

This article was downloaded by:

On: 23 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713617200>

Carbohydrate-Based Peptido Mimetics. Synthesis of Two New Scaffolds for Combinatorial Libraries.

Barbara Becattini; Giuseppe Capozzi; Chiara Falciani; Stefano Menichetti; Cristina Nativi; Antonella Salvini

To cite this Article Becattini, Barbara , Capozzi, Giuseppe , Falciani, Chiara , Menichetti, Stefano , Nativi, Cristina and Salvini, Antonella(2000) 'Carbohydrate-Based Peptido Mimetics. Synthesis of Two New Scaffolds for Combinatorial Libraries.', *Journal of Carbohydrate Chemistry*, 19: 4, 653 – 657

To link to this Article: DOI: 10.1080/07328300008544108

URL: <http://dx.doi.org/10.1080/07328300008544108>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

COMMUNICATION

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

Barbara Becattini, Giuseppe Capozzi,* Chiara Falciani, Stefano Menichetti, Cristina Nativi* and Antonella Salvini

Centro CNR "Chimica e Struttura dei Composti Eterociclici", Dipartimento di Chimica Organica, Università di Firenze. Via Gino Capponi 9, I-50121. Firenze - Italy.

Received September 28, 1999 - Final Form April 12, 2000

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 (Ac₂O) and catalytic dimethylaminopyridine (DMAP) of the primary hydroxyl group, afforded **5** in 90% yield.

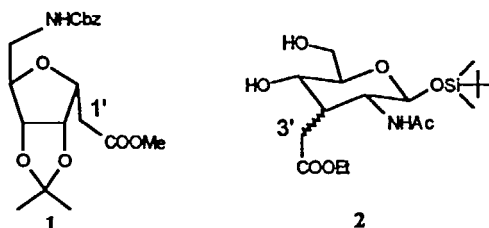
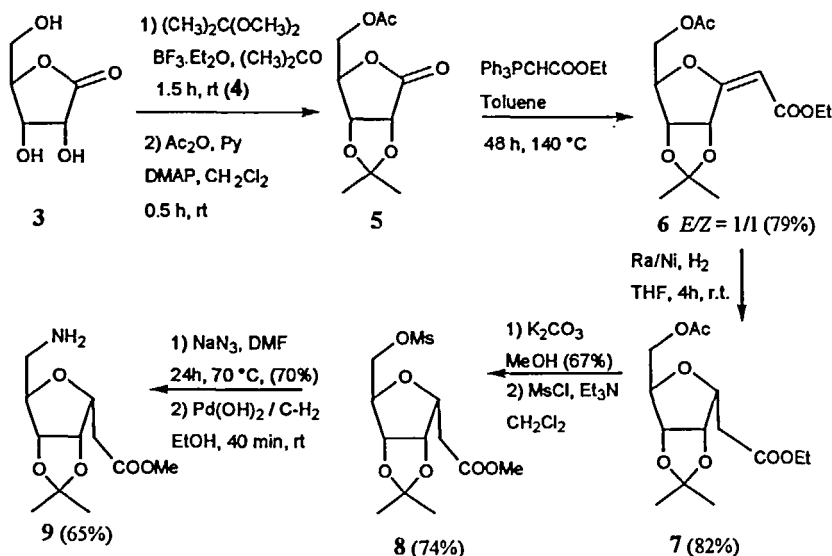


Figure 1. Structure of sugar aminoacids **1** and **2**.

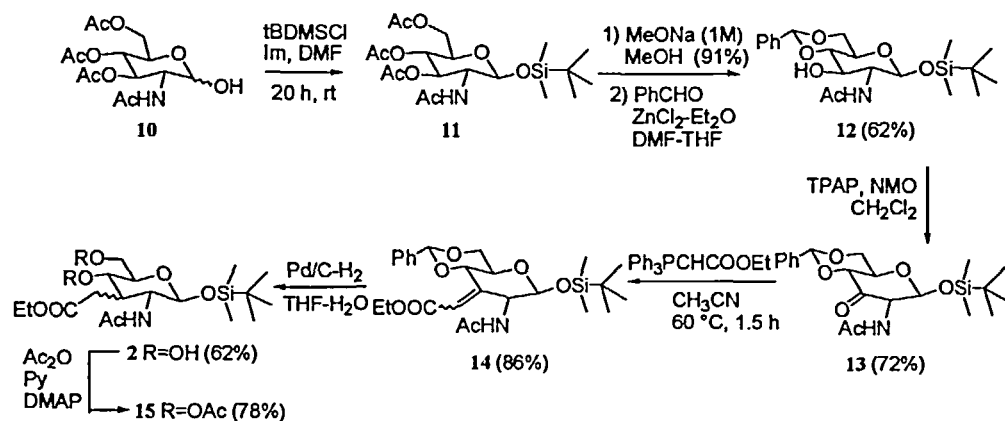


Scheme 1

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 vessel⁷ and gave **6** in 1/1, *Z/E* mixture and in 79% overall yield. The ¹H 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, [α]_D = -10°

(CHCl₃). 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**, $[\alpha]_D = -3^\circ$ (CHCl₃), 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, 2CH₂-1') 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.

ACKNOWLEDGEMENT

We thank the University of Florence for financial support and Dr. Maria Altamura (Menarini Ricerche - Firenze) for helpful discussions.

REFERENCES AND NOTES

1. Presented as a poster at the *First Euroconference on Carbohydrates in Drug Research*, Sardinia, September 16-19, 1999.
2. R. Hirschmann, K. C. Nicolaou, S. Pietranico, J. Salvino, E. M. Leahy, P. A. Sprengeler, G. Furst, and A. B. Smith, *J. Am. Chem. Soc.*, **114**, 9217 (1992).
3. R. Hirschmann, W. Yao, M. A. Cascieri, C. D. Strader, L. Maechler, M. A. Cichy-Knight, J. Hynes, R. D. van Rijn, P. A. Sprengeler, and A. B. Smith, *J. Med. Chem.*, **39**, 2441 (1996).
4. M. J. Sofia, *Med. Chem. Res.*, 362 (1998).
5. E. G. van Roedern, E. Lohof, G. Hessler, M. Hoffmann, and H. Kessler, *J. Am. Chem. Soc.*, **118**, 10156 (1996).
6. P. J. Kociensky, *Protecting Groups*, George Thieme Verlag, Eds., Stuttgart, 1994.
7. M. Lakhri, and Y. Chapleur, *Angew. Chem. Int. Ed.*, **35**, 750 (1996).
8. Compound **1**: $[\alpha]_D^{25} = +25^\circ$ (CHCl₃); ¹H NMR (200 MHz, CDCl₃): 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 = 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 ; ¹³C NMR (50 MHz, CDCl₃): 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 .
9. S. G. Bowers, D. M. Coe, and G.-J. Boons, *J. Org. Chem.*, **63**, 4570 (1998).
10. S. V. Ley, J. Normann, W. P. Griffith, and S. P. Marsden, *Synthesis*, 640 (1994).
11. Compound **15** (1:1 mixture of two isomers): ¹H NMR (200 MHz, CDCl₃): 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 .