

Full Paper

### Novel Furanoid α-Substitued α-Amino Acid as a Potent Turn Mimic in Peptide Synthesis

Miroslava Martinková \*, Jozef Gonda and Jana Raschmanová

Institute of Chemical Sciences, Department of Organic Chemistry, P. J. Šafárik University, Moyzesova 11, SK-040 01 Košice, Slovak Republic. Tel.: (+ 421) 556228332; Fax: (+ 421) 556222421 E-mails: Jozef Gonda: jgonda@kosice.upjs.sk, Jana Raschmanova: jrasch@pobox.sk

\* Author to whom correspondence should be addressed; e-mail: mmartin@kosice.upjs.sk

*Received: 23 June 2006; in revised form: 20 July 2006 / Accepted: 21 July 2006 / Published: 26 July 2006* 

**Abstract:** A stereoselective approach has been developed to the new sugar amino acid and potential potent turn mimic 5-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*isopropylidene-3-methoxycarbonylamino- $\alpha$ -D-xylofuranose 3-C-carboxylic acid (**12**), via the [3,3]-sigmatropic rearrangement of allylic thiocyanates (*Z*)-6 and (*E*)-7, prepared from D-xylose. The synthesis of a new dipeptide **13** is also described.

**Keywords:** Sugar amino acids, stereoselectivity, sigmatropic rearrangement, carbohydrate-based mimetics, peptidomimetic,  $\beta$ -turn mimic

#### Introduction

Sugar amino acids (SAAs) can be found in nature largely as a molecules that combine the structural features of simple amino acids with those of simple carbohydrates [1]. The resulting hybrid is a highly substitued polyfunctionalized synthon which can be used for the preparation of modified analogues of biologically active peptides and/or oligosaccharides. Sugar amino acids represent an important class of conformationally constrained templates that have been used extensively in recent years in many peptidomimetic studies [1, 2] and have emerged as attractive building blocks for the incorporation of a sugar moiety into short peptide sequences using standard peptide coupling techniques, thus opening the door to novel peptidomimetics. They are also known as  $\beta$ -turn mimics

and introduction of conformationally restricted nonpeptide isosteres into the peptide backbone to achieve desirable secondary structures is a great interest of many synthetic chemists [3].

#### **Results and Discussion**

We report herein a synthetic approach to 5-O-(tert-butyldimethylsilyl)-3-deoxy-1,2-Oisopropylidene-3-methoxycarbonylamino- $\alpha$ -D-xylofuranose 3-C-carboxylic acid (12) as a building block for peptide scaffold and conformationally restrained peptidomimetics. The Wittig reaction of 5-O-TBDMS-1,2-O-isopropylidene-α-D-erytro-pentofuranos-3-ulose known (1)[4] with ethoxycarbonylmethyl-enetriphenylphosphorane in dry dichloromethane gave, after chromatographic separation, pure (Z)- $\alpha$ , $\beta$ -unsaturated ester 2 and its (E)-isomer 3 (9.6:1, 90.5%) (Scheme 1). The Z and E configurations of the exocyclic double bond in 2 and 3 were determined by <sup>1</sup>H-NMR spectral analysis, including NOE data. The irradiation of the H-4 proton in 2 led to a 3.4 % enhancement of the intensity of H-6, while the irradiation of the H-6 proton resulted in a 3.9 % enhancement of the intensity of the H-4 signal, along with a small 1.3 % enhancement of the H-2 proton. On the other hand, when the H-2 proton in **3** was irradiated, a strong (5.0 %) NOE enhancement of the H-6 signal was observed, while the irradiation of the H-6 proton resulted in a 4.2 % enhancement of the intensity of the H-2 signal. Finally, the irradiation of the H-4 proton in 3 resulted in a 1.2 % enhancement of the intensity of the H-6 proton signal. Reduction of esters with LiAlH<sub>4</sub> in dry diethyl ether afforded the allylic alcohols (Z)-4 and (E)-5 in 96 and 72% yields, respectively, after silica-gel chromatography. The thiocyanates (Z)-6 and (E)-7 were prepared by  $S_N^2$  substitution of the O-mesyl group in the corresponding mesylates, derived from allylic alcohols (Z)-4 and (E)-5, by the thiocyanate group (KSCN/CH<sub>3</sub>CN) (Scheme 1).



The thermal rearrangements of thiocyanates (*Z*)-**6** and (*E*)-**7** was carried out in heptane under a N<sub>2</sub> atmosphere at 90 °C for 16 h and gave isothiocyanate **8** as the sole reaction product in 82 and 70% yields, respectively, after silica-gel chromatography. The epimeric isothiocyanate **8a** was not detected in the reaction mixtures. The stereochemistry of the new quarternary carbon center (C-3) introduced in **8** was determined as (*S*) by <sup>1</sup>H-NMR spectral analysis, including NOE data. Thus, when the H-4 proton was irradiated, a strong (8.2%) enhancement of the intensity of the H-6 signal was noted and the irradiation of the H-6 proton resulted in a 5.4 % enhancement of the intensity of the H-4 signal, indicating a *cis* relationship between the vinyl group and the H-4 proton on the furanoside ring (Figure 1).



In our subsequent strategy, the isolated isothiocyanate **8** was converted into the desired  $\alpha$ -substitued  $\alpha$ -amino acid **12**. In the first step, the isothiocyanate group was transformed into the thiourethane **9** in 95% yield after silica-gel chromatography by its reaction with CH<sub>3</sub>ONa in dry methanol at room temperature for 4 h. The thus prepared thiocarbamate **9** was converted into the corresponding oxygen derivative **10** by the action of mesitylnitrile oxide in acetonitrile (23 h, 93%) (Scheme 2).



#### Scheme 2.

The oxidation of carbamate **10** was accomplished with a catalytic amount of ruthenium (III) chloride and NaIO<sub>4</sub> in 2:2:3 CCl<sub>4</sub>/CH<sub>3</sub>CN/H<sub>2</sub>O to give aldehyde **11** in 70% yield. This aldehyde was then oxidized to the protected amino acid **12** in 74% yield (after flash chromatography) by treatment with sodium chlorite/2-methyl-2-butene (Scheme 2).

Among the methods available for the linkage of amino acids and peptides coupling with carbodiimides is one of the most frequently used. Our coupling reaction with DCC [5] and glycine methyl ester hydrochloride was performed in dry dichloromethane in the presence of  $Et_3N$  at 0 °C for 1 h and then for 18 h at room temperature to afford dipeptide **13** in 78% yield after silica-gel chromatography (Scheme 2).

#### Conclusions

In summary, a stereocontrolled synthesis of the nonproteinogenic  $\alpha$ -substitued  $\alpha$ -amino acid 12 employing thiocyanates (Z)-6 and (E)-7 as the educts has been reported. The coupling reaction between this sugar amino acid 12 and glycine methyl ester provided dipeptide 13 as a potent peptidomimetic.

#### Experimental

#### General

The melting points were determined on the Kofler block and are uncorrected. Optical rotations were measured in chloroform with a P3002 Krűss polarimeter and reported as follows:  $[\alpha]_D^{25}$  (*c* in g per 100 mL). NMR spectra were recorded at room temperature on a Varian Mercury *Plus* 400 FT NMR spectrometer (<sup>1</sup>H at 400.13 MHz and <sup>13</sup>C at 100.6 MHz). Chemical shifts are referenced either to tetramethylsilane used as internal standard for <sup>1</sup>H or to the solvent signal (<sup>13</sup>C-NMR,  $\delta$  CDCl<sub>3</sub>=77.0). <sup>13</sup>C-NMR multiplicities were determined by using a DEPT pulse sequence. Reactions were routinely monitored by TLC (Merck 60 F<sub>254</sub>) and the products were visualized by UV light absorption at 254 nm or by spraying with Mo-reagent or KMnO<sub>4</sub>-reagent. All reactions were performed under an atmosphere of nitrogen. Solvents were purified by standard procedures and distilled before use. Column chromatography was carried out on the glass columns using Kieselgel (0.035-0.070 mm) silica gel. *5-O-(tert-Butyldimethylsilyl)-1,2-O-isopropylidene-a-D-erythro-pentofuranosyl-3-ulose* (1) was prepared according to a published procedure [4].

### 5-O-(tert-Butyldimethylsilyl)-3-C-(Z)-carboethoxymethylene-3-deoxy-1,2-O-isopropylidene- $\alpha$ -D-xylo-furanose (2) and its (E)-isomer (3)

(Carboethoxymethylene)triphenylphosphorane (7.84 g, 22.4 mmol) was added to a solution of ketone **1** [4] (6.18 g, 20.4 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (80 mL). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (hexane-ethyl acetate, 13:1) to afford (*E*)-**3** (0.65 g, 8.5%) and (*Z*)-**2** (6.21 g, 82%) as colorless oils. Compound **3**:  $[\alpha]_D^{25} = +233.9$  (*c* 0.20); <sup>1</sup>H-NMR:  $\delta$  -0.01 (3H, s, CH<sub>3</sub>),

0.02 (3H, s, CH<sub>3</sub>), 0.86 (9H, s, 3 x CH<sub>3</sub>), 1.30 (3H, t, J = 7.2 Hz, CH<sub>3</sub>), 1.40 (3H, bs, CH<sub>3</sub>), 1.43 (3H, bs, CH<sub>3</sub>), 3.78 (1H, dd,  $J_{5,5}=10.4$  Hz,  $J_{5,4}=2.2$  Hz, H<sub>5</sub>), 3.93 (1H, dd,  $J_{5,5}=10.4$  Hz,  $J_{5,4}=1.6$  Hz, H<sub>5</sub>), 4.19 (2H, q, J = 7.2 Hz, CH<sub>2</sub>O), 5.03 (1H, ddd,  $J_{2,1}=4.7$  Hz,  $J_{2,4}=1.8$  Hz,  $J_{6,2}=1.8$  Hz, H<sub>2</sub>), 5.57-5.59 (1H, m, H<sub>4</sub>), 5.95 (1H, d,  $J_{2,1}=4.7$  Hz, H<sub>1</sub>), 6.13 (1H, dd,  $J_{6,4}=1.8$  Hz,  $J_{6,2}=1.8$  Hz, H<sub>6</sub>); <sup>13</sup>C-NMR:  $\delta$  -5.7, -5.5, 14.2, 18.2, 25.9 (3 x C), 27.7, 27.8, 60.5, 65.8, 82.4, 82.6, 104.5, 113.2, 116.2, 160.8, 165.5; Anal. Calcd for C<sub>18</sub>H<sub>32</sub>O<sub>6</sub>Si (372.54): C 58.03, H 8.66; found C 57.91, H 8.78. Compound **2**:  $[\alpha]_D^{25} = +131.3$  (c 0.20); <sup>1</sup>H-NMR:  $\delta$  0.05 (3H, s, CH<sub>3</sub>), 0.06 (3H, s, CH<sub>3</sub>), 0.88 (9H, s, 3 x CH<sub>3</sub>), 1.30 (3H, t, J = 7.1 Hz, CH<sub>3</sub>), 1.43 (3H, bs, CH<sub>3</sub>), 1.48 (3H, bs, CH<sub>3</sub>), 3.74 (1H, dd,  $J_{5,5}=10.7$  Hz,  $J_{5,4}=3.5$  Hz, H<sub>5</sub>), 3.79 (1H, dd,  $J_{5,5}=10.7$  Hz,  $J_{5,4}=4.3$  Hz, H<sub>5</sub>), 4.25 (2H, q, J = 7.1 Hz, CH<sub>2</sub>O), 4.84-4.87 (1H, m, H<sub>4</sub>), 5.64-5.66 (1H, m, H<sub>2</sub>), 5.91 (1H, d,  $J_{1,2}=4.1$  Hz, H<sub>1</sub>), 6.01 (1H, dd,  $J_{6,2}=1.7$  Hz,  $J_{6,4}=1.7$  Hz H<sub>6</sub>); <sup>13</sup>C-NMR:  $\delta$  -5.6, -5.5, 14.1, 18.1, 25.7(3 x C), 27.2, 27.5, 60.5, 65.3, 78.8, 81.0, 105.4, 112.7, 116.5, 156.8, 164.9; Anal. Calcd for C<sub>18</sub>H<sub>32</sub>O<sub>6</sub>Si (372.54): C 58.03, H 8.66; found C 58.15, H 8.55.

# $5-O-(tert-Butyldimethylsilyl)-3-deoxy-3-C-(E)-(2-hydroxyethylidene)-1,2-O-isopropylidene-\alpha-D-xylo-furanose (5)$

LiAlH<sub>4</sub> (0.045 g, 1.18 mmol) was added at 0 °C to a solution of (*E*)-**3** (0.44 g, 1.18 mmol) in dry Et<sub>2</sub>O (7.2 mL). The reaction mixture was stirred at 0 °C for 15 min and then for 1.5 h at room temperature. The reaction was quenched by careful addition of water (0.3 mL) and the precipitate was removed by filtration. The filtrate was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 0.28 g (72 %) of allylic alcohol **5** as a white solid; m.p. 42 – 43 °C;  $[\alpha]_D^{25} = +79.6$  (*c* 0.20); <sup>1</sup>H-NMR:  $\delta$  -0.01 (3H, s, CH<sub>3</sub>), 0.06 (3H, s, CH<sub>3</sub>), 0.88 (9H, s, 3 x CH<sub>3</sub>), 1.41 (3H, bs, CH<sub>3</sub>), 1.45 (3H, bs, CH<sub>3</sub>), 2.18-2.30 (1H, m, OH), 3.68 (1H, dd, *J*<sub>5,5</sub>=10.8 Hz, *J*<sub>5,4</sub>=4.0 Hz, H<sub>5</sub>), 3.72 (1H, dd, *J*<sub>5,5</sub>=10.8 Hz, *J*<sub>5,4</sub>=2.9 Hz, H<sub>5</sub>), 4.16-4.18 (2H, m, H<sub>7</sub>), 4.95-4.97 (1H, m, H<sub>2</sub>), 5.05-5.09 (1H, m, H<sub>4</sub>), 5.84 (1H, d, *J*<sub>2,1</sub>=4.4 Hz, H<sub>1</sub>), 5.99-6.04 (1H, m, H<sub>6</sub>); <sup>13</sup>C-NMR:  $\delta$  -5.6, -5.4, 18.3, 25.8 (3 x C), 27.6, 27.9, 60.1, 66.1, 80.2, 82.4, 104.5, 112.8, 126.6, 140.8; Anal. Calcd for C<sub>16</sub>H<sub>30</sub>O<sub>5</sub>Si (330.50): C 58.15, H 9.15; found C 58.25, H 9.05.

### 5-O-(tert-Butyldimethylsilyl)-3-deoxy-3-C-(Z)-(2-hydroxymethylidene)-1,2-O-isopropylidene- $\alpha$ -D-xylo-furanose (4)

To a solution of (*Z*)-**2** (6.03 g, 16.2 mmol) in dry Et<sub>2</sub>O (100 mL) was added LiAlH<sub>4</sub> (0.61 g, 16.2 mmol) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C and then for 1 hour at room temperature. The reaction was quenched with water (4.2 mL) and the precipitate was removed by filtration. The filtrate was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue (hexane-ethyl acetate, 3:1) gave 5.14 g (96 %) of allylic alcohol **4** as a colorless oil;  $[\alpha]_D^{25}$ = +136.3 (*c* 0.79); <sup>1</sup>H-NMR:  $\delta$  0.04 (3H, s, CH<sub>3</sub>), 0.05 (3H, s, CH<sub>3</sub>), 0.88 (9H, s, 3 x CH<sub>3</sub>), 1.40 (3H, bs, CH<sub>3</sub>), 1.47 (3H, bs, CH<sub>3</sub>), 2.29-2.35 (1H, m, OH), 3.61 (1H, dd, *J*<sub>5,5</sub>=10.6 Hz, *J*<sub>5,4</sub>=3.4 Hz, H<sub>5</sub>), 3.74 (1H, dd, *J*<sub>5,5</sub>=10.6 Hz, *J*<sub>5,4</sub>=3.6 Hz, H<sub>5</sub>), 4.29 (1H, m, H<sub>7</sub>), 4.37 (1H, m, H<sub>7</sub>) 4.76-4.80 (1H, m, H<sub>4</sub>), 5.18-5.21 (1H, m, H<sub>2</sub>), 5.84 (1H, dddd, *J*<sub>7,6</sub>=6.3 Hz, *J*<sub>7,6</sub>=6.2 Hz, *J*<sub>6,2</sub>=1.9 Hz, *J*<sub>6,4</sub>=1.9 Hz, H<sub>6</sub>), 5.92 (1H, d, *J*<sub>2,1</sub>=4.5 Hz, H<sub>1</sub>); <sup>13</sup>C-NMR:  $\delta$  -5.5, -5.4, 18.2, 25.8 (3 x C), 27.5, 27.6, 60.3, 66.4, 79.1, 81.9,

### 105.5, 112.4, 125.9, 141.5; Anal. Calcd for $C_{16}H_{30}O_5Si$ (330.50): C 58.15, H 9.15; found C 58.03, H 9.25.

### 5-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-3-C-(E)-(2-thiocyanatoethylidene)- $\alpha$ -D-xylofuranose (7)

To a solution of (*E*)-5 (0.23 g, 0.70 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.7 mL) were added Et<sub>3</sub>N (0.15 mL, 1.04 mmol) and CH<sub>3</sub>SO<sub>2</sub>Cl (0.07 mL, 0.83 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 45 min. The solvent was evaporated under reduced pressure. The residue was diluted with diethyl ether (3 mL) and the solid was removed by filtration. Evaporation of the solvent under reduced pressure afforded crude mesylate which was used directly in the next reaction without any further purification. To a solution of crude mesylate (0.27 g, 0.66 mmol) in CH<sub>3</sub>CN (3 mL), KSCN (0.08 g, 0.82 mmol) was added. After stirring for 3 h at room temperature under a nitrogen atmosphere, the solvent was evaporated. The residue was diluted with diethyl ether (3 mL) and the solid was removed by filtration. The evaporation of the solvent under reduced pressure and chromatography of the residue (hexane-ethyl acetate, 7:1) afforded 0.18 g (70% from 5) of pure thiocyanate 7 as a colorless oil;  $[\alpha]_D^{25} = +164.3$  (c 0.21); <sup>1</sup>H-NMR:  $\delta$  0.05 (3H, s, CH<sub>3</sub>), 0.06 (3H, s, CH<sub>3</sub>), 0.88 (9H, s, 3 x CH<sub>3</sub>), 1.42 (3H, bs, CH<sub>3</sub>), 1.47 (3H, bs, CH<sub>3</sub>), 3.61-3.67 (2H, m, H<sub>7</sub>, H<sub>5</sub>), 3.74 (1H, dd,  $J_{5,5}$ =10.6 Hz,  $J_{5,4}$ =3.8 Hz, H<sub>5</sub>), 3.80 (1H, dd,  $J_{7,7}$ = 13.0 Hz,  $J_{7,6}$ = 8.8 Hz, H<sub>7</sub>), 4.98-5.03 (2H, m, H<sub>2</sub>, H<sub>4</sub>), 5.89 (1H, d,  $J_{2,1}$ =4.4 Hz, H<sub>1</sub>), 5.95 (1H, dddd,  $J_{7,6}$ = 8.8 Hz,  $J_{7,6}$ =7.6 Hz,  $J_{6,4}$ =1.8 Hz,  $J_{6,2}$ =1.8 Hz, H<sub>6</sub>); <sup>13</sup>C-NMR: δ -5.5, -5.4, 18.2, 25.8 (3 x C), 27.7, 27.9, 32.5, 66.3, 80.3, 81.9, 105.0, 111.4, 113.2, 119.4, 147.0; Anal. Calcd for C<sub>17</sub>H<sub>29</sub>NO<sub>4</sub>SSi (371.57): C 54.95, H 7.87, N 3.77, S 8.63; found C 54.83, H 7.77, N 3.85, S 8.50.

# $5-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-3-C-(Z)-(2-thiocyanatoethylidene)-\alpha-D-xylofuranose (6)$

Et<sub>3</sub>N (3.18 mL, 22.9 mmol) and CH<sub>3</sub>SO<sub>2</sub>Cl (1.42 mL, 18.3 mmol) were added at 0 °C to a solution of (*Z*)-4 (5.05 g, 15.3 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (36 mL). The reaction mixture was stirred for 15 min at 0 °C and then for 45 min at room temperature. The solvent was evaporated under reduced pressure. The residue was diluted with diethyl ether (60 mL) and the solid was removed by filtration. Evaporation of the solvent under reduced pressure afforded crude mesylate which was used directly in the next reaction without further purification. To a solution of crude mesylate (5.99 g, 14.7 mmol) in CH<sub>3</sub>CN (55 mL), KSCN (1.78 g, 18.3 mmol) was added. After stirring for 5 h at room temperature the solvent was evaporated. The residue was diluted with diethyl ether (60 mL) and the solid was removed by fitration. The evaporation of the solvent at reduced pressure and chromatography of the residue (hexane-ethyl acetate, 7:1) gave 4.13 g (73% from 4) of pure thiocyanate **6** as a white solid; m.p. 58 – 60 °C;  $[\alpha]_D^{25} = +159.3$  (*c* 0.34); <sup>1</sup>H NMR:  $\delta$  0.06 (3H, s, CH<sub>3</sub>), 0.07 (3H, s, CH<sub>3</sub>), 0.89 (9H, s, 3 x CH<sub>3</sub>), 1.41 (3H, bs, CH<sub>3</sub>), 1.46 (3H, bs, CH<sub>3</sub>), 3.66 (1H, dd, *J*<sub>5,5</sub>=10.5 Hz, *J*<sub>5,4</sub>=3.2 Hz, H<sub>5</sub>), 3.74 (1H, dd, *J*<sub>5,5</sub>=10.5 Hz, *J*<sub>5,4</sub>=4.1 Hz, H<sub>5</sub>), 3.75 (1H, ddd, *J*<sub>7,7</sub>=13.1 Hz, *J*<sub>7,6</sub>=7.5 Hz, *J*<sub>7,2</sub>=1.2 Hz, H<sub>7</sub>), 3.95 (1H, dd, *J*<sub>7,7</sub>=13.1 Hz, *J*<sub>7,6</sub>=8.5 Hz, H<sub>7</sub>), 4.79-4.82 (1H, m, H<sub>4</sub>), 5.13-5.15 (1H, m, H<sub>2</sub>), 5.79-5.85 (1H, m, H<sub>6</sub>), 5.92 (1H, d, *J*<sub>2,1</sub>= 4.5 Hz, H<sub>1</sub>); <sup>13</sup>C-NMR:  $\delta$  -5.5, -5.4, 18.2, 25.9 (3 x C), 27.6, 27.9, 32.3, 66.3, 78.9,

81.7, 105.6, 111.7, 113.0, 119.0, 146.8; Anal. Calcd for C<sub>17</sub>H<sub>29</sub>NO<sub>4</sub>SSi (371.57): C 54.95, H 7.87, N 3.77, S 8.63; found C 54.86, H 7.95, N 3.85, S 8.55.

### 5-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-3-isothiocyanato-3-C-vinyl- $\alpha$ -D-xylo-furanose (8)

A solution of (*E*)-**7** (0.10 g, 0.27 mmol) in dry heptane (1 mL) was heated at 90 °C for 16 h. The solvent was evaporated under reduced pressure and chromatography of the residue on silica gel (hexane-ethyl acetate, 13:1) afforded 0.07 g (70%) of isothiocyanate **8**. Alternatively, a solution of (*Z*)-**6** (1.0 g, 2.69 mmol) in dry heptane (5.8 mL) was heated at 90 °C for 16 h under a nitrogen atmosphere. The solvent was evaporated under reduced pressure and the chromatography of the residue (hexane-ethyl acetate, 13:1) gave 0.82 g (82%) of isothiocyanate **8** as a colorless oil;  $[\alpha]_D^{25} = +49.8$  (*c* 0.22); <sup>1</sup>H-NMR:  $\delta$  0.06 (3H, s, CH<sub>3</sub>), 0.07 (3H, s, CH<sub>3</sub>), 0.88 (9H, s, 3 x CH<sub>3</sub>), 1.33 (3H, bs, CH<sub>3</sub>), 1.56 (3H, bs, CH<sub>3</sub>), 3.78 (1H, dd, *J*<sub>5,5</sub>=11.1 Hz, *J*<sub>5,4</sub>=5.5 Hz, H<sub>5</sub>), 3.86 (1H, dd, *J*<sub>5,5</sub>=11.1 Hz, *J*<sub>5,4</sub>=5.8 Hz, H<sub>5</sub>), 4.19 (1H, dd, *J*<sub>5,4</sub>=5.8 Hz, *J*<sub>5,4</sub>=5.5 Hz, H<sub>4</sub>), 4.50 (1H, d, *J*<sub>2,1</sub>=3.5 Hz, H<sub>2</sub>), 5.39 (1H, d, *J*<sub>7cis,6</sub>=10.6 Hz, H<sub>7cis</sub>), 5.56 (1H, d, *J*<sub>7trans,6</sub>=17.0 Hz, H<sub>7trans</sub>), 5.93 (1H, dd, *J*<sub>7trans,6</sub>=17.0 Hz, *J*<sub>7cis,6</sub>=10.6 Hz, H<sub>6</sub>), 5.96 (1H, d, *J*<sub>2,1</sub>=3.5 Hz, H<sub>1</sub>); <sup>13</sup>C-NMR:  $\delta$  -5.5, -5.4, 18.3, 25.8 (3 x C), 26.5, 26.7, 61.1, 74.9, 82.7, 87.9, 104.3, 113.1, 118.0, 130.7, 138.2; Anal. Calcd for C<sub>17</sub>H<sub>29</sub>NO<sub>4</sub>SSi (371.57): C 54.95, H 7.87, N 3.77, S 8.63; found C 54.82, H 7.98, N 3.68, S 8.71.

#### 5-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-3-methoxythiocarbonylamino-3-C-vinyl- $<math>\alpha$ -D-xylofuranose (**9**)

To a solution of isothiocyanate **8** (0.58 g, 1.56 mmol) in dry methanol (15.5 mL) was added sodium methoxide (0.093 g, 1.72 mmol). The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and water (5 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated under reduced pressure. Chromatography of the residue (hexane–ethyl acetate, 11:1) afforded 0.60 g (95%) of compound **9** as a colorless oil;  $[\alpha]_D^{25} = +62.1$  (*c* 0.49); <sup>1</sup>H-NMR:  $\delta$  0.17 (3H, s, CH<sub>3</sub>), 0.18 (3H, s, CH<sub>3</sub>), 0.97 (9H, s, 3 x CH<sub>3</sub>), 1.35 (3H, bs, CH<sub>3</sub>), 1.52 (3H, bs, CH<sub>3</sub>), 3.71 (1H, dd, *J*<sub>5,4</sub>=3.0 Hz, *J*<sub>5,4</sub>=0.8 Hz, H<sub>4</sub>), 3.97-4.04 (2H, m, H<sub>5</sub>), 4.01 (3H, s, CH<sub>3</sub>O), 4.81 (1H, d, *J*<sub>2,1</sub>=3.7 Hz, H<sub>2</sub>), 5.29 (1H, dd, *J*<sub>7trans,6</sub>=17.5 Hz, *J*<sub>7trans,7cis</sub>=0.8 Hz, H<sub>7trans</sub>), 5.33 (1H, dd, *J*<sub>7cis,6</sub>=10.9 Hz, *J*<sub>7trans,7cis</sub>=0.8 Hz, H<sub>7cis</sub>), 5.92 (1H, d, *J*<sub>2,1</sub>=3.7 Hz, H<sub>1</sub>), 6.01 (1H, dd, *J*<sub>7trans,6</sub>=17.5 Hz, *J*<sub>7cis,6</sub>=10.9 Hz, H<sub>6</sub>), 9.37 (1H, bs, NH); <sup>13</sup>C-NMR:  $\delta$  -5.6, -5.3, 18.5, 26.0 (3 x C), 26.4, 26.7, 57.9, 59.1, 71.6, 78.6., 83.7, 104.5, 112.2, 117.0, 131.9, 191.3; Anal. Calcd for C<sub>18</sub>H<sub>33</sub>NO<sub>5</sub>SSi (403.62): C 53.57, H 8.24, N 3.47, S 7.94; found C 53.80, H 8.38, N 3.66, S 7.70.

### 5-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-3-methoxycarbonylamino-3-C-vinyl- $\alpha$ -D-xylofuranose (10)

To a solution of **9** (0.56 g, 1.39 mmol) in CH<sub>3</sub>CN (13.5 mL) was added mesitylnitrile oxide (0.25 g, 1.53 mmol). The reaction mixture was stirred at room temperature for 23 h, acetonitrile was

evaporated under reduce pressure. Chromatography of residue (hexane-ethyl acetate, 9:1) gave 0.50 g (93%) of **10** as a white crystals; m.p. 103 – 106 °C;  $[\alpha]_D^{25}$ = +69.5 (*c* 0.28); <sup>1</sup>H-NMR:  $\delta$  0.11 (3H, s, CH<sub>3</sub>), 0.12 (3H, s, CH<sub>3</sub>), 0.92 (9H, s, 3 x CH<sub>3</sub>), 1.33 (3H, bs, CH<sub>3</sub>), 1.52 (3H, bs, CH<sub>3</sub>), 3.62 (3H, s, CH<sub>3</sub>O), 3.79 (1H, m, H<sub>4</sub>), 3.94 (1H, d, *J*<sub>5,5</sub>=12.4 Hz, H<sub>5</sub>), 4.06 (1H, dd, *J*<sub>5,5</sub>=12.4 Hz, *J*<sub>5,4</sub>=3.0 Hz, H<sub>5</sub>), 5.07 (1H, d, *J*<sub>2,1</sub>=3.5 Hz, H<sub>2</sub>), 5.32 (1H, d, *J*<sub>7trans,6</sub>=17.5 Hz, H<sub>7trans</sub>), 5.37 (1H, d, *J*<sub>7cis,6</sub>=10.8 Hz, H<sub>7cis</sub>), 5.88 (1H, d, *J*<sub>2,1</sub>=3.5 Hz, H<sub>1</sub>), 6.08 (1H, dd, *J*<sub>7trans,6</sub>=17.5 Hz, *J*<sub>7cis,6</sub>=10.8 Hz, H<sub>6</sub>), 7.57 (1H, bs, NH); <sup>13</sup>C-NMR:  $\delta$  -5.7, -5.5, 18.2, 25.7 (3 x C), 26.3, 26.8, 51.8, 59.4, 68.6, 78.7., 83.4, 104.5, 112.1, 116.6, 132.6, 155.8; Anal. Calcd for C<sub>18</sub>H<sub>33</sub>NO<sub>6</sub>Si (387.55): C 55.79, H 8.58, N 3.61; found C 55.58, H 8.27, N 3.42.

# 5-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-3-methoxycarbonylamino- $\alpha$ -D-xylo-furanose 3-C-carbaldehyde (11)

To a solution of **10** (0.30 g, 0.77 mmol) in 2:2:3 CCl<sub>4</sub>/CH<sub>3</sub>CN/H<sub>2</sub>O (8.5 mL) were added sodium periodate (0.68 g, 3.16 mmol) and ruthenium trichloride hydrate (4.2 mg, 2.5 mol %). The reaction mixture was stirred at room temperature for 20 h, then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 7:1) to afford 0.21 g (70%) of compound **11** as a colorless oil;  $[\alpha]_D^{25} = +69.3$  (*c* 0.29); <sup>1</sup>H-NMR:  $\delta$  0.09 (3H, s, CH<sub>3</sub>), 0.10 (3H, s, CH<sub>3</sub>), 0.90 (9H, s, 3 x CH<sub>3</sub>), 1.35 (3H, bs, CH<sub>3</sub>), 1.56 (3H, bs, CH<sub>3</sub>), 3.67 (3H, s, CH<sub>3</sub>O), 3.92 (1H, dd, *J*<sub>5,5</sub>=12.1 Hz, *J*<sub>5,4</sub>=1.8 Hz, H<sub>5</sub>), 4.01 (1H, dd, *J*<sub>5,5</sub>=12.1 Hz, *J*<sub>5,4</sub>=4.2 Hz, H<sub>5</sub>), 4.27 (1H, dd, *J*<sub>5,4</sub>=4.2 Hz, *J*<sub>5,4</sub>=1.8 Hz, H<sub>4</sub>) 5.12 (1H, d, *J*<sub>2,1</sub>=3.6 Hz, H<sub>2</sub>), 5.99 (1H, d, *J*<sub>2,1</sub>=3.6 Hz, H<sub>1</sub>), 7.31 (1H, bs, NH), 9.91 (1H, s, CHO); <sup>13</sup>C-NMR:  $\delta$  -5.7, -5.6, 18.1, 25.7 (3 x C), 26.3, 26.7, 52.4, 60.3, 71.8, 76.2, 84.4, 105.3, 113.3, 156.5, 197.4; Anal. Calcd for C<sub>17</sub>H<sub>31</sub>NO<sub>7</sub>Si (389.53): C 52.42, H 8.02, N 3.60; found C 52.27, H 8.27, N 3.42.

#### 5-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-3-methoxycarbonylamino-α-D-xylofuranose 3-C-carboxylic acid (12)

A solution of NaClO<sub>2</sub> (0.23 g, 2.54 mmol) and NaH<sub>2</sub>PO<sub>4</sub> (0.285 g, 1.83 mmol) in water (1.55 mL) was added dropwise to the solution of aldehyde **11** (0.107 g, 0.275 mmol) in 4:4:1 acetonitrile/tertbutyl alcohol/2-methyl-2-butene (6.2 mL) at 0 °C over 5 min and then stirred at the same temperature for 25 min. The reaction mixture was poured into brine (8 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by chromatography (1:2 hexane–ethyl acetate) to give 0.082 g (74%) of carboxylic acid **12** as a colorless oil;  $[\alpha]_D^{25} = +45.4$  (*c* 0.57); <sup>1</sup>H-NMR:  $\delta$  0.11 (3H, s, CH<sub>3</sub>), 0.12 (3H, s, CH<sub>3</sub>), 0.91 (9H, s, 3 x CH<sub>3</sub>), 1.35 (3H, bs, CH<sub>3</sub>), 1.53 (3H, bs, CH<sub>3</sub>), 3.76 (3H, s, CH<sub>3</sub>O), 4.22 (2H, m, H<sub>5</sub>), 4.42 (1H, m, H<sub>4</sub>), 5.04 (1H, d, *J*<sub>2,1</sub>=3.9 Hz, H<sub>2</sub>), 5.95 (1H, d, *J*<sub>2,1</sub>=3.9 Hz, H<sub>1</sub>), 8.30 (1H, bs, NH); <sup>13</sup>C-NMR:  $\delta$  -5.7, -5.6, 18.2, 25.6 (3 x C), 26.3, 26.5, 53.4, 61.0, 70.6, 76.8, 82.1, 104.3, 113.2, 159.5, 167.6; Anal. Calcd for C<sub>17</sub>H<sub>31</sub>NO<sub>8</sub>Si (405.52): C 50.35, H 7.71, N 3.45; found C 50.17, H 7.53, N 3.20.

### $5-O-[(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-3-methoxycarbonylamino-<math>\alpha$ -D-xylo-furanosyl-3-C-carbonyl]glycine methyl ester (13)

To a solution of glycine methyl ester hydrochloride (11 mg, 0.0886 mmol) in dry dichloromethane (0.5 mL) was added Et<sub>3</sub>N (0.041 mL, 0.30 mmol). The suspension was cooled to 0 °C. Then, a solution of aminoacid **12** (24 mg, 0.059 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.3 mL) and DCC (24.4 mg, 0.12 mmol) were added. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 18 h. Dichloromethane (3 mL) was added and solution was washed with ice water (0.5 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by chromatography (2:1 hexane–ethyl acetate) to afford 22 mg (78%) of dipeptide **13** as a colorless oil;  $[\alpha]_D^{25} = +35.1$  (*c* 0.14); <sup>1</sup>H-NMR:  $\delta$  0.11 (3H, s, CH<sub>3</sub>), 0.12 (3H, s, CH<sub>3</sub>), 0.91 (9H, s, 3 x CH<sub>3</sub>), 1.37 (3H, bs, CH<sub>3</sub>), 1.58 (3H, bs, CH<sub>3</sub>), 3.67 (3H, s, CH<sub>3</sub>O), 3.75 (3H, s, CH<sub>3</sub>O), 4.01 (1H, dd, *J*=18.4 Hz, *J*<sub>CH2,NH</sub>= 4.7 Hz, CH<sub>2</sub>NH), 4.13 (1H, dd, *J*<sub>5,5</sub>=12.4 Hz, *J*<sub>5,4</sub>=2.8 Hz, H<sub>5</sub>), 4.18 (1H, m, H<sub>5</sub>), 4.19 (1H, dd, *J*=18.4 Hz, *J*<sub>CH2,NH</sub>= 5.7 Hz, CH<sub>2</sub>NH), 4.25 (1H, m, H<sub>4</sub>), 5.15 (1H, d, *J*<sub>2,1</sub>=3.6 Hz, H<sub>1</sub>), 7.93 (1H, bs, NH), 8.28 (1H, dd, *J*<sub>CH2,NH</sub>= 5.7 Hz, *J*<sub>CH2,NH</sub>= 4.7 Hz, NH); <sup>13</sup>C-NMR:  $\delta$  -5.7, -5.6, 18.2, 25.7 (3 x C), 26.5, 26.8, 41.5, 52.2, 52.3, 61.0, 69.7, 78.2, 82.6, 104.9, 113.1, 157.2, 168.3, 170.1; Anal. Calcd for C<sub>20</sub>H<sub>36</sub>N<sub>2</sub>O<sub>9</sub>Si (476.60): C 50.40, H 7.61, N 5.88; found C 50.22, H 7.49, N 5.61.

#### Acknowledgements

This work was supported by the Grant Agency (No.1/2472/05) of the Ministry of Education, Slovak Republic. NMR experiments were supported by Establishment of the "top-class" laboratory for Nuclear Magnetic Resonance (No. 200280203/2003) of the Ministry of Education, Slovak Rebublic.

#### **References and Notes**

- (a) Lohof, E.; Burkhart, F.; Born, M. A.; Planker, E.; Kesler, H. In Advances in Amino Acid Mimetics and Peptidomimetics; Abell, A., Ed.; JAI Press Inc: Stanford, Connecticut, 1999; Vol. 2, p. 263; (b) Schweizer, F. Glycosamino Acids: Building Blocks for Combinatorial Synthesis-Implications for Drug Discovery. Angew. Chem. Int. Ed. 2002, 41, 230-253; (c) Gruner, S. A. V.; Locardi, E.; Lohof, E.; Kessler, H. Carbohydrate-Based Mimetics in Drug Design: Sugar Amino Acids and Carbohydrate Scaffolds. Chem. Rev. 2002, 102, 491-514.
- (a) Graf von Roedern, E.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. Synthesis and Conformational Analysis of Linear and Cyclic Peptides Containg Amino Acids. *J. Am. Chem. Soc.* **1996**, *118*, 10156-10167; (b) Le Tiran, A.; Stables, J. P.; Kohn, H. Functionalized Amino Acid Anticonvulsants: Synthesis and Pharmacological Evaluation of Conformationally Restricted Analogues. *Bioorg. Med. Chem.* **2001**, *9*, 2693-2708; (c) Chakraborty, T. K.; Jayaprakash, S.; Srinivasu, P.; Madhavendra, S. S.; Ravi Sankar, A.; Kunwar, A. C. Furanoid sugar amino acid based peptidomimetics: well-defined solution conformations to gel-like structures. *Tetrahedron* **2002**, *58*, 2853-2859.

- 3. (a) Chakraborty, T. K; Jayaprakash, S.; Diwan, P. V.; Nagaraj, R.; Jampani, S. R. B.; Kunwar, A. C. Folded Conformation in Peptide Containing Furanoid Sugar Amino Acids. J. Am. Chem. Soc. 1998, 120, 12962-12963; (b) Dondoni, A.; Marra, A. Methods for Anomeric Carbon-linked and Fused Sugar Amino Acid Synthesis: The Gateway to Artificial Glycopeptides. Chem. Rev. 2000, 100, 4395-4421; (c) Locardi, E.; Stöckle, M.; Gruner, S.; Kessler, H. Cyclic Homooligomers from Sugar Amino Acids: Synthesis, Conformational Analysis, and Significance. J. Am. Chem. Soc. 2001, 123, 8189-8196; (d) De Borggraeve, W. M.; Rombouts, F. J. R.; Van der Eycken, E. V.; Toppet, S. M.; Hoornaert, G. J. Synthesis of a conformationally restricted dipeptide analogue and its evaluation as a β-turn mimic. Tetrahedron Lett. 2001, 42, 5693-5695; (e) Nguyen Van Nhien, A.; Ducatel, H.; Len, Ch.; Postel, D. Novel conformationally restricted glycoamino acids from glyco- $\alpha$ -aminonitriles as potent turn mimics in peptide synthesis. *Tetrahedron Lett.* 2002, 43, 3805-3808; (f) McGarvey, G. J.; Benedum, T. E.; Schmidtmann, F. W. Development of Co- and Post-Translational Synthetic Strategies to C-Neoglycopeptides. Org. Lett. 2002, 4, 3591-3594; (g) Xie, J. Synthesis of new sugar amino acid derivatives of D-glucosamine. Carbohydr. Res. 2003, 338, 399-406; (h) Billing, J. F.; Nilsson, U. J. Cyclic peptides containing a δ-sugar amino acidsynthesis and evaluation as artificial receptors. Tetrahedron 2005, 61, 863-874; (i) Simone, M. I.; Soengas, R.; Newton, Ch. R.; Watkin, D. J.; Fleet, G. W. J. Branched tetrahydrofuran a,adisubstitued-\delta-sugar amino acid scaffolds from branched sugar lactones: a new family of foldamers? Tetrahedron Lett. 2005, 46, 5761-5765; (j) Schmidtmann, F. W.; Benedum, T. E.; McGarvey, G. J. The preparation of C-glycosyl amino acids - an examination of olefin crossmetathesis. Tetrahedron Lett. 2005, 46, 4677-4681; (k) Schweizer, F; Hindsgaul, O. Synthesis of a galacto-configured C-ketoside-based  $\gamma$ -sugar-amino acid and its use in peptide coupling reactions. Carbohydr. Res. 2006, 341, 1730-1736.
- 4. Lu, Y.; Just, G. Stereoselective synthesis of dithymidine phosphorothioates using D-xylose derived chiral auxiliaries. *Tetrahedron* **2001**, *57*, 1677-1687.
- 5. Podlech, J. In *Houben-Weyl*, *Bd*.; Thieme: New York, **2001**; Vol. E 22a, pp. 517-533.

Sample Availability: Samples of the compounds (Z)-6, 8, 10 are available from the authors.

© 2006 by MDPI (http://www.mdpi.org). Reproduction is permitted for noncommercial purposes.