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1,3-Dipolar Cycloaddition of D-Xylose Derived Nitrone with Methyl Acrylate and its Utilization in Synthesis of Chiral Polyhydroxylated Pyrrolidinones and Pyrrolidines

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Abstract

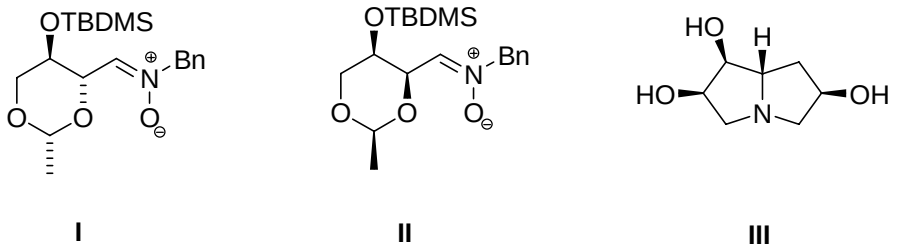
The cycloaddition of the chiral nitrone **IV** derived from D-xylose with methyl acrylate proceeded with very good diastereoselectivity for the *anti-trans* isoxazolidine **Va**. Its subsequent transformations to novel chiral polyhydroxylated pyrrolidinones and pyrrolidines are described. The results show that the method has potential use in the preparation of pyrrolidinones and pyrrolidines containing carbohydrate residues.

Keywords: chiral nitrones, pyrrolidines, cycloadditions

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 (Osborn 2002). 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 (Pellissier 2007). 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 (Fišera 2007). With the goal of developing a simple route to the synthesis of polyhydroxylated derivatives (**III**) such as of pyrrolizidines displaying antiviral activities, we

have developed 1,3-dipolar cycloadditions of D-erythrose (**I**) and D-threose (**II**) derived nitrones with alkenes (Kubáň 2001, Fig. 1). With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions (Blanáriková-Hlobilová 2003, Dugovič 2005, Fischer 2002, Hýrošová 2008,), we are now extending the 1,3-dipolar cycloaddition approach to synthesize novel chiral polyhydroxylated pyrrolidinones and pyrrolidines by reaction of readily available chiral sugar derived D-xylosyl nitrone **IV** (Fischer 2002) to methyl acrylate with the subsequent reductions of the formed isoxazolidines. 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 (Daly 2005, Dong 2008).



I **II** **III**

Fig. 1

Experimental

All commercially available starting materials and reagents (Fluka, Merck, Across or Aldrich) were used without further purification. Solvents were dried before use. Thin-layer chromatography (TLC, ALUGRAM Sil G/UV_{254} Macherey-Nagel) was used for monitoring of reaction courses; eluents are given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040-0.063 mm, Merck). The ^{1}H and ^{13}C NMR spectra of deuterochloroform solutions were obtained using Varian INOVA-600 (600 MHz) and VXR-300 (300 MHz) instruments, tetramethylsilane (TMS) being the internal reference. Specific rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell. MS and HRMS analyses were performed on Varian Ionspec QFT-7 (ESI-FT ICRMS).

1,3-Dipolar cycloaddition of nitrone IV with methyl acrylate

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

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

Yield 62 % (colorless oil). $[\alpha]_D$ = -2.3 (CH_2Cl_2, c 0.44). ^{1}H NMR δ: 1.28, 1.38, 1.39, 1.41 [s, 12H, $C(CH_3)_2$], 2.75 (m, 1H, H-4a), 2.81 (m, 1H, H-4b), 3.33 (m, 1H, H-3), 3.48 (dd, 1H, H-2´, J = 5.3 Hz, 6.7 Hz), 3.75 (m, 1H, H-1´), 3.77 (d, 1H, NCH_2Ph, J = 12.3 Hz), 3.79 (s, 3H, COOMe), 3.94 (d, 2H, H-4´a, H-4´b, J = 7.0 Hz), 4.16 (dd, 1H, H-3´, J = 6.7 Hz, 12.0 Hz), 4.25 (d, 1H, NCH_2Ph, J = 12.3 Hz), 4.63 (dd, 1H, H-5, J = 8.5 Hz), 7.31 (m, 5H, NCH_2Ph). ^{13}C NMR δ: 25.8, 26.4, 27.2, 27.4 [$C(CH_3)_2$], 33.7 (C-4), 52.5 (COOMe), 62.4 (NCH_2Ph), 67.4 (C-3), 68.5 (C-4´), 76.7 (C-1´, C-3´), 76.8 (C-5), 80.9 (C-2´), 109.5, 109.9 [$C(CH_3)_2$], 127.6-136.4 (NCH_2Ph), 173.0 (C=O). IR (film) $\tilde{\nu}$ = 3435, 3088, 2986, 2937, 1748 HRMS: (ESI-TOF) Calcd. for $[M+H]^+$, 444.1998, found: 444.1999.

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

Yield 12 % (colorless oil). $[\alpha]_D$ = -26.6 (CH_2Cl_2, c 0.62). ^{1}H NMR δ: 1.26, 1.38, 1.41 [s, 12H, $C(CH_3)_2$], 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-2´, J = 5.9 Hz), 3,75 (m, 1H, H-1´), 3.80 (m, 5H, NCH_2Ph, OMe, H-1‘), 3.95 (m, 2H, H-4‘), 4.12 (m, 2H, H-3´, NCH_2Ph), 4.80 (dd, 1H, H-5, J = 5.9, 9.5 Hz), 7.32 (m, 5H, NCH_2Ph). ^{13}C NMR δ: 25.7, 26.4, 27.2, 27.4 [$C(CH_3)_2$], 34.4 (C-4), 52.4 (COOMe), 61.1 (NCH_2Ph), 65.8 (C-4´), 66.5 (C-3), 75.5 (C-5), 76.8 (C-3´), 77.6 (C-1’) 80.9 (C-2´), 109.5, 109.7 [$C(CH_3)_2$], 127.9-135.7 (NCH_2Ph), 171.2 (C=O). IR (film) $\tilde{\nu}$ = 3435, 3088, 2986, 2937, 1748. HRMS: (ESI-TOF) Calcd. for $[M+H]^+$, 444.1998, found: 444.2009.

(*3S,5S*)-1-Benzyl-3-hydroxy-5-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl]pyrrolidin-2-one (VI) and (*3S,5S*)-1-benzyl-3-hydroxy-5-[1,2-*O*-isopropylidene-3,4-dihydroxy-D-*xylo*-1-yl]pyrrolidin-2-one (VII).

A solution of cycloadduct **Va** (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 ^{o}C for 5 h. Reaction was controlled with TLC. Saturated solution $NaHCO_3$ was added after reaction and 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 ethyl acetate – hexanes (50 /50) to give 0.143 g of **VI** (33%) a 0.181 g of **VII** (46%).

VI. Yield 33 % (m.p. 183 °C). $[\alpha]_D$ = -1.6 (CH_2Cl_2, c 0.96). ^{1}H NMR δ: 1.30, 1.35, 1.44 [s, 12H, $C(CH_3)_2$], 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, J = 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, NCH_2Ph, J = 15.3 Hz), 4.28 (m, 1H, H-3), 4.32 (m, 1H, H-3´), 5.02 (d, 1H, NCH_2Ph, J = 15.3 Hz), 7.27 (m, 5H, NCH_2Ph). ^{13}C NMR δ: 25.4, 26.0, 26.8, 27.0 [$C(CH_3)_2$], 27.9 (C-4), 44.6 (NCH_2Ph), 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 [$C(CH_3)_2$], 127.9-135.7 (NCH_2Ph), 174.2 (C-2).

VII. Yield 46 % (colourless oil). $[\alpha]_D$ = -9.6 (CH_2Cl_2, c 0.25). ^{1}H NMR δ: 1.34, 1.44 [s, 6H, $C(CH_3)_2$], 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, NCH_2Ph, 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, NCH_2Ph, J = 15.4 Hz), 7.29 (m, 5H, NCH_2Ph). ^{13}C NMR δ: 26.7, 27.0 [$C(CH_3)_2$], 27.9 (C-4), 44.8 (NCH_2Ph), 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 [$C(CH_3)_2$], 127.9-135.7 (NCH_2Ph), 174.5 (C-2). IR (film) $\tilde{\nu}$ = 3470, 3400, 3205 cm^{-1} (-OH), 3065- 2855 (=C-H, C-H), 1690 (C=O). 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 (VIII).

The pyrrolidinone **VI** (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 $NaHCO_3$ (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 on a silica gel using ethyl acetate – hexanes (50 /50) gave 25 mg (50%) of pyrrolidine **VIII** as slightly yellow oil and 8 mg of starting material **VI**.

Yield 50 % $[\alpha]_D$ = -35.2 (CH_2Cl_2, c 0.27). ^{1}H NMR δ: 1.37, 1.41, 1.48 [s, 12H, $C(CH_3)_2$], 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-3), 3.03 (dd, 1H, H-2b, J = 2.9, 9.6 Hz), 3.57 (dd, 1H, H-2′, J = 4.3, 8.6 Hz), 3.71 (m, 2H, H-4′a, NCH_2Ph), 3.98 (m, 5H, H-4′b, NCH_2Ph, H-1′, H-3′, OH), 4.15 (m, 1H, H-5), 7.31 (m, 5H, NCH_2Ph). ^{13}C NMR δ: 25.6, 26.2, 26.9, 27.1 $[C(CH_3)_2]$, 34.2 (C-4), 58.1 (NCH_2Ph), 61.5 (C-3), 62.5 (C-2), 65.5 (C-4′), 70.1 (C-5), 75.4 (C-3′), 76.9 (C-1′), 78.5 (C-2′), 109.6, 109.7 $[C(CH_3)_2]$, 127.2-138.4 (NCH_2Ph). IR (film) $\tilde{\nu}$ = 3485 cm^{-1} (-OH), 3090- 2795 cm^{-1}(=C-H, C-H). HRMS: (ESI-TOF) Calcd. for $[M+H]^+$, 378.2289, found: 378.2280.

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

The pyrrolidinone **VII** (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 4h and reaction was quenched by adding of saturated $NaHCO_3$ (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 on a silica gel using ethyl acetate – hexanes (50 /50) gave 22 mg (51%) of pyrrolidine **IX** as slightly yellow oil.

Yield 51 %. ^{1}H NMR δ: 1.42, 1.46 [s, 6H, $C(CH_3)_2$], 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′, NCH_2Ph), 3.96 (d, 1H, NCH_2Ph, J = 13.5 Hz), 4.16 (m, 3H, H-5, H-1′, OH), 7.31 (m, 5H, NCH_2Ph). ^{13}C NMR δ: 26.9, 27.2 $[C(CH_3)_2]$, 34.5 (C-4), 58.5 (NCH_2Ph), 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 $[C(CH_3)_2]$, 127.2-138.2 (NCH_2Ph).

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

Solution of ester **Va** (0.65 g, 1.54 mmol) under an argon atmosphere was dissolved in dry THF (10 mL) and cooled down to -10 ^{o}C. Afterwards a solution of DIBAL in toluene (2.6 ml, 3.2 mmol, 2.5 equiv) was dropped during 25 min. The reaction was quenched by adding MeOH (1 mL) after 2h. 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, water layer was extracted with ethyl acetate (4 x 30 mL). Combined organic layers were dried with sodium sulfate and evaporated.

Yield 99 % (colourless oil). $[\alpha]_D$ = -11.3 (CH_2Cl_2, c 0.4). ^{1}H NMR δ: 1.32, 1.39, 1.42 [s, 12H, $C(CH_3)_2$], 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-2´, J = 4.4, 6.7 Hz), 3.62 (dd, 1H, H-5´a, J = 5.2 , 11.9 Hz), 3.81 (m, 1H, H-5´b), 3.86 (m, 1H, H-1´), 3.89 (d, 1H, NCH_2Ph, J = 12.7 Hz), 3.94 (m, 2H, H-4´a, H-4´b), 4.10 (d, 1H, NCH_2Ph, J = 12.7 Hz), 4.15 (dd, 1H, H-3´, J = 6.7, 11.6 Hz), 4.28 (m, 1H, H-5), 7.33 (m, 5H, NCH_2Ph). ^{13}C NMR δ/ppm: 25.8, 26.4, 27.1, 27.4 [$C(CH_3)_2$], 30.8 (C-4), 62.8 (NCH_2Ph), 64.1 (C-5´), 65.8 (C-4´), 66.8 (C-3), 76.2 (C-3´), 76.3 (C-1´), 79.6 (C-5), 80.2 (C-2´), 109.6, 109.8 [$C(CH_3)_2$], 127.8-136.4 (NCH_2Ph). IR (film) $\tilde{\nu}$ = 3479, 2985, 2932.

(*3S,5S*)-5-(4-Methylphenyl)oxymethyl-2-benzyl-3-[1,2:3,4-di-*O*-isopropylidene-D-*xylo*-1-yl]isoxazolidine (XI).

Hydroxymethylisoxazolidine **X** (0.2 g, 0.506 mmol) was placed into reaction flask under an argon atmosphere and dissolved in dry CH_2Cl_2 (5 mL). Et_3N (0.21 mL, 1.52 mmol), solution of DMAP (0.014 g, 0.1 mmol) and tosylchloride (0.12 g, 0.607 mmol) in CH_2Cl_2 (5 mL) were added successively. Mixture was stirred for 24 h and controlled using TLC ethyl acetate – hexanes (50 /50). When all the starting material was consumed, reaction mixture was concentrated and submitted to flash column chromatography (silica gel, ethyl acetate – hexanes (50 /50) to give compound **XI** as colourless oil, later solidified in the fridge.

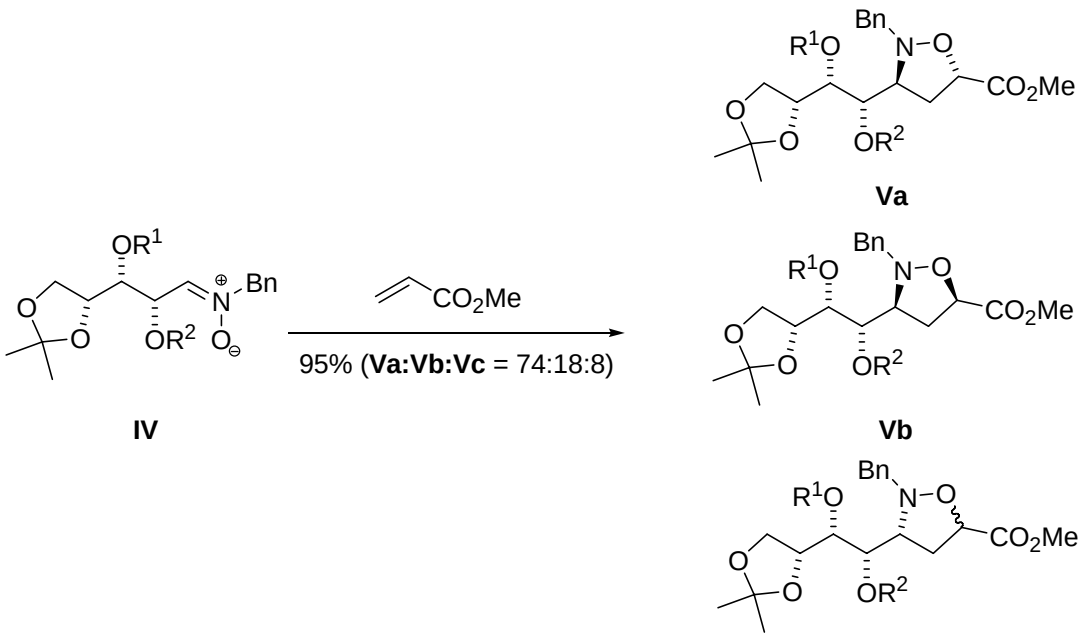
Yield 98 % (m.p. 105 °C). $[\alpha]_D$ = -7.5 (CH_2Cl_2, c 2.0). ^{1}H NMR δ: 1.28, 1.37, 1.39 [s, 12 H, $C(CH_3)_2$], 2.31 (m, 1 H, H-4), 2.44 (s, 3 H, (-O-SO_2Ph-Me), 2.52 (ddd, 1 H, H-4, J = 2.2, 7.6, 12.7 Hz), 3.19 (ddd, 1 H, H-3, J = 2.2, 7.6 Hz), 3.45 (dd, 1 H, H-2´, J = 4.9 Hz, 6.9 Hz), 3.75 (d, 1 H, NCH_2Ph, J = 12.7 Hz), 3.79 (m, 1 H, H-1´), 3.90 (m, 2 H, H-4´), 4.00 (d, 1 H, NCH_2Ph, J = 12.7 Hz), 4.12 (m, 3 H, H-5´, H-1´), 4.33 (m, 1 H, H-5), 7.30 [m, 7 H, (-O-SO_2Ph-Me), (NCH_2Ph)], 7.78 [d, 2 H, (-O-SO_2Ph-Me), J = 8.2 Hz]. ^{13}C NMR δ: 21.6 (-O-SO_2Ph-Me), 25.7, 26.3, 27.0, 27.3 [$C(CH_3)_2$], 31.3 (C-4), 62.8 (NCH_2Ph), 65.7 (C-4´), 66.8 (C-3), 69.9 (C-5´), 76.2 (C-3´), 76.4 (C-1´, C-5), 80.3 (C-2´), 109.6, 109.8 [$C(CH_3)_2$], 127.7, 128.5, 129.4, 136.4 (NCH_2Ph), 127.9, 129.9, 132.6, 145.0 (-O-SO_2Ph-Me). HRMS: (ESI-TOF) Calcd. for $[M+H]^+$, 548.2318 , found: 548.2314.

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

The solution of SmI_2 (4.2 ml, 0.411 mmol) in THF was dropwise added at room temperature to degassed solution of isoxazolidine **XI** (0.075 g, 0.137 mmol) in THF (3 ml) under an argon atmosphere. After 30 minutes 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 using ethyl acetate – hexanes (50 /50) gave 52 mg (100%) of pyrrolidine **VIII** as slightly yellow oil.

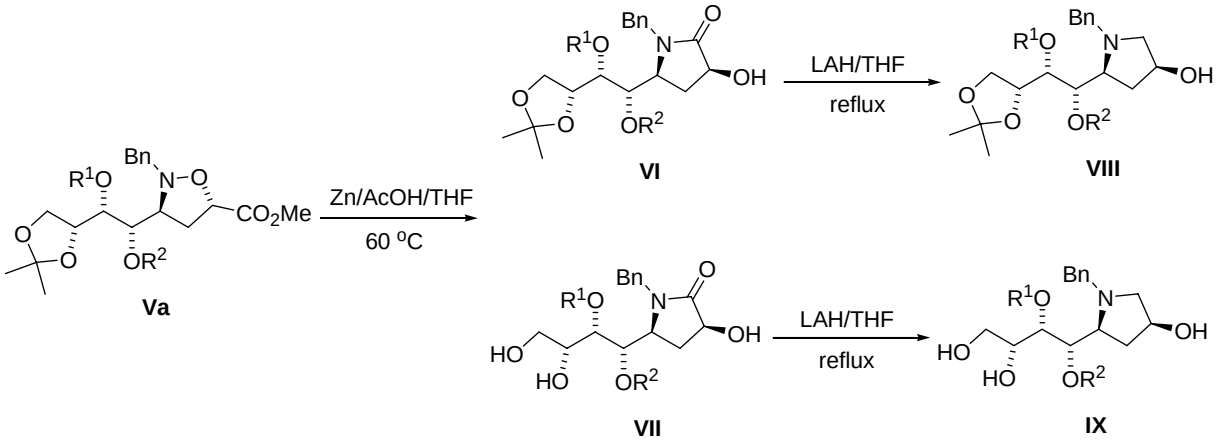
Results and Discussion

Nitrone **IV** reacted smoothly in methyl acrylate at room temperature over 24 h to give a 74:18:8 mixture of diastereoisomeric isoxazolidines **Va-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 **Va** 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 **Va**, with C-3/C-5 *trans* and *exo*-adduct **Vb**, with C-3/C-5 *cis* relative configuration identified by spectroscopic analysis, particularly NOE difference experiments. Based on our previous results from 1,3-dipolar cycloadditions of sugar derived nitrones bearing a protected hydroxy group in the α-position (Kubáň 2001) as well as to the fact that 1,3-dipolar cycloaddition of alkenes to chiral α-alkoxy nitrones gave preferentially *anti* adducts (Merino 2000, Fišera 2007) we assigned to isomers **Va** and **Vb** a C-1'/C-3 *anti* relationship as a result of dipolarophile attack from the less sterically hindered *si* diastereotopic face of nitrone **IV**. The relative configuration at the new stereogenic center in **Va** could not be assigned at this stage; however it was deduced from the structure of isoxazolidine **XI**, whose structure was established by X-ray diffraction studies (J. Kožíšek, unpublished results).



Scheme 1

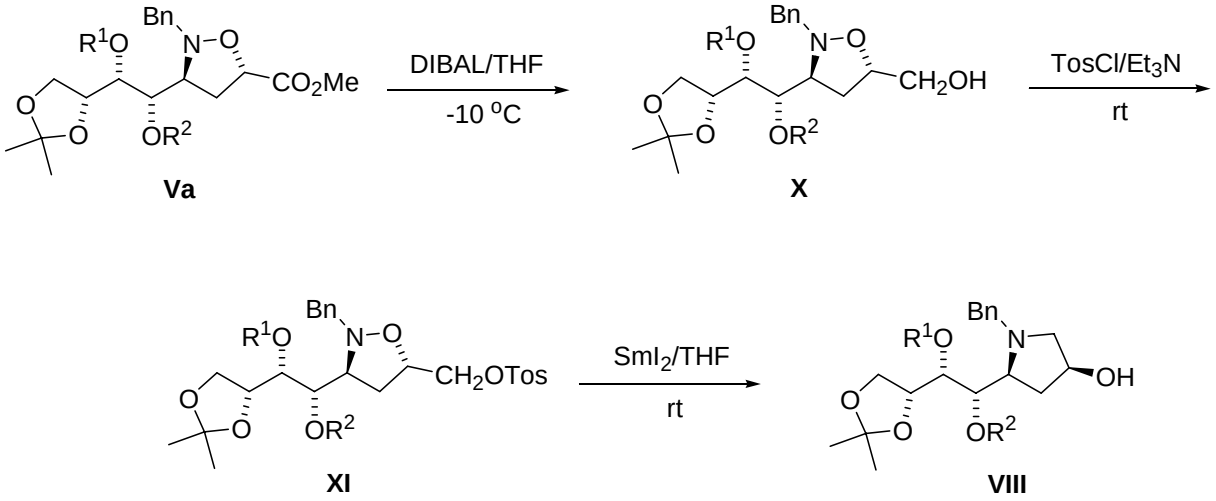
Considering the well-known propensity of isoxazolidines to be reduced to amines (Dugovič 2005, Fišera 2007), we have next prepared chiral polyhydroxylated pyrrolidinones (Rehák 2008) **VI** and **VII** in a single step from the major isoxazolidine **Va** involving N–O cleavage with Zn/AcOH and subsequent spontaneous cyclization in 33% and 46% yield, respectively. The origin of the pyrrolidinone **VII** can be explained by the partially hydrolysis of the primary formed pyrrolidinone **VI**. Finally, the pyrrolidinones **VI** and **VII** were reduced with $LiAlH_4$ in THF to afford the chiral polyhydroxylated pyrrolidines **VIII** and **IX** in 50% and 51% yield, respectively (Scheme 2).



R^1, R^2 = CMe_2

Scheme 2

As has been mentioned, the C-CO_2Me functionalized isoxazolidine **Va** 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 **Va** was reduced with DIBAL to yield the primary alcohol **X**. Treatment of the hydroxymethyl derivative **X** with excess tosyl chloride in the presence of triethylamine and catalytic amount of DMAP in CH_2Cl_2 furnished the spectroscopically pure tosylate **XI** in 98 % yield (Scheme 3). Finally, samarium diiodide-induced direct hydrogenolysis of **XI** in THF at room temperature resulted in a cascade reaction sequence involving isoxazolidine N–O bond cleavage and spontaneous cyclization affording pyrrolidine **VIII** in an excellent yield (100%).



R^1, R^2 = CMe_2

Scheme 3

In conclusion, the cycloaddition of the chiral nitrone **IV** derived from D-xylose with methyl acrylate proceeded with very good diastereoselectivity for the *anti-trans* isoxazolidine **Va**. Its reductive transformations provide entry to the optically active pyrrolidinones and pyrrolidines possessing structural similarities to the HIV inhibitors. This method opens a novel, short, and general route for the synthesis of biologically important hydroxylated pyrrolidinones and pyrrolidines containing carbohydrate residues.

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