, 3281, 1760 cm^{-1}; δ_H (200 MHz, $CDCl_3$+D_2O) 5.98 (d, 1H, *J* 3.5 Hz, H-1), 4.96 (s, 1H, H-4′), 4.66 (d, 1H, *J* 3.5 Hz, H-2), 4.43–4.48 (m, 1H, H-4), 4.40 (d, 1H, *J* 3.0 Hz, H-3), 3.75 (d, 2H, *J* 3.0 Hz, H-5a, H-5b), 1.41 (s, 3H, Me), 1.34 (s, 3H, Me), 1.33, 1.50 (2s, 6H, isoprop.); HRMS (EI) *m/z*: $(M—CH_3)^+$ found 300.1073. $C_{13}H_{18}O_7N$ requires 300.1083.

3.1.11. X-Ray structure determination of compound 29. Single crystals of **29** suitable for X-ray structure analysis were obtained by a slow evaporation of the *i*-propanol solution. Unit cell dimensions were obtained by least-squares fit of setting angles of 25 reflections collected in the θ range 18.97–43.08°. Data were collected on the Nonius BV MACH 3 diffractometer with graphite monochromatized CuK_α radiation. Intensities were corrected for Lorentz polarization and ψ-scan-based absorption factors (min. and max. transmission 87.4 and 99.3%, respectively). Structures were solved by direct methods with the use of SHELX86[25] and refined against F^2 using SHELX97[26] programs. All hydroxyl H-atoms were placed in ideal positions and refined with the riding model and fixed isotropic displacement parameters. Position for hydroxyl hydrogens were found from different Fourier maps and refined without constraints. Crystal data, details of data collection and refinement procedure are deposited at the Cambridge Crystallographic Data Center. (Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC #151371.) The molecular structure of **29** is shown in Fig. 1.

3.1.12. (4′*R*) 3-*O*:5-*C*-[Azetidin-2′,3′-dion-1′,4′-di-yl)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylo-furanose (32). To the solution of the diol **29** (0.053 g, 0.17 mmol) in dry ethyl acetate (5 mL) H_6IO_5 (0.043 g, 0.192 mmol) was added, and the mixture was stirred under argon for ~2.5 h (TLC) at room temperature. The precipitate was filtered off, washed with AcOEt (2×5 mL) and the combined filtrates were concentrated in vacuo to give the crude α-keto β-lactam **32** (0.062 g); ν_{max} (CH_2Cl_2): 3343, 1782, 1761cm^{-1}; δ_H (500 MHz, acetone-d_6) 6.13 (d, 1H, *J* 4.0 Hz, H-1), 5.50 (s, 1H, H-4′), 4.79 (d, 1H, *J* 4.0 Hz, H-2), 4.70–4.71 (m, 1H, H-4), 4.48 (d, 1H, *J* 3.0 Hz,

H-3), 3.99 (dd, 1H, *J* 4.0, 13.5 Hz, H-5b), 3.79 (dd, 1H, *J* 2.0, 13.5 Hz, H-5a), 1.30, 1.42 (2s, 6H, isoprop.).

3.1.13. (3′*S*,4′*R*) 5-Deoxy-3-*O*:5-*C*-[3′-hydroxy-azetidin-2′-on-1′,4′-di-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (33). To the solution of the crude compound **32** (0.05 g) in MeOH (4 mL), $NaBH_4$ (0.0075 g, 0.2 mmol) was added. After being stirred for 25 min at room temperature, AcOH (0.05 mL) was added to the reaction mixture. The mixture was evaporated and purified by column chromatography on silica gel (50% ethyl acetate/hexane) to give the title compound **33** (0.027 g), which was characterized as the 3′-acetate **34**. Oil; $[\alpha]_D^{22}=+117.3$ (0.4, CH_2Cl_2); ν_{max} ($CHCl_3$): 1783, 1756 cm^{-1}; δ_H (500 MHz, acetone-d_6) 6.03 (d, 1H, *J* 4.0 Hz, H-1), 5.56 (dd, 1H, *J* 1.5, 3.0 Hz, H-3′), 5.15 (d, 1H, *J* 3.0 Hz, H-4′), 4.62 (d, 1H, *J* 4.0 Hz, H-2), 4.31 (ddd, 1H, *J* 1.5, 3.0, 5.0 Hz, H-4), 4.32 (dd, 1H, *J* 0.5, 3.0 Hz, H-3), 3.90 (dd, 1H, *J* 4.5, 14.0 Hz, H-5b), 3.39 (dt, 1H, *J* 1.5, 14.0 Hz, H-5a), 2.11 (s, 3H, Ac), 1.30, 1.43 (2s, 6H, isoprop); HRMS (EI) *m/z*: $(M-CH_3)^+$ found 284.0757. $C_{12}H_{14}O_7N$ requires 284.07703.

3.1.14. (4′*S*,4′*S*) and (4′*R*,4′*S*) 5-Deoxy-3-*O*:5-*C*-[3′-hydroxy-3′-(1-hydroxy-1-methyl-ethyl)-azetidin-2′-on-1′,4′-di-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (30/31). The mixture of stereoisomers **30/31**, in a ratio *ca*. 6.4:1 (de 73%), was obtained from **15** according to the procedure described for **29** (79%); [Found: C, 53.56; H, 7.00; N, 4.27. $C_{14}H_{21}O_7N$ (315.33) requires C, 53.33; H, 6.71; N, 4.44%]; ν_{max} (KBr) 3455, 3367, 1769, 1759 cm^{-1}; **30** (major isomer): δ_H (500 MHz, acetone-d_6+D_2O) selective signals taken from the spectrum of the mixture: 5.90 (d, 1H, *J* 4.0 Hz, H-1), 4.94 (s, 1H, H-4′), 4.66 (d, 1H, *J* 4.0 Hz, H-2), 4.30–4.32 (m, 1H, H-3), 4.12–4.14 (m, 1H, H-4), 3.92 (d, 1H, *J* 15.0 Hz, H-5b), 3.52 (dd, 1H, *J* 4.0, 15.0 Hz, H-5a).

31 (minor isomer): δ_H (500 MHz, acetone-d_6+D_2O) selective signals taken from the spectrum of the mixture: 5.98 (d, 1H, *J* 3.5 Hz, H-1), 5.03 (s, 1H, H-4′), 4.60 (d, 1H, *J* 3.5 Hz, H-2), 4.35–4.37 (m, 1H, H-3), 4.09–4.11 (m, 1H, H-4), 3.89 (d, 1H, *J* 15.0 Hz, H-5b), 3.44 (dd, 1H, *J* 3.5, 15.0 Hz, H-5a); HRMS (EI) *m/z*: M^+ found 315.1316. $C_{14}H_{21}O_7N$ requires 315.1318.

3.1.15. (4′*S*) 3-*O*:5-*C*-[Azetidin-2′,3′-dion-1′,4′-di-yl)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose and (4′*S*) 5-Deoxy-3-*O*:5-*C*-[3′,3′-dihydroxy-azetidin-2′-on-1′,4′-di-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (35) and (36). The mixture of **35/36** was obtained from the mixture of stereoisomers **30/31** according to the procedure described for **32**; ν_{max} (KBr): 3420, 1794, 1762cm^{-1}; 35: δ_H (500 MHz, acetone-d_6) 5.87 (d, 1H, *J* 4.0 Hz, H-1), 5.61 (s, 1H, H-4′), 4.55 (d, 1H, *J* 4.0 Hz, H-2), 4.44 (d, 1H, *J* 1.5 Hz, H-3), 4.29 (d, 1H, *J* 15.0 Hz, H-5b), 4.20–4.21 (m, 1H, H-4), 4.03 (dd, 1H, *J* 3.5, 15.0 Hz, H-5a), 1.28, 1.42 (2s, 6H, isoprop.).

36: δ_H (500 MHz, acetone-d_6) 5.90 (d, 1H, *J* 3.5 Hz, H-1), 5.55 (s, 1H, H-4′), 4.59 (d, 1H, *J* 3.5 Hz, H-2), 4.53 (d, 1H, *J* 1.5 Hz, H-3), 4.24–4.26 (m, 1H, H-4), 4.18 (d, 1H, *J* 15.0 Hz, H-5b), 3.79 (dd, 1H, *J* 3.0, 15.0 Hz, H-5a), 2.78 (br s, 1H, —OH), 1.29, 1.43 (2s, 6H, isoprop.). Due to low stability, the crude mixture **35/36** was used for the next steps.

3.1.16. (3′*R*,4′*S*) 5-Deoxy-3-*O*:5-*C*-[3′-hydroxy-azetidin-2′-on-4′-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (37). Compound **37** was obtained from **35/36** according to the procedure described for **33** (65%). Colorless crystals; mp 229–232°C; $[\alpha]_D^{22}=+9.3$ (0.12, MeOH); ν_{max} (KBr) 3428, 1751 cm^{-1}; δ_H (500 MHz, acetone-d_6+D_2O) 5.92 (d, 1H, *J* 3.5 Hz, H-1), 4.99 (d, 1H, *J* 3.0 Hz, H-4′), 4.78–4.80 (m, 1H, H-3′), 4.56 (d, 1H, *J* 3.5 Hz, H-2), 4.29–4.31 (m, 1H, H-3), 4.04–4.06 (m, 1H, H-4), 3.85 (d, 1H, *J*15.0 Hz, H-5b), 3.39 (ddd, 1H, *J* 1.5, 3.5, 15.0 Hz, H-5a), 1.28, 1.42 (2s, 6H, isoprop.); HRMS (EI) *m/z*: $(M-CH_3)^+$ found 242.0687. $C_{11}H_{15}O_6N$ requires 242.0664.

3.1.17. (3′*R*,4′*S*) 3-*O*:5-*C*-[3′-Acetoxy-azetidin-2′-on-4′-yl]-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (38). Acetylation of **37** (acetic anhydride/pyridine mixture, 2:1 v/v; 1 h), gave the title compound **38** (88%). Colorless crystals; mp 227–229°C; $[\alpha]_D^{22}=-61.9$ (0.33, CH_2Cl_2); ν_{max} (KBr) 1776, 1748 cm^{-1}; δ_H (500 MHz, acetone-d_6) 5.86 (d, 1H, *J* 3.5 Hz, H-1), 5.54 (dd, 1H, *J* 1.5, 3.0 Hz, H-3′), 5.11 (d, 1H, *J* 3.0 Hz, H-4′), 4.52 (d, 1H, *J* 3.5 Hz, H-2), 4.27–4.29 (m, 1H, H-3), 4.08–4.10 (m, 1H, H-4), 3.90 (d, 1H, *J*15.0 Hz, H-5b), 3.45 (ddd, 1H, *J* 1.5, 3.5, 15.0 Hz, H-5a), 2.07 (s, 3H, Ac), 1.28, 1.41 (2s, 6H, isoprop.); HRMS (EI) *m/z*: $(M-CH_3)^+$ found 284.0782. $C_{12}H_{14}O_7N$ requires 284.077.

3.1.18. (4′*S*) 5-Deoxy-3-*O*:5-*C*-[3′-hydroxyimino-azetidin-2′-on-4′-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (39). To the crude oil containing **35/36** (0.058 g) dissolved in dry pyridine (2 mL), $NH_2OH{\cdot}HCl$ (0.031 g, 0.45 mmol) was added and the solution was stirred at room temperature for 3 days. Subsequently, water was added and the aqueous layer was extracted with EtOAc, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel, using EtOAc/hexane 2:3 v/v as an eluent, to give the title compound **39** as a mixture of *syn* and *anti* isomers (0.023 g, ~50%). White solid; ν_{max} (CH_2Cl_2) 3568, 1787, 1744 cm^{-1}; **39** (major isomer): δ_H (500 MHz, acetone-d_6) selective signals taken from the spectrum of the mixture: 11.41 (br s, 1H, —OH), 5.85 (d, 1H, *J* 3.5 Hz, H-1), 5.63 (s, 1H, H-4′), 4.53 (d, 1H, *J* 3.5 Hz, H-2), 4.04 (d, 1H, *J*15.0 Hz, H-5b), 3.67 (dd, 1H, *J* 4.0, 15.0 Hz, H-5a).

39 (minor isomer): δ_H (500 MHz, acetone-d_6) selective signals taken from the spectrum of the mixture: 11.40 (br s, 1H, —OH), 5.87 (d, 1H, *J* 4.0 Hz, H-1), 5.40 (s, 1H, H-4′), 4.03 (d, 1H, *J*15.0 Hz, H-5b); HRMS (EI) *m/z*: $(M-CH_3)^+$ found 255.0592. $C_{10}H_{11}O_6N_2$ requires 255.0617.

3.1.19. (3′*R*,4′*S*) 3-*O*:5-*C*-[3′-Acetylamino-azetidin-2′-on-4′-yl]-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (40). A solution of **39** (0.014 g, 0.052 mmol), AcONa (0.0072 g, 0.088 mmol) and Ac_2O (0.03 mL) in AcOEt (0.5 mL) was stirred at room temperature for 14 h. An additional AcOEt (5 mL) and PtO_2 (0.005 g) was added to the solution, and the mixture was stirred under 30 psi of H_2 for 12 h. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluted with

AcOEt/hexane 8:2 v/v, to give the title compound **40** (0.01 g, 65%). White crystals; mp 284–289°C; $[\alpha]_D^{22}=-11.4$ (0.3, MeOH); ν_{max} ($CHCl_3$) 3448, 1780, 1686 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.97 (br d, 1H, *J* 9.5 Hz, NH), 5.92 (d, 1H, *J* 3.5 Hz, H-1), 5.50 (ddd, 1H, *J* 1.5, 3.5, 9.5 Hz, H-3′), 4.96 (d, 1H, *J* 3.5 Hz, H-4′), 4.57 (d, 1H, *J* 3.5 Hz, H-2), 4.19 (d, 1H, *J* 1.5 Hz, H-3), 4.07–4.09 (m, 1H, H-4), 4.08 (d, 1H, *J*15.0 Hz, H-5b), 3.29 (ddd, 1H, *J* 1.5, 4.0, 15.0 Hz, H-5a), 2.04 (s, 3H, Ac), 1.33, 1.50 (2s, 6H, isoprop.); HRMS (EI) *m/z*: M^+ found 298.1168. $C_{13}H_{18}O_6N_2$ requires 298.1165.

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