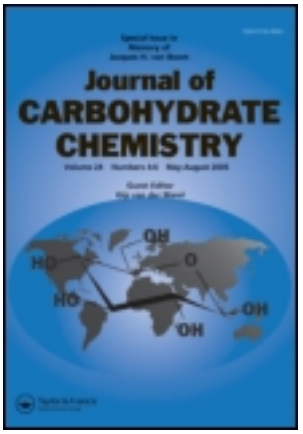

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COMMUNICATION

CARBOHYDRATE-BASED PEPTIDO MIMETICS. SYNTHESIS OF TWO NEW SCAFFOLDS FOR COMBINATORIAL LIBRARIES.[1]

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The recent utilisation of the glucopyranose ring as scaffold for the synthesis of a potent somatostatin agonist demonstrated the use of monosaccharides as viable templates in drug design.[2,3] Monosaccharide-based mimics provide enantiomerically pure, rigid moieties (able to give precise orientation of functional groups), with a high degree of oxygenation to assure water solubility.[4] Moreover, carbohydrates exhibit a high combinatorial density. These advantages prompted us to synthesise new monosaccharide derivatives as carbohydrate scaffolds for potential drug design.

The target compounds **1** and **2** (Figure 1) contain five- and six-membered rings, respectively, which present a carboxylic and an amine group (SAA)[5] for the coupling of critical amino acid side chains (peptide backbone) and hydroxyls that allow chemoselective protections, necessary for combinatorial synthesis. Moreover, the presence of chemically different hydroxyl groups makes combinatorial reaction sequences affordable on solid phase.

The synthesis of **1** began with the commercially available D-ribonolactone **3** (Scheme 1). Chemoselective formation of the C(2)-(3) ketal **4**[6] (90%), followed by acetylation with acetyl anhydride (Ac_2O) and catalytic dimethylaminopyridine (DMAP) of the primary hydroxyl group, afforded **5** in 90% yield.

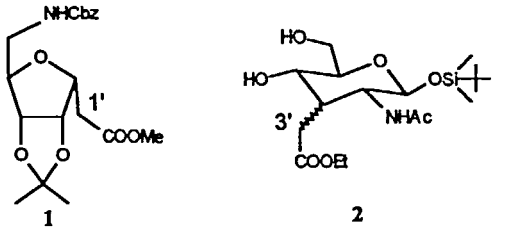
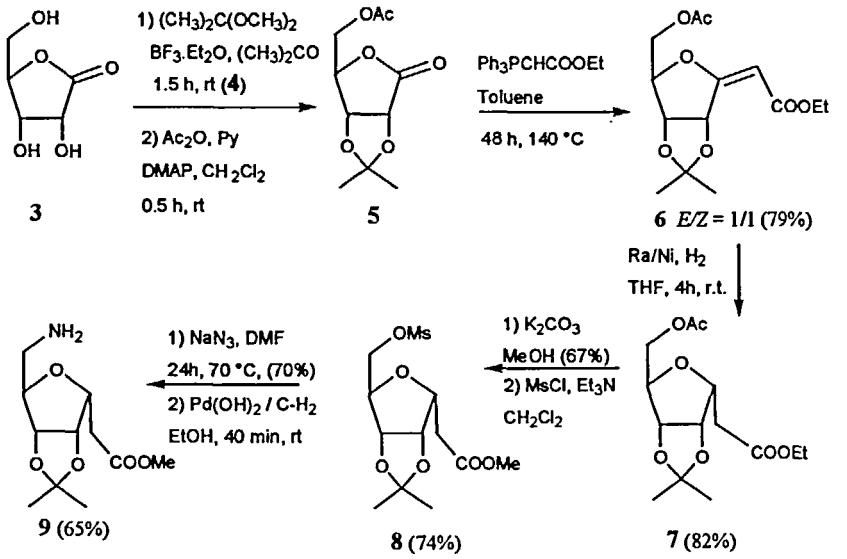


Figure 1. Structure of sugar aminoacids **1** and **2**.

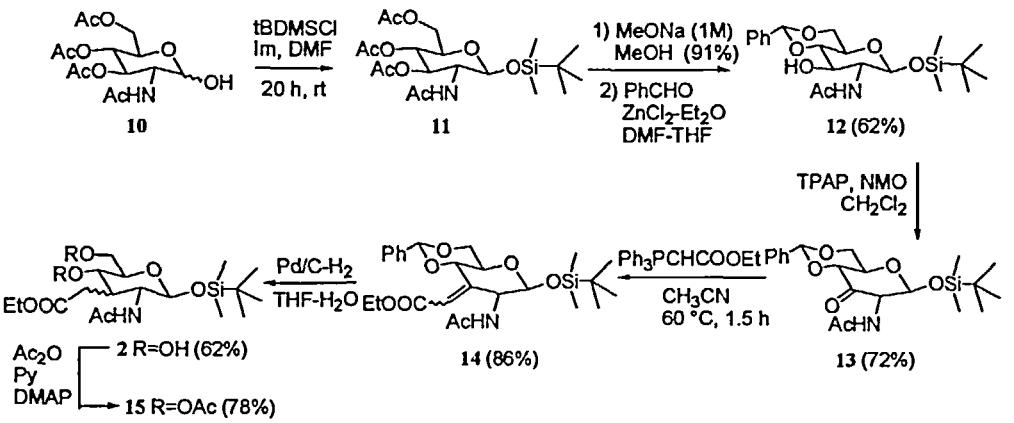


Scheme 1

The Wittig olefination between **5** (2.7 mmol equiv.) and the stabilised ylide ethoxycarbonylmethyltriphenyl phosphine (5.4 mmol) was performed at 140°C in a sealed vessel[7] and gave **6** in 1/1, *Z/E* mixture and in 79% overall yield. The ^{1}H NMR spectrum of **6** showed the diagnostic signal for the vinylic proton at δ 5.42 (d, $J_{1',2}$ = 1.0 Hz, H-1') for the *E* isomer and at δ 5.01-5.07 (m, 2H, H-1' + H-2) for the *Z* isomer. Catalytic hydrogenation of **6** with Raney-nickel (0.5 mL) afforded **7** stereoselectively, $[\alpha]_D$ = -10°

($CHCl_3$). Deacetylation of **7** and subsequent protection as the mesyl derivative, gave **8** which in turn was transformed into the corresponding azido sugar, which was reduced, with palladium hydroxide on charcoal in hydrogen atmosphere, to afford the amino derivative **9**. Compound **9** was fully characterised as benzyloxy carbonyl derivative **1**.[8]

For the synthesis of the pyranose scaffold **2** we converted the tetraacetylamino glucose **10**[9] (5.7 mmol equiv) with *tert*-butyldimethylsilyl chloride (tBDMSCl, 8.5 mmol equiv) and imidazole (Im, 12.7 mmol equiv) into the corresponding monosilyl β-anomer **11**, $[\alpha]_D = -3°$ ($CHCl_3$), in 50% yield. The ^1H NMR spectrum of **11** showed the anomeric proton signal at δ 4.83 (d, $J_{1,2} = 9.2$ Hz, H-1) (Scheme 2).



Scheme 2

The removal of acetyl groups on C(3), C(4), and C(6) of **11** and chemoselective formation of the C(4)-C(6) acetal **12** were performed under standard conditions in 91% and 62% yield respectively. Oxidation of **12** (0.3 mmol) with catalytic amounts of tetrapropylammonium perruthenate (TPAP, 0.02 mmol) in the presence of 4-methylmorpholine-*N*-oxide (NMO, 0.3 mmol) as cooxidant, [10] afforded the ketosugar **13** which underwent a Wittig olefination with a twofold molar quantity of ethoxycarbonylmethyltriphenylphosphine to give **14** as a 1/1 mixture of *E/Z* isomers in 86% yield. Reduction of the double bond performed with palladium on charcoal (10%) in wet THF produced **2** as a mixture of diastereoisomers in 62% yield. Fully characterisation of **2** was accomplished on the corresponding 4,6-*O*-diacetyl derivative **15**.[11] The ^1H NMR

spectrum of **15** showed a diagnostic signal at δ 2.38-2.33 (m, 4H, $2CH_2$-1') for the methylene group at C(3).

In conclusion two new carbohydrate-based scaffolds were prepared: a furanose and a pyranose derivative with a carbonyl and an amino group in geometrically suitable position for peptide coupling. The presence of hydroxyl groups that permits a chemoselective functionalization make these new molecules highly appealing for combinatorial and solid phase synthesis.

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8. Compound **1**: $[\alpha]_D$ = +25° ($CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 7.38-7.32 (m, 5H,), 5.10 (bs, 2H), 4.57 (bs, 1H, NH), 4.75 (dd, 1H, J = 4.0, 6.0 Hz, H-2), 4.57 (ad, 1H, J = 6.2 Hz, H-3), 4.30-4.22 (m, 1H, H-1), 4.10 (dd, 1H, J 0 5.2, 4.2 Hz, H-4), 3.70 (s, 3H), 3.46-3.32 (m, 1H, H-5), 3.19-3.05 (m, 1H, H-5'); 2.85-2.63 (ad, 2H, J = 16.8 Hz), 1.46 (s, 3H), 1.31(s, 3H) δ; ^{13}C NMR (50 MHz, $CDCl_3$): 24.9, 26.1, 33.9, 40.5, 51.8, 66.9, 76.2, 81.0, 82.6, 83.1, 112.9, 128.1, 128.2, 128.5, 136.3, 156.4, 171.4 δ.
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11. Compound **15** (1:1 mixture of two isomers): ^{1}H NMR (200 MHz, $CDCl_3$): 0.07, 0.09, 0.14, 0.17 (4s, 12H), 0.86, 0.92 (2s, 18H), 1.24 (2t, 6H, J = 7.2 Hz), 1.93,

2.01, 2.04, 2.05, 2.08, 2.14 (6s, 18H), 2.33-2.38 (m, 4H), 2.43-2.55 (m, 1H), 2.96-3.05 (m, 1H), 3.61-3.78 (m, 2H), 4.96-4.16 (m, 8H), 4.30-4.46 (m, 2H), 4.71 (d, 1H, J 0 8.0 Hz, H-1), 4.79 (t, 1H, J = 9.8 Hz), 4.99 (d, 1H, J = 1.8 Hz), 5.06 (s, 1H), 5.46 (bd, 1H, NH), 6.29 (bd, 1H, NH) δ; ^{13}C NMR (50 MHz, $CDCl_3$): -5.5, -5.4, -4.8, -4.1, 14.0, 17.8, 20.7, 21.0, 23.2, 23.5, 25.5, 25.6, 26.1, 32.8, 33.7, 40.4, 50.0, 55.9, 60.8, 62.9, 64.4, 69.7, 73.6, 74.5, 93.9, 97.4, 169.0, 169.2, 170.6, 170.5, 172.9 δ.