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1,3-DIPOLAR CYCLOADDITION OF D-XYLOSE DERIVED NITRONE WITH METHYL ACRYLATE. SYNTHESIS OF CHIRAL PYRROLIDINONES AND PYRROLIDINES

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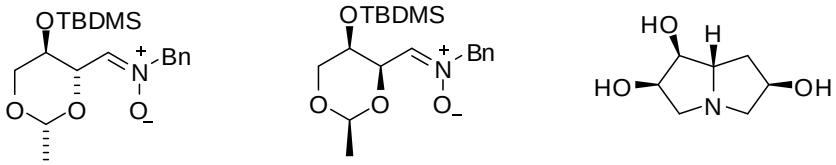
Abstract – Several new 3-hydroxysubstituted pyrrolidinones and pyrrolidines with a long-polyolic chain were prepared from chiral isoxazolidines. The cycloaddition of the chiral nitrone **4** derived from D-xylose with methyl acrylate proceeded with very good diastereoselectivity for the *anti-trans* isoxazolidine **5a**. The results show that the method has potential use in the preparation of pyrrolidinones and pyrrolidines containing carbohydrate residues.

Dedicated to Professor Albert Padwa on the occasion of his 75th birthday

INTRODUCTION

Cyclic glycosides are important as enzyme inhibitors and as chiral synthons, suitable for the synthesis of many natural products. Since the 1,3-dipolar cycloaddition has a nearly singular capability of establishing large numbers of stereogenic centers in one synthetic step in the last years the attention has been focused to the preparation of chiral sugar derived nitrones.[1] The configuration of the newly generated stereogenic centers would be determined by the nitrone. Asymmetric induction in 1,3-dipolar cycloaddition has been efficiently achieved by using nitrones with chiral groups at either the nitrogen atom or the carbon atom.[2] Among nitrones, the sugar derived nitrones represent versatile substrates as they provide a

polyhydroxylated carbon framework with multiple avenues of chirality as well as an access for amino group transformation required for the synthesis of polyhydroxylated piperidine, pyrrolidine, pyrrolizidine, indolizidine and quinolizidine alkaloids.[3] With the goal of developing a simple route to the synthesis of polyhydroxylated derivatives **3** such as pyrrolizidines displaying antiviral activities, we have developed 1,3-dipolar cycloadditions of D-erythrose **1** and D-threose **2** derived nitrones with alkenes (Figure 1).[4] Chiral pyrrolidinones are widespread among natural products and biologically active molecules and are used as excellent building blocks for the synthesis of a plethora of nitrogen-containing natural products, such as pyrrolizidines and indolizidines.[5] Hydroxylated pyrrolidines constitute one of the main classes of naturally occuring sugar mimics having nitrogen in the ring.[6] A number of hydroxysubstituted pyrrolidines with polyolic side chains have been described and shown to be inhibitors of glycosidases. Moreover, long-chain pyrrolidines present the additional advantage of being interesting intermediates in the synthesis of polyhydroxylated bicyclic alkaloids.[7] Various synthetic methods for the synthesis of hydroxysubstituted pyrrolidines have been reported either from carbohydrates, as a chiral pool starting material, or from other sources.[8]



1 **2** **3**

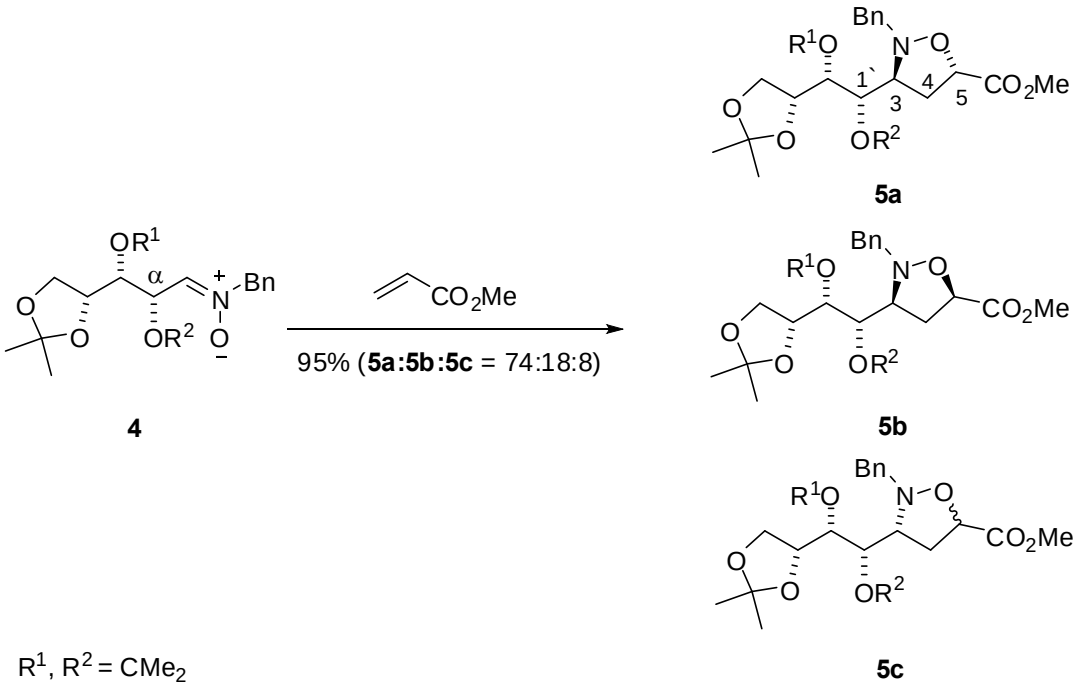
Figure 1

With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions,[9-11] we have now focused our attention to develop a simple and efficient route for the synthesis of these biologically important polyhydroxylated alkaloids. In this communication we wish to describe a synthetic strategy based on 1,3-dipolar cycloaddition of readily available chiral sugar derived D-xylosyl nitrone **4**[10] with methyl acrylate followed by subsequent N-O bond cleavage accompanied with spontaneous cyclization into novel chiral polyhydroxylated pyrrolidinones and pyrrolidines possessing a long-polyolic chain.

RESULTS AND DISCUSSION

Nitrone **4** can be readily prepared from D-xylose as described by us[10] in four steps and 38% overall yield, and it has already been used in our laboratory for the preparation of the isoxazolidinyl nucleosides.[11] D-Xylose derived nitrone **4** reacted smoothly with methyl acrylate at room temperature over 24 h to give a 74:18:8 mixture of diastereoisomeric isoxazolidines **5a-c** in 95% yield (Scheme 1). The ratio of diastereomeric isoxazolidines was determined from quantitative ^{13}C NMR spectra, by integration of the

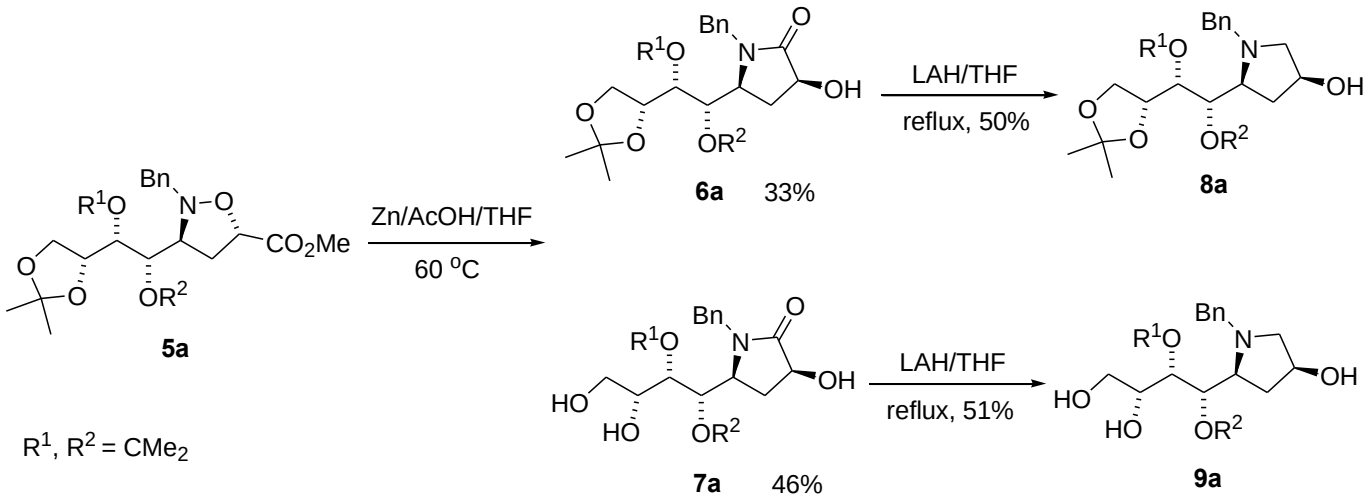
peaks from C-4 of the isoxazolidines. The cycloaddition proceeded with very good diastereoselectivity for the *anti-trans* isoxazolidine **5a** and is completely regioselective with only the sterically favoured 5-substituted isoxazolidines being detected. Purification by flash chromatography allowed the isolation of pure *endo*-adduct **5a**, with C-3/C-5 *trans* and *exo*-adduct **5b**, with C-3/C-5 *cis* relative configuration identified by spectroscopic analysis, particularly NOE difference experiments.



Scheme 1

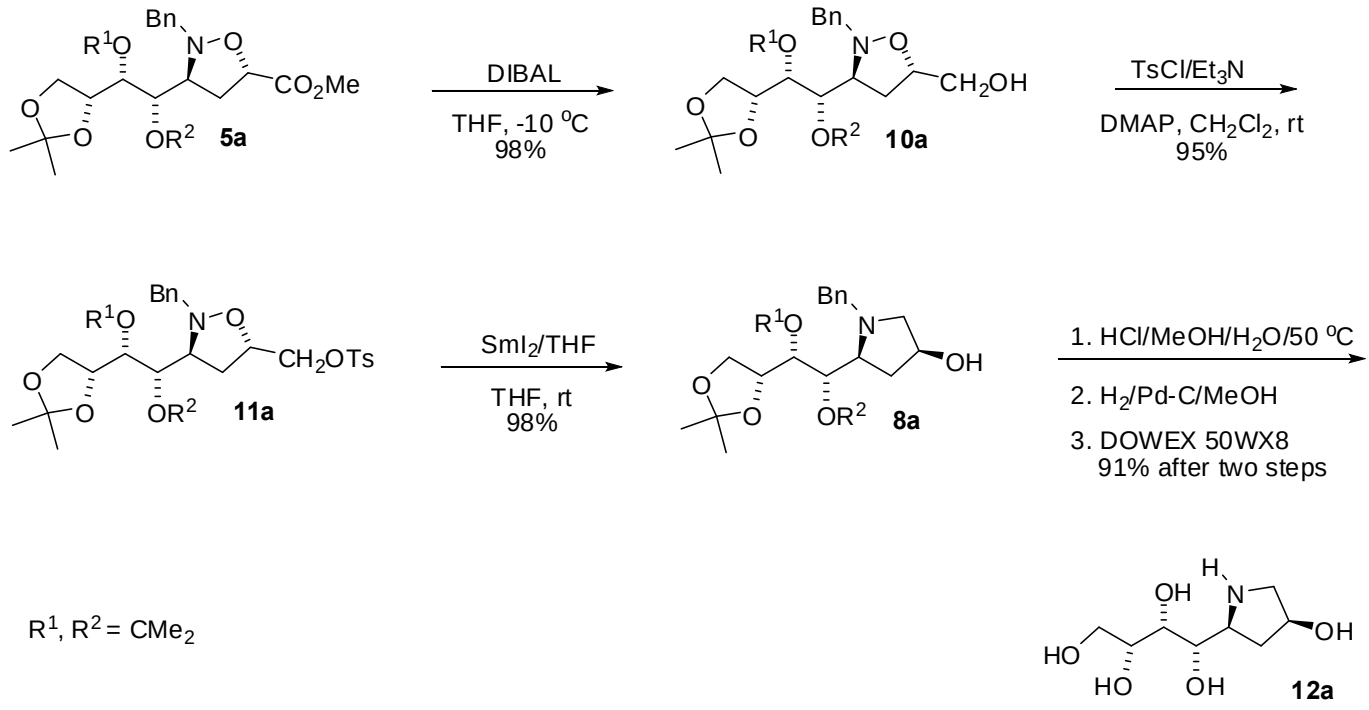
Based on our previous results from 1,3-dipolar cycloadditions of sugar derived nitrones bearing a protected hydroxy group in the α-position[4] as well as to the fact that 1,3-dipolar cycloaddition of alkenes to chiral α-alkoxy nitrones gave preferentially *anti* adducts[3,12] we assigned to isomers **5a** and **5b** a C-1'/C-3 *anti* relationship as a result of dipolarophile attack from the less sterically hindered *Si* diastereotopic face of nitrone **4**. The relative configuration at the new stereogenic center in **5a** and **5b** could not be assigned at this stage; however it was deduced from the structures of isoxazolidines **11a** and **11b**, whose structures were established by X-ray diffraction studies (Figures 2 and 3).[13]

Considering the well-known propensity of isoxazolidines to be reduced to amines,[3,9] we have next prepared chiral polyhydroxylated pyrrolidinones **6a** and **7a** in a single step from the major isoxazolidine **5a** involving N–O cleavage with Zn/AcOH and subsequent spontaneous cyclization in 33% and 46% yield, respectively.[14] The origin of the pyrrolidinone **7a** can be explained by the partially hydrolysis of the primary formed pyrrolidinone **6a**. Finally, the pyrrolidinones **6a** and **7a** were reduced with $LiAlH_4$ in THF to afford the chiral polyhydroxylated pyrrolidines **8a** and **9a** in 50% and 51% yield, respectively (Scheme 2).



Scheme 2

As has been mentioned, the C-CO_2Me functionalized isoxazolidine **5a** represents a sub-unit with potential for cleavage and recyclisation to form the pyrrolidine derivatives**.** This opens a new route to the stereocontrolled formation of polyhydroxysubstituted pyrrolidines. To demonstrate this, the diastereoisomerically pure isoxazolidine **5a** was reduced with DIBAL to yield the primary alcohol **10a** in 98% yield. The hydroxymethyl derivative **10a** was subsequently treated with *p*-toluene sulfonyl chloride and Et_3N in the presence of a catalytic amount of DMAP in CH_2Cl_2 to furnish tosylate **11a** in 95% yield (Scheme 3). The samarium diiodide-induced direct hydrogenolysis of **11a** in THF at room temperature resulted in a cascade reaction sequence involving isoxazolidine N–O bond cleavage and spontaneous



Scheme 3

cyclization affording pyrrolidine **8a** in an excellent yield (98%). Finally, the deprotection of the benzyl as well as isopropylidene groups furnished the desired 3-hydroxylated pyrrolidine **12a** in 91% yield after two steps (Scheme 3). The synthesis of **12a** has been achieved in five steps with an overall yield of 82% from isoxazolidine **5a**. The X-ray analysis of the isoxazolidine **11a** confirmed the configuration of the new stereogenic centers (Figure 2).

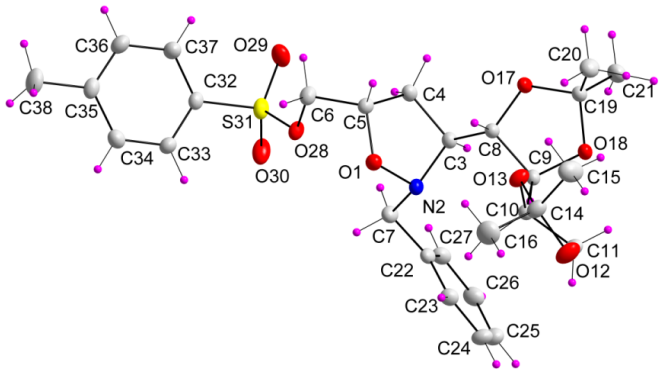
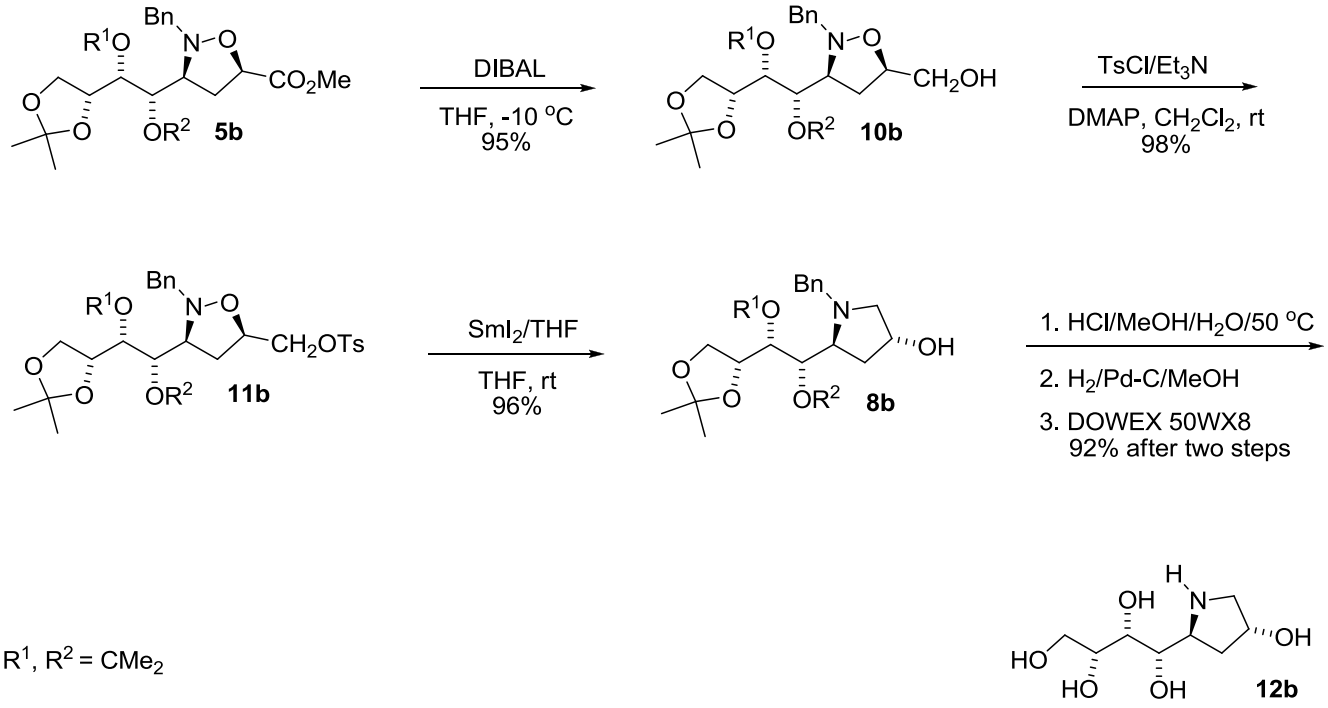


Figure 2. X-Ray analysis of tosylate **11a**

Following the same five-step reaction sequence, the minor isoxazolidine **5b** was analogously transformed into pyrrolidine **12b** with an overall yield of 83% from isoxazolidine **5b**. (Scheme 4). The X-ray analysis of the tosylated isoxazolidine **11b** confirmed the configuration of the new stereogenic centers (Figure 3).



Scheme 4

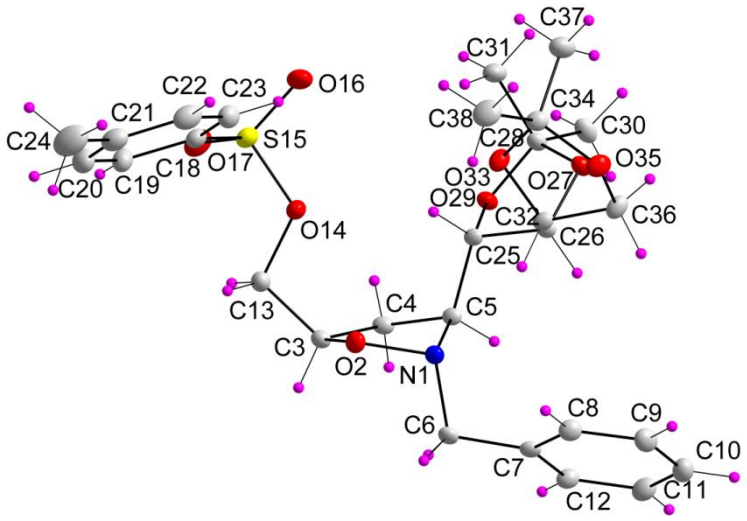


Figure 3. X-Ray analysis of tosylate **11b**

EXPERIMENTAL

All reactions involving moisture-sensitive reagents were carried out under argon atmosphere using standard vacuum line techniques and glassware that were flame dried and cooled under argon before use. All commercially available starting materials and reagents (Fluka, Merck, Across or Aldrich) were used without further purification. All solvents were distilled and dried before use. Flash column liquid chromatography (FLC) was performed on silica gel Kieselgel 60 (40-63 μm, 230-400 mesh) and analytical thin-layer chromatography (TLC) was performed on aluminum plates pre-coated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm silica gel 60 F254 (ALUGRAM® SIL G/UV254, Macherey-Nagel). Melting points were obtained using a Boecius apparatus and are uncorrected. Optical rotations were measured with a POLAR L-μP polarimeter (IBZ Messtechnik) with a water-jacketed 10.000 cm cell at the wavelength of sodium line D (λ=589 nm). Specific rotations are reported in 10^{-1} deg.cm^2.g^{-1} and concentrations in g/ 100 cm^3. FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron) equipped with a Smart Orbit (diamond crystal ATR) accessory, using the reflectance technique (4000-400 cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on either 300 (75) MHz MercuryPlus or 600 (150) MHz Unity Inova spectrometers from Varian. Chemical shifts (δ) are quoted in ppm and are referenced to the tetramethylsilane (TMS) as an internal standard. High resolution mass spectra (HRMS) were recorded on a Q-Tof PremierTM mass spectrometer with nanoACQUITY UPLCTM (Waters), and are accurate to ± 70 ppm. Nitrone **4** has been prepared from D-xylose as described by us[10] in four steps and 38% overall yield.

Methyl [(*3S,5S*)-2-benzyl-3-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl]isoxazolidine-5-yl]carboxylate (5a).

A mixture of nitrone **4** (1.43 g, 4.3 mmol) and methyl acrylate (1.55 mL, 17.2 mmol, 4 eq) was stirred in tetrahydrofuran (20 mL) for 32 h at room temperature. When the starting nitrone has been consumed (TLC), solvent was evaporated under the vacuum and the obtained mixture of diastereoisomers in the ratio 74:18:8 (**5a**:**5b**:**5c**) in a combined yield of 95% was purified by flash column chromatography (silica gel, EtOAc/hexanes 15/85).

Colorless oil, $[\alpha]_D$ -2.3 (*c* 0.44, CH_2Cl_2); IR (film) 3435, 3088, 2986, 2937, 1748, 1604, 1352, 1025, 605, 527 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.28, 1.38, 1.39, 1.41 4x[s, 12H, C($\underline{CH_3}$)$_2$], 2.75 (m, 1H, H-4a), 2.81 (m, 1H, H-4b), 3.33 (m, 1H, H-3), 3.48 (dd, 1H, H-7, *J* = 5.3, 6.7 Hz), 3.75 (m, 1H, H-6), 3.77 (d, 1H, N$\underline{CH_2}$Ph, *J* = 12.3 Hz), 3.79 (s, 3H, COO$\underline{Me}$), 3.94 (d, 2H, H-9a, H-9b, *J* = 7.0 Hz), 4.16 (dd, 1H, H-8, *J* = 6.7, 12.0 Hz), 4.25 (d, 1H, N$\underline{CH_2}$Ph, *J* = 12.3 Hz), 4.63 (dd, 1H, H-5, *J* = 8.5 Hz), 7.31 (m, 5H, NCH$_2\underline{Ph}$); **^{13}C NMR** ($CDCl_3$) δ: 25.8, 26.4, 27.2, 27.4 [C($\underline{CH_3}$)$_2$], 33.7 (C-4), 52.5 (COO$\underline{Me}$), 62.4 (N$\underline{CH_2}$Ph), 67.4 (C-3), 68.5 (C-9), 76.7 (C-6, C-8), 76.8 (C-5), 80.9 (C-7), 109.5, 109.9 [$\underline{C}$(CH$_3$)$_2$], 127.6-136.4 (NCH$_2\underline{Ph}$), 173.0 (C=O); HRMS: (ESI-TOF) calcd. for $C_{22}H_{32}NO_7$ (MH^+) 422.2179, found 422.1999.

Methyl [(*3S,5R*)-2-benzyl-3-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl]isoxazolidine-5-yl]carboxylate (5b).

Colorless oil; $[\alpha]_D^{25}$ -26.6 (*c* 0.62, CH_2Cl_2); IR (film) 3447, 3121, 2986, 2937, 1748, 1496, 1352, 1172, 1027, 601 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.26, 1.38, 1.41 [4xs, 12H, C($\underline{CH_3}$)$_2$], 2.64 (ddd, 1H, H-4a, *J* = 2.4, 5.9, 13.5 Hz), 2.83 (ddd, 1H, H-4b, *J* = 7.9, 9.5, 13.5 Hz), 3.26 (ddd, 1H, H-3, *J* = 2.4, 7.9 Hz), 3.50 (dd, 1H, H-7, *J* = 5.9 Hz), 3.75 (m, 1H, H-6), 3.80 (m, 4H, N-$\underline{CH_2}$Ph, OMe), 3.95 (m, 2H, H-9a, H-9b), 4.12 (m, 2H, H-8, N-$\underline{CH_2}$Ph), 4.80 (dd, 1H, H-5, *J* = 5.9, 9.5 Hz), 7.32 (m, 5H, N-CH$_2\underline{Ph}$); **^{13}C NMR** ($CDCl_3$) δ: 25.7, 26.4, 27.2, 27.4 [C($\underline{CH_3}$)$_2$], 34.4 (C-4), 52.4 (COO$\underline{Me}$), 61.1 (N-$\underline{CH_2}$Ph), 65.8 (C-9), 66.5 (C-3), 75.5 (C-5), 76.8 (C-8), 77.6 (C-6), 80.9 (C-7), 109.5, 109.7 [$\underline{C}$(CH$_3$)$_2$], 127.9-135.7 (N-CH$_2\underline{Ph}$), 171.2 (C=O); HRMS: (ESI-TOF) calcd. for $C_{22}H_{32}NO_7$ (MH^+) 422.2179, found 422.2009.

(*3S,5S*)-1-Benzyl-3-hydroxy-5-((*4R,4'R,5S*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl) pyrrolidin-2-one (6a).

A solution of cycloadduct **5a** (0.47 g, 1.11 mmol) in THF (10 mL), acetic acid (20 mL) and water (10 mL) was stirred with zinc dust (0.22 g, 3.33 mmol) at 60 °C for 5 h. Reaction was controlled with TLC. Saturated aqueous solution of $NaHCO_3$ was added after reaction and the mixture was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in rotatory evaporator. The resulting mixture was separated by flash chromatography on a silica gel using EtOAc/hexanes 50/50 to give 0.143 g of **6a** (33%) and 0.181 g of **7a** (46%).

Colorless solid, mp 183 °C; $[\alpha]_D$ -1.6 (*c* 0.96, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$) δ: 1.30, 1.35, 1.44 [4xs, 12H, C($\underline{CH_3}$)$_2$], 2.00 (m, 1H, H-4a), 2.30 (m, 1H, H-4b), 3.49 (m, 2H, H-5, OH), 3.64 (dd, 1H, H-2′, *J* = 3.5, 8.8 Hz), 3.69 (d, 1H, H-4′a, *J* = 8.1 Hz), 3.82 (m, 1H, H-4′b), 3.94 (m, 1H, H-1′), 4.13 (d, 1H, N$\underline{CH_2}$Ph, *J* = 15.3 Hz), 4.28 (m, 1H, H-3), 4.32 (m, 1H, H-3′), 5.02 (d, 1H, N$\underline{CH_2}$Ph, *J* = 15.3 Hz), 7.27 (m, 5H, NCH$_2\underline{Ph}$); **^{13}C NMR** ($CDCl_3$) δ: 25.4, 26.0, 26.8, 27.0 [C($\underline{CH_3}$)$_2$], 27.9 (C-4), 44.6 (N$\underline{CH_2}$Ph), 54.4 (C-5), 65.3 (C-4′), 69.3 (C-3), 73.0 (C-3′), 74.3 (C-1′), 76.3 (C-2′), 109.7, 110.3 [$\underline{C}$(CH$_3$)$_2$], 127.9-135.7 (NCH$_2\underline{Ph}$), 174.2 (C-2).

(*3S,5S*)-1-Benzyl-5-((*4S,5S*)-5-((*R*)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-pyrrolidin-2-one (7a)

Colorless oil; $[\alpha]_D$ -9.6 (*c* 0.25, CH_2Cl_2); IR (film) 3470, 3400, 3205, 3065, 2855, 1690 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.34, 1.44 [2xs, 6H, C($\underline{CH_3}$)$_2$], 2.01 (m, 1H, H-4a), 2.34 (m, 1H, H-4b), 2.83 (br, 1H, OH), 3.05 (br, 1H, OH), 3.51 (m, 2H, H-3′, H-4′a), 3.61 (m, 2H, H-5, H-4′b), 3.72 (dd, 1H, H-2′, *J* = 2.9, 8.8 Hz), 4.02 (br, 1H, OH), 4.18 (d, 1H, N$\underline{CH_2}$Ph, *J* = 15.4 Hz), 4.31 (dd, 1H, H-3, *J* = 5.9, 7.3 Hz), 4.40 (m, 1H, H-1′), 5.00 (d, 1H, N$\underline{CH_2}$Ph, *J* = 15.4 Hz), 7.29 (m, 5H, NCH$_2\underline{Ph}$). **^{13}C NMR** ($CDCl_3$) δ: 26.7, 27.0 [C($\underline{CH_3}$)$_2$], 27.9 (C-4), 44.8 (N$\underline{CH_2}$Ph), 54.4 (C-5), 64.1 (C-4′), 69.3 (C-3), 70.0 (C-3′), 73.2 (C-1′), 78.2 (C-2′), 110.2 [$\underline{C}$(CH$_3$)$_2$], 127.9-135.7 (NCH$_2\underline{Ph}$), 174.5 (C-2); HRMS: (ESI-TOF) Calcd. for $[M+H]^+$, 352.1760, found: 352.1762.

(*3S,5S*)-1-Benzyl-3-hydroxy-5-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl]pyrrolidine (8a).

The pyrrolidinone **6a** (0.05 g, 0.128 mmol) in THF (5 mL) was added to a refluxed suspension of LAH (0.03 g, 0.768 mmol) in THF (5 mL) under an argon atmosphere. The mixture was allowed to stirr for another 4h and reaction was quenched by adding of saturated aqueous $NaHCO_3$ (5 mL), filtered and washed with THF. Water phase was extracted with Et_2O and combined organic layers were dried and concentrated in rotatory evaporator. The separation using flash chromatography (silica gel, EtOAc/hexanes 50/50) gave 25 mg (50%) of pyrrolidine **8a** and 8 mg of starting material **6a**.

A solution of SmI_2 (4.2 mL, 0.411 mmol, 3 eq) in THF was added dropwise at room temperature to a degassed solution of isoxazolidine **11a** (0.075 g, 0.137 mmol) in THF (3 mL) under an argon atmosphere. After 30 min full conversion was reached and the reaction mixture was filtered through the alumina and solvent was evaporated. The purification using flash chromatography on a silica gel (EtOAc/hexanes 50/50) gave 51 mg (98%) of pyrrolidine **8a**.

Slightly yellow oil; $[\alpha]_D^{25}$ -35.2 (*c* 0.27, CH_2Cl_2); IR (film) 3485, 3090, 2795 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.37, 1.41, 1.48 [4xs, 12H, C($\underline{CH_3}$)$_2$], 1.88 (m, 1H, H-4a), 2.14 (ddd, 1H, H-4b, *J* = 4.4, 10.4, 15.6 Hz), 2.49

(dd, 1H, H-2a, *J* = 2.9, 9.6 Hz), 2.86 (m, 1H, H-5), 3.03 (dd, 1H, H-2b, *J* = 2.9, 9.6 Hz), 3.57 (dd, 1H, H-7, *J* = 4.3, 8.6 Hz), 3.71 (m, 2H, H-9a, N-$\underline{CH_2}$Ph), 3.98 (m, 5H, H-9b, N-$\underline{CH_2}$Ph, H-6, H-8, OH), 4.15 (m, 1H, H-3), 7.31 (m, 5H, N-CH$_2\underline{Ph}$); **^{13}C NMR** ($CDCl_3$) δ: 25.6, 26.2, 26.9, 27.1 [C($\underline{CH_3}$)$_2$], 34.2 (C-4), 58.1 (N-$\underline{CH_2}$Ph), 61.5 (C-5), 62.5 (C-2), 65.5 (C-9), 70.1 (C-3), 75.4 (C-8), 76.9 (C-6), 78.5 (C-7), 109.6, 109.7 [$\underline{C}$(CH$_3$)$_2$], 127.2-138.4 (N-CH$_2\underline{Ph}$); HRMS: (ESI-TOF) calcd. for $C_{21}H_{32}NO_5$ (MH^+) 378.2289, found 378.2280.

(*3R,5S*)-1-Benzyl-3-hydroxy-5-[1.2:3.4-di-*O*-isopropylidene-D-*xylo*-1-yl]pyrrolidine (8b).

A solution of SmI_2 (15 mL, 1.589 mmol, 3 eq) in THF was added dropwise at room temperature to degassed solution of the isoxazolidine **11b** (0.290 g, 0.530 mmol) in THF (5 mL) under an argon atmosphere. After 30 min full conversion was reached and the reaction mixture was filtered through the alumina and solvent was evaporated. The purification using flash chromatography on a silica gel (EtOAc/hexanes 50/50) gave 0.195 g (96%) of pyrrolidine **8b**.

Yellow oil; $[\alpha]_D^{25}$ -36.9 (*c* 0.32, $CHCl_3$); IR (film) 3400, 2984, 2931, 1454, 1379, 1247, 1213, 1156, 1065, 875, 700, 506 cm^{-1}; **^{1}H NMR** ($CDCl_3$), δ: 1.39, 1.40, 1.42, 1.43 [4xs, 12H, C($\underline{CH_3}$)$_2$], 1.77 (m, 1H, H-4a), 2.27 (m, 1H, H-4b), 2.46 (dd, 1H, H-2a, *J* = 5.1, 9.9 Hz), 3.04 (ddd, 1H, H-5, *J* = 2.6, 6.6, 10.3 Hz), 3.05 (br, 1H, O$\underline{H}$), 3.25 (dd, 1H, H-2b, *J* = 5.1, 9.9 Hz), 3.63 (dd, 1H, H-7, *J* = 4.0, 8.4 Hz), 3.73 (d, 1H, N-C$\underline{H_2}$Ph, *J* = 13.2 Hz), 3.76 (dd, 1H, H-9a, *J* = 6.6, 8.1 Hz), 3.90 (dd, 1H, H-9b, *J* = 6.6, 8.1 Hz), 4.00 (d, 1H, N-C$\underline{H_2}$Ph, *J* = 13.2 Hz), 4.01 (m, 1H, H-8), 4.16 (dd, 1H, H-6, *J* = 2.6, 8.4 Hz), 4.41 (m, 1H, H-3), 7.31 (m, 5H, N-CH$_2\underline{Ph}$); **^{13}C NMR** ($CDCl_3$), δ: 25.7, 26.2, 26.8, 27.1 [C($\underline{CH_3}$)$_2$], 34.8 (C-4), 58.4 (N-$\underline{CH_2}$Ph), 61.5 (C-5), 62.9 (C-2), 65.6 (C-9), 70.1 (C-3), 75.3 (C-8), 76.1 (C-6), 78.0 (C-7), 109.5, 109.6 [$\underline{C}$(CH$_3$)$_2$], 127.2-138.7 (N-CH$_2\underline{Ph}$); TOF MS ESI: calcd. for $C_{21}H_{32}NO_5$ (MH^+) 378.2280, found 378.2053.

(*3S,5S*)-1-Benzyl-3-hydroxy-5-[1,2-*O*-isopropylidene-3,4-dihydroxy-D-*xylo*-1-yl]pyrrolidine (9a).

The pyrrolidinone **7a** (0.045 g, 0.127 mmol) in THF (5 mL) was added to a refluxed suspension of LAH (0.03 g, 0.768 mmol) in THF (5 mL) under an argon atmosphere. The mixture was allowed to stirr for another 4 h and reaction was quenched by adding of saturated aqueous $NaHCO_3$ (5 mL), filtered and washed with THF. Water phase was extracted with Et_2O and combined organic layers were dried and concentrated in rotatory evaporator. The separation using flash chromatography (silica gel, EtOAc/hexanes 50/50) gave 22 mg (51%) of pyrrolidine **9a**.

Slightly yellow oil; **^{1}H NMR** ($CDCl_3$) δ: 1.42, 1.46 [2xs, 6H, C($\underline{CH_3}$)$_2$], 1.88 (m, 1H, H-4a), 2.16 (m, 2H, H-4b, OH), 2.50 (dd, 1H, H-2a, *J* = 3.2, 9.9 Hz), 2.51 (br, 1H, OH), 2.93 (m, 1H, H-3), 3.01 (m, 1H, H-2b), 3.58 (m, 1H, H-3′), 3.66 (m, 4H, H-4′, H-2′, N$\underline{CH_2}$Ph), 3.96 (d, 1H, N$\underline{CH_2}$Ph, *J* = 13.5 Hz), 4.16 (m, 3H, H-5, H-1′, OH), 7.31 (m, 5H, NCH$_2\underline{Ph}$); **^{13}C NMR** ($CDCl_3$) δ: 26.9, 27.2 [C($\underline{CH_3}$)$_2$], 34.5 (C-4), 58.5

(N$\underline{CH_2}$Ph), 61.6 (C-3), 62.3 (C-2), 64.4 (C-4′), 70.2 (C-3′), 70.4 (C-5), 77.2 (C-1′), 79.8 (C-2′), 109.5 [$\underline{C}(CH_3)_2$], 127.2-138.2 (NCH$_2\underline{Ph}$).

(*3S,5S*)-2-Benzyl-5-hydroxymethyl-3-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl] isoxazolidine (10a)

A solution of ester **5a** (0.65 g, 1.54 mmol) under an argon atmosphere was dissolved in dry THF (10 mL) and cooled down to -10 °C. Afterwards a solution of DIBAL in toluene (2.6 mL, 3.2 mmol, 2.5 eq) was dropped during 25 min. The reaction was quenched by adding MeOH (1 mL) after 2 h. Subsequently a solution of sodium-potassium tartrate in water was poured into a mixture and it was vigorously stirred during 30 min. Then 20 mL of CH_2Cl_2 was added to the mixture, layers were separated and water layer was extracted with EtOAc (4 x 30 mL). Combined organic layers were dried with sodium sulfate and evaporated. The reaction mixture was concentrated and submitted to flash column chromatography (silica gel, EtOAc/hexanes 50/50) to furnish hydroxymethyl derivative **10a** in 98% yield.

Colorless oil; $[\alpha]_D^{25}$ -11.3 (*c* 0.4, CH_2Cl_2); IR (film) 3479, 2985, 2932, 2862, 1604, 1453, 1275, 1088, 1073, 733 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.32, 1.39, 1.42 [4xs, 12H, C($\underline{CH_3}$)$_2$], 1.96 (br, 1H, OH), 2.32 (m, 1H, H-4b), 2.46 (ddd, 1H, H-4a, *J* = 2.4, 7.4, 10.0 Hz), 3.20 (ddd, 1H, H-3, *J* = 2.4, 7.4, 10.0 Hz), 3.51 (dd, 1H, H-7, *J* = 4.4, 6.7 Hz), 3.62 (dd, 1H, H-10a, *J* = 5.2, 11.9 Hz), 3.86 (m, 1H, H-6), 3.81 (m, 1H, H-10b), 3.89 (d, 1H, N-$\underline{CH_2}$Ph, *J* = 12.7 Hz), 3.94 (m, 2H, H-9a, H-9b), 4.10 (d, 1H, N-$\underline{CH_2}$Ph, *J* = 12.7 Hz), 4.15 (dd, 1H, H-8, *J* = 6.7, 11.6 Hz), 4.28 (m, 1H, H-5), 7.33 (m, 5H, N-CH$_2\underline{Ph}$); **^{13}C NMR** ($CDCl_3$) δ: 25.8, 26.4, 27.1, 27.4 [C($\underline{CH_3}$)$_2$], 30.8 (C-4), 62.8 (N-$\underline{CH_2}$Ph), 64.1 (C-10), 65.8 (C-9), 66.8 (C-3), 76.2 (C-8), 76.3 (C-6), 79.6 (C-5), 80.2 (C-7), 109.8, 109.6 [$\underline{C}(CH_3)_2$], 127.8-136.4 (N-CH$_2\underline{Ph}$); TOF MS ESI: calcd. for $C_{21}H_{32}NO_6$ (MH^+) 394.2230, found 394.2224.

(*3S,5R*)-2-Benzyl-5-hydroxymethyl-3-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl] isoxazolidine (10b).

A solution of ester **5b** (0.45 g, 1.07 mmol) under an argon atmosphere was dissolved in dry THF (10 mL) and cooled down to -10 °C. Afterwards a solution of DIBAL in toluene (1.8 mL, 2.2 mmol, 2.5 eq) was dropped during 25 min. The reaction was quenched by adding MeOH (1 mL) after 2 h. Subsequently a solution of sodium-potassium tartrate in water was poured into a mixture and it was vigorously stirred during 30 min. Then 20 mL of CH_2Cl_2 was added to the mixture, layers were separated and water layer was extracted with EtOAc (4 x 30 mL). Combined organic layers were dried with sodium sulfate and the solvent was evaporated. The obtained residue was then submitted to flash column chromatography (silica gel, EtOAc/hexanes 50/50) to furnish product **10b** (95%).

Colorless oil; $[\alpha]_D^{25}$ -25.9 (*c* 0.56, $CHCl_3$); IR (film) 3446, 2985, 2934, 1455, 1369, 1250, 1211, 1064, 881, 845, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$), δ: 1.30, 1.38, 1.39, 1.41 [4xs, 12H, C($\underline{CH_3}$)$_2$], 2.25 (ddd, 1H, H-4a, *J* = 3.2, 7.1, 12.9 Hz), 2.29 (br, 1H, O$\underline{H}$), 2.56 (dt, 1H, H-4b, *J* = 8.4, 12.9 Hz), 3.23 (ddd, 1H, H-3, *J* = 3.2, 8.4

Hz), 3.45 (dd, 1H, H-7, *J* = 4.8, 6.7 Hz), 3.67 (m, 1 H, H-10a), 3.80 (m, 1H, H-10b), 3.81 (d, 1H, N-C$\underline{H_2}$Ph, *J* = 12.5 Hz), 3.86 (m, 1H, H-6), 3.92 (m, 2H, H-9a, H-9b), 4.08 (d, 1H, N-C$\underline{H_2}$Ph, *J* = 12.5 Hz), 4.15 (ddd, 1H, H-8, *J* = 4.8, 6.4, 11.2 Hz), 4.50 (m, 1H, H-5), 7.33 (m, 5H, N-CH$_2\underline{Ph}$); **^{13}C NMR** ($CDCl_3$), δ: 27.4, 27.1, 26.3, 25.7 [C($\underline{CH_3}$)$_2$], 31.8 (C-4), 61.0 (N-$\underline{CH_2}$Ph), 63.3 (C-10), 65.9 (C-9), 66.9 (C-3), 76.3 (C-3′), 77.8 (C-5), 78.4 (C-1′), 80.5 (C-2′), 109.5, 109.6 [$\underline{C}$(CH$_3$)$_2$], 127.8-136.3 (N-CH$_2\underline{Ph}$); TOF MS ESI: calcd. for $C_{21}H_{32}NO_6$ (MH^+) 394.2230, found 394.2155.

(*3S,5S*)-2-Benzyl-5-tosyl-oxymethyl-3-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl]isoxazolidine (11a).
Hydroxymethyl isoxazolidine **10a** (0.2 g, 0.506 mmol) was placed into the reaction flask under an argon atmosphere and dissolved in dry CH_2Cl_2 (5 mL). Et_3N (0.21 mL, 1.52 mmol, 3 eq), solution of DMAP (0.014 g, 0.1 mmol) and TosCl (0.12 g, 0.607 mmol, 1.2 eq) in CH_2Cl_2 (5 mL) were added successively. The mixture was stirred for 24 h and controlled using TLC (EtOAc/hexanes 50/50). When all the starting material was consumed, reaction mixture was concentrated and submitted to flash column chromatography (silica gel, EtOAc/hexanes 50/50) to give compound **11a** in 95% yield.
Colorless solid; mp 105-108 °C; $[\alpha]_D^{25}$ -7.5 (*c* 2.0, CH_2Cl_2); IR (film) 3030, 2984, 2866, 1368, 1250, 1069, 1028, 879, 734, 698, 607, 508 cm^{-1}; **^{1}H NMR** δ: 1.28, 1.37, 1.39 [4xs, 12H, C($\underline{CH_3}$)$_2$], 2.31 (m, 1H, H-4b), 2.44 (s, 3H, O-SO$_2$Ph-$\underline{Me}$), 2.52 (ddd, 1H, H-4a, *J* = 2.2, 7.6, 12.7 Hz), 3.19 (ddd, 1H, H-3, *J* = 2.2, 7.6 Hz), 3.45 (dd, 1H, H-7, *J* = 4.9, 6.9 Hz), 3.75 (d, 1H, N-$\underline{CH_2}$Ph, *J* = 12.7 Hz), 3.79 (m, 1H, H-6), 3.90 (m, 2H, H-9a, H-9b), 4.00 (d, 1H, N-$\underline{CH_2}$Ph, *J* = 12.7 Hz), 4.12 (m, 3H, H-10a, H-10b, H-6), 4.33 (m, 1H, H-5), 7.30 [m, 7H, (O-SO$_2\underline{Ph}$-Me), (N-$\underline{CH_2}$Ph)], 7.78 [d, 2H, (O-SO$_2\underline{Ph}$-Me), *J* = 8.2 Hz]; **^{13}C NMR** δ: 21.6 (O-SO$_2$Ph-$\underline{Me}$), 25.7, 26.3, 27.0, 27.3 [C($\underline{CH_3}$)$_2$], 31.3 (C-4), 62.8 (N-$\underline{CH_2}$Ph), 65.7 (C-9), 66.8 (C-3), 69.9 (C-10), 76.2 (C-8), 76.4 (C-6, C-5), 80.3 (C-7), 109.6, 109.8 [C($\underline{CH_3}$)$_2$], 127.7-136.4 (N-CH$_2\underline{Ph}$), 145.0 (O-SO$_2\underline{Ph}$-Me); HRMS: (ESI-TOF) calcd. for $C_{28}H_{38}NO_8S$ (MH^+) 548.2318 , found 548.2314.

(*3S,5R*)-2-Benzyl-5-tosyl-oxymethyl-3-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl]isoxazolidine (11b).
Hydroxymethyl isoxazolidine **10b** (0.12 g, 0.306 mmol) was placed into the reaction flask under an argon atmosphere and dissolved in dry CH_2Cl_2 (5 mL). Et_3N (0.12 mL, 0.918 mmol, 3 eq), DMAP (0.012 g, 0.306 mmol) and TosCl (0.065 g, 0.337 mmol, 1.1 eq) were added successively. The reaction mixture was stirred at room temperature and controlled using TLC EtOAc/hexanes 50/50. After 2 h all the starting material was consumed, reaction mixture was concentrated and submitted to flash chromatography (silica gel, EtOAc/hexanes 50/50) to give compound **11b** in 98% yield.
Colorless solid; mp 84-86 °C; $[\alpha]_D^{25}$ -22.7 (*c* 0.19, $CHCl_3$); IR (film) 2984, 2933, 1366, 1189, 1175, 1157, 1067, 969, 813, 664, 554 cm^{-1}; **^{1}H NMR** δ: 1.25, 1.36, 1.37, 1.40 [4xs, 12H, C($\underline{CH_3}$)$_2$], 2.17 (ddd, 1H, H-4, *J* = 2.9, 6.4, 13.2 Hz), 2.45 (s, 3H, (O-SO$_2$Ph-$\underline{Me}$), 2.60 (dt, 1H, H-4, *J* = 8.4, 13.2 Hz), 3.19 (ddd, 1H, H-3,

J = 2.9, 8.0 Hz), 3.38 (dd, 1H, H-7, *J* = 5.5, 6.4 Hz), 3.65 (dd, 1H, H-6, *J* = 6.4, 8.0 Hz), 3.73 (d, 1H, N-C$\underline{H_2}$Ph, *J* = 12.5 Hz), 3.86 (m, 2H, H-9a, H-9b), 4.04 (d, 1H, N-C$\underline{H_2}$Ph, *J* = 12.5 Hz), 4.14 (m, 3H, H-10a, H-10b, H-8), 4.55 (m, 1H, H-5), 7.32 [m, 7H, (O-$SO_2\underline{Ph}$-Me), (N-$CH_2\underline{Ph}$)], 7.80 [d, 2H, (O-$SO_2\underline{Ph}$-Me), *J* = 8.2 Hz]; **^{13}C NMR** δ: 21.6 (O-SO_2Ph-$\underline{Me}$), 25.7, 26.4, 27.1, 27.4 [C($\underline{CH_3}$)$_2$], 32.5 (C-4), 60.8 (N-$\underline{CH_2}$Ph), 65.8 (C-9), 66.6 (C-3), 69.6 (C-10), 74.8 (C-5), 76.7, 77.9 (C-6), (C-8), 80.8 (C-7), 109.5, 109.7 [C($\underline{CH_3}$)$_2$], 127.9-144.9 (N-$CH_2\underline{Ph}$, O-$SO_2\underline{Ph}$-Me); TOF MS ESI: calcd. for $C_{28}H_{38}NO_8S$ (MH^+) 548.2276, found 548.2318.

(*3S,5S*)-3-Hydroxy-5-[1,2,3,4-tetrahydroxy-D-*xylo*-1-yl]pyrrolidine (12a).

Pyrrolidine **8a** (0.150 g, 0.398 mmol) was dissolved in MeOH/water (8/4 mL) and conc. HCl (0.2 mL) was added subsequently. Reaction mixture was stirred at 50 ^{o}C for 12 h, concentrated and dissolved in MeOH (6 mL). Pd-C (50 mg) was added and hydrogenation with baloon was performed. After 20 h, reaction was finished and the reaction mixture was concentrated and purified through DOWEX 50WX8 200-400 resin (H^+ form) to give polyhydroxylated pyrrolidine **12a** in a yield of 91% (0.077 g) after two steps.

Slightly yellow foam; $[\alpha]_D^{25}$ -18.9 (*c* 0.35, MeOH); IR (film) 3267, 2930, 1615, 1541, 1405, 1336, 1232, 1033, 861, 750, 603 cm^{-1}; **^{1}H NMR** (CD_3OD) δ: 1.85 (ddd, 1H, H-4a, *J* = 3.8, 7.7, 13.5 Hz), 2.25 (m, 1H, H-4b), 3.02 (m, 2H, H-2a, H-2b), 3.52 (ddd, 1H, H-5, *J* = 7.7, 13.5 Hz), 3.70 (m, 3H, H-8, H-9a, H-9b), 3.76 (m, 1H, H-7), 3.87 (dd, 1H, H-6, *J* = 4.5 Hz), 4.43 (m, 1H, H-3); **^{13}C NMR** (CD_3OD) δ: 36.8 (C-4), 55.0 (C-2), 61.5 (C-5), 64.2 (C-9), 72.1 (C-3), 72.8 (C-8), 73.4 (C-6), 73.7 (C-7); TOF MS ESI: calcd. for $C_8H_{18}NO_5$ (MH^+) 208.1185, found 208.1183.

(*3R,5S*)-3-Hydroxy-5-[1,2,3,4-tetrahydroxy-D-*xylo*-1-yl]pyrrolidine (12b).

Pyrrolidine **8b** (0.25 g, 0.663 mmol) was dissolved in MeOH/water (10/5 mL) and conc. HCl (0.4 mL) was added subsequently. Reaction mixture was stirred at 50 ^{o}C for 12 h, concentrated and dissolved in MeOH (10 mL). Pd-C (75 mg) was added and hydrogenation with baloon was performed. After 48 h, the reaction was concentrated and purified through DOWEX 50WX8 200-400 resin (H^+ form) to give polyhydroxylated pyrrolidine **12b** in 94% (0.130 g) overall yield after two steps.

Slightly yellow oil $[\alpha]_D^{25}$ -11.6 (*c* 0.85, H_2O); IR (film) 3260, 2930, 1621, 1532, 1409, 1213, 1054, 748, 602 cm^{-1}; **^{1}H NMR** (CD_3OD) δ: 1.87 (ddd, 1H, H-4a, *J* = 5.3, 9.7, 13.5 Hz), 1.94 (ddd, 1H, H-4b, *J* = 6.6, 13.5 Hz), 2.89 (dd, 1H, H-2a, *J* = 12.0 Hz), 3.12 (dd, 1H, H-2b, *J* = 4.4, 12.0 Hz), 3.68 (m, 6H, H-9a, H-9b, H-5, H-6, H-7, H-8), 4.40 (m, 1H, H-5); **^{13}C NMR** (CD_3OD) δ: 37.8 (C-4), 55.2 (C-2), 60.5 (C-5), 64.2 (C-9), 72.7 (C-3), 72.9, 73.8, 73.9 (C-6, C-7, C-8); TOF MS ESI: calcd. for $C_8H_{18}NO_5$ (MH^+) 208.1185, found 208.1198.

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13. Crystallograhic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 829 834 and CCDC 829 835. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1E2, UK, (fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.uk).
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