Synthesis of Conformationally Restricted Glycoamino Acids using Fluorinating Agents

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Abstract

A route for the preparation of five- and six-membered ring α/β- and α/γ-glycoamino acids is described starting from D-Glucose. The α/β glycoamino acids were synthesized using a DAST-promoted ring contraction as a key step followed by hydrolysis, acetylation, oxidation and attachment of the α-amino acid. The α/γ- glycoamino acids were synthesized by cleavage of the benzylidene protecting group as the first step, accompanied with subsequent oxidation, acetylation and attachment of the α-amino acid. At the present, we are focusing our attention in synthesizing these α/β-glycoamino acids at a higher scale by using other non-corrosive fluorinating agents.

Keywords

DAST-promoted ring contraction, glycopyranosides, foldamers, glycoamino acids.

Introduction

It is known that the biological function of proteins and RNA, including catalysis and recognition, depends on the folding pattern of these macromolecules that leads to well organized structures[1]. Proteins are usually inefficient as drugs due to the bioavailability problems as a consequence of their conformation unstability, proteolytic degradation susceptibility, low penetration through the cell membranes and disfavorable pharmacokinetics properties. Since many proteins exert their biological activity through relatively small regions of their folded surface, their activity could be reproduced by smaller molecules designed in that way that they not only conserve the function of the protein but also have better pharmacokinetic and pharmacodynamic properties. It has been shown, in contrast to α-aminoacids which are components of proteins, that short β, γ, and δ-amino acids oligomers, especially those that have conformational restrictions, adopt well defined tridimensional structures[2]. Gellman and col. have obtained peptides based on 5 and 6 member cyclic β-amino acids which can adopt well defined folded conformations having only 6 monomer subunits (foldamers)[3]. In the past three years several research groups have published works on hetero-oligomers containing an alternating pattern of α and β amino acids[4] which offer the advantage of more diversity compared to that of a homogeneous backbone.

Adding to the bioavailability issue, the fluorination of bioactive molecules not only increases frequently their biological power as in the case of Taxol[5], but also usually improves their lipidic permeability and metabolic stability. Diethylaminosulfur trifluoride (DAST) has been widely used for the fluorination of organic compounds, particularly of carbohydrates, because it allows replacing directly a hydroxyl group by one atom of fluorine in mild conditions. However, it is not appropriate for high scale usage because of its corrosive properties. Other fluorinating agents, such as triethylamine tris(hydrogen fluoride) and tetrabutylammonium fluoride (TBAF) have been used at a large scale and they replace OH groups with F in carbohydrates, if they have been previously transformed in good leaving groups (i.e. triflate)[6].

Since carbohydrates are conformationally restricted structures with the added hydrogen bond capability, we pursued the goal of synthesizing α/β- and α/γ-glycoamino acids, some of them fluorinated, as potential hybrid monomer structures for foldamers.

Results and Discussion

The synthesis of α/β glycoaminoacids (e.g., *C*-glycofuranosyl β-amino acid precursor **3**) was carried out starting from **1**[7] by using DAST as a key step since this fluorinating agent favors the formation of a 5 member ring that can be hydrolyzed, oxidized, and then subsequently attached to the α-amino acid (Figure 1). Since DAST is corrosive and it only allows synthesis at a low scale, other fluorinating agents such as triethylamine tris (hydrogen fluoride), and TBAF (tetrabutylamonium fluoride) were tested. However, these agents only favored the production of a six member ring elimination compound (not described herein). At the moment we are working on changing the reaction conditions to favor the formation of a ring contracted structure. This latter attempt can be useful for the synthesis of α/β-glycoamino acids at a higher scale.

The synthesis of α/γ glycoaminoacids (e.g., **5**) from compound **1**[7] was achieved in a straightforward way by hydrolysis of the benzylidene group, oxidizing the primary alcohol with TEMPO, acetylating the hydroxyl groups at positions 2 and 4, and attaching the α-amino acid to the sugar structure at the carboxylic side (Figure 2).

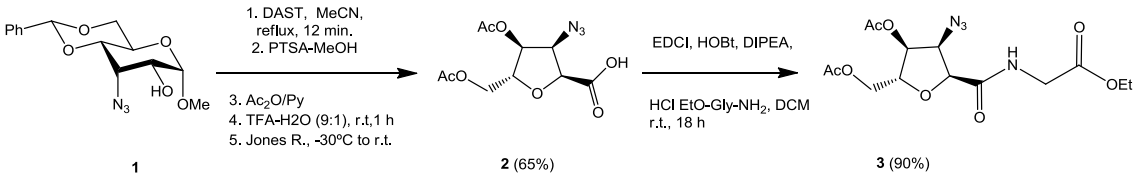

Figure 1. Route for the synthesis of α/β-glycoamino acids.

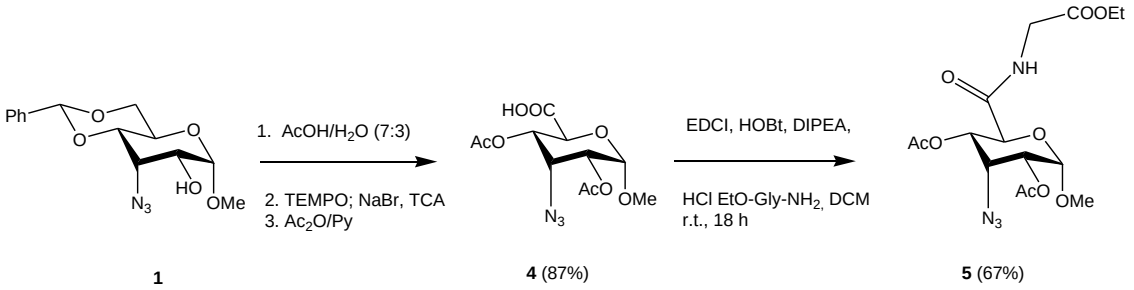

Figure 2. Route for the synthesis of α/γ-glycoamino acids.

Experimental

All new compounds were characterized by their IR, ^{1}H-NMR (500 MHz), ^{13}C-NMR (125.7 MHz), and HRMS spectral data.

Synthesis of α/β-glycoamino acids (e.g., 3)

The fluorination assay with DAST was carried out with 200 mg of methyl 3-azide-4,6-O-benzylidene-3-deoxy-α-D-allopyranoside **1**[7] in acetonitrile under reflux conditions for 12 minutes and then dissolved in MeOH and PTSA (p-toluenesulfonic acid) followed by acetylation with Ac_2O/pyridine. Hydrolysis of the crude product by treatment with a 9:1 mixture of TFA:H_2O at room temperature for 1 hour followed by oxidation with Jones reactive applied at -30 ^{o}C to room temperature gave compound **2** in 65% yield.
Subsequently EDCI, HOBt, DIPEA, and HCl-Gly-Et were added to a solution of **2** in DCM, and the reaction proceeded for 18 hours as described in reference 8 to obtain the α/β-glycoamino acid **3**[8] (90 %).

Synthesis of α/γ-glycoamino acids (e.g., 5)

Compound **1** was dissolved in a 7:3 mixture of AcOH/H_2O as described by Baer[7] to remove the benzylidene functionality and once purified, the obtained triol (150 mg, 0.68 mmol) was oxidized with a mixture of NaBr, TCCA, and TEMPO to obtain **4** (138 mg, 87%) after conventional acetylation of the crude product. L-Glycine was attached to the carboxyl site (reference 8a) as indicated above for compound **2** to obtain the α/γ-glycoamino acid methyl 2,4-di-*O*-acetyl-3-azide-3-deoxy-*N*-(etoxycarbonylmethyl)-α-D-aluronamide **5** (67%) as a syrup.

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References

[1] Kotha, S. *Acc. Chem. Res*. **2003**, 36, 342-351.

[2] a) Gademann, K.; Häne, A.; Rueping, M.; Jaun, B.; Seebach, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 1534-1537; (b) Hungerford, N.L.; Fleet, G.W.J. *J. Chem. Soc., Perkin Trans. I*, **2000**, 3680-3685; (c) Smith, M.D.; Claridge, T.D.W.; Sansom, M.S.P.; Fleet, G.W.J. *Org. Biomol. Chem.* **2003**, *1*, 3647-3655; (d) Cheng, R. P. Gellman, S.H.; DeGrado, W.F. *Chem. Rev.* **2001**, *101*, 3219-3232.

[3] Wang, X.; Espinosa, J.F.; Gellman, S.H. *J. Am. Chem. Soc.* **2000**, *122*, 4821-4822.

[4] (a) Sharma, G. V. M.; Babu, B. S.; Chatterjee, D.; Ramakrishna, K. V. S.; Kunwar, A. C.; Schramm, P.; Hofmann, H.–H. *J. Org. Chem.* **2009**, *74*, 6703. (b) Horne, W. S.; Gellman, S. H. *Acc Chem. Res*. **2008**, *41*, 1399–1408. (c) Choi, S. H.; Guzei, I. A.; Spencer, L. C.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 6544. (d) Prabhakaran, P.; Kale, S. S.; Puranik, V. G.; Rajamohanan, P. R.; Chetina, O.; Howard, J. A. K.; Hofmann, H.-J.; Sanjayan, G. J. *J. Am. Chem. Soc.* **2008**, *130*, 17743.

[5] Ojima, I.; Imone, T.; Slater, J. C.; Lin, S. N.; Kudnk, S. N.; Walsh, J. J.; Cresteil, T.; Monsarrat, B.; Pera, P.; Bermacki, R. J. *Asymm. Fluoroorg. Chem. ACS Symp. Ser.* **2000,** *746*, 158-181.

[6] (a) Chou, T.S. ; Becke, L.M. ; O'Toole, J.C. ; Carr, M.A. ; Parker, B.E. *Tetrahedron Lett.* **1996**, *37*, 17-20. (b) Cox, D.P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216-3219. (c) McClinton, M.A. *Aldrichimica Acta* **1995**, *28*, 31-35.

[7] Baer, H., Gan, Y. *Carbohydr. Res*. **1991**, *210*, 233-245.

[8] (a) Vera Ayoso, Y. *Síntesis estereoselectiva de nuevos fluoroazúcares, "formil C-glicósidos", derivados de glicoaminoácidos y peptidomiméticos sencillos*, Tesis Doctoral, Universidad de Sevilla, **2005**. (b) Vera-Ayoso, Y.; Borrachero, P.; Cabrera-Escribano, F.; Gómez-Guillén, M.; Caner, J.; Farrás, J. *Synlett*, **2010**, 271-275.