Glycotriazolophane Synthesis via Click Chemistry

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Received 31 March 2009

Abstract: A glycotriazolophane (carbohydrate–triazole–cyclophane hybrid) has been synthesized from a sugar amino acid via copper-catalysed azide–alkyne cycloaddition.

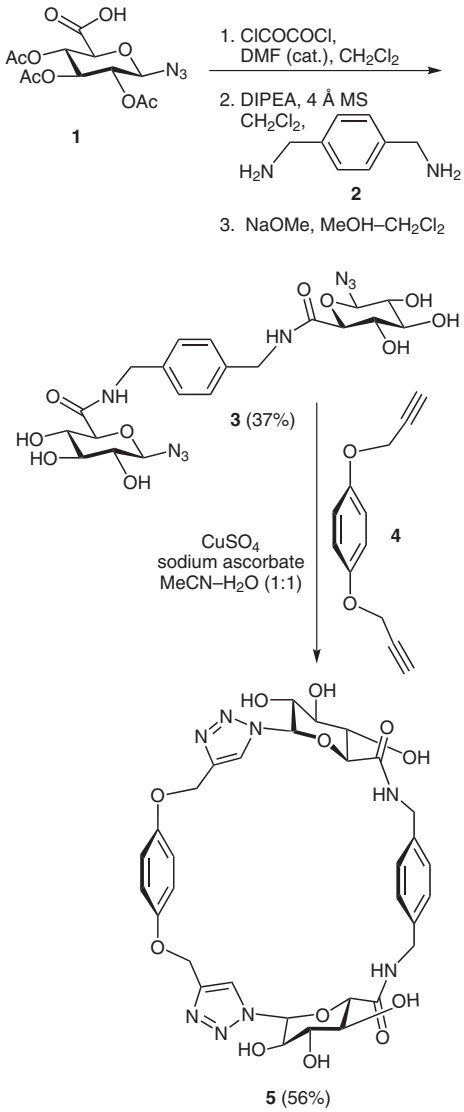
Key words: cyclophane, carbohydrates, macrocycle, 1,2,3-triazole, azide–alkyne cycloaddition

Macrocyclic compounds incorporating carbohydrates have been of interest as they have application in bioorganic and supramolecular chemistry. Such compounds have been investigated as inhibitors of carbohydrate–protein or carbohydrate–RNA interactions where the embedded carbohydrate structures are involved in binding to a receptor.[1] Macrocyclic carbohydrates have also found application in host–guest chemistry. This includes the use of glycophanes (carbohydrate–cyclophane hybrids) for studying carbohydrate–carbohydrate interactions[2] or of cyclodextrins[3] and cyclodextrin mimetics and their application. The incorporation of carbohydrates into macrocycles[4] facilitates modification of properties through modification of the reactive functional groups of the saccharide. Saccharides and their derivatives have thus found wide application as scaffolds for novel bioactive molecule design and synthesis.[5] Macrocyclic compounds, such as cyclophanes and their analogues, have also displayed properties as scaffolds in bioactive molecule development.[6] Herein we describe the synthesis of a new class of cyclophane[7] derivatives from sugar amino acid building blocks.

Sugar amino acids[8] (SAA) are monosaccharide-based building blocks that feature a carboxylic acid and an amine (or azide) functional group, and they have found application in peptidomimetic[9] and foldamer[10] synthesis. The use of SAA **1**[11] was investigated as a building block to generate novel macrocycles. Thus treatment of **1** with oxalyl chloride in the presence of DMF in dichloromethane gave the acid chloride, which was reacted with *p*-xylene-1,4-diamine **2** in the presence of DIPEA in dichloromethane followed by de-*O*-acetylation gave the bisazide **3** in 37% yield from **1**.

p-Bispropargyloxybenzene **4** was prepared as described previously,[12] and its reaction with **3** was investigated. Thus reaction of **3** and **4** in the presence of copper sulfate and sodium ascorbate in acetonitrile–water gave the desired cyclophane derivative **5** in 56% yield (Scheme 1).[13] Formation of the macrocyclic product **5** as opposed to oligomeric products was supported by NMR and MS {725.2549 $[M + H]^+$}.[14] A low energy structure for **5** was generated using a conformational search (SUMM method) in Macromodel (Figure 1).[15] The low solubility of the macrocycle precluded an investigation of its molecular-recognition phenomena in water.

In summary a new application for sugar amino acids leading to glycotriazolophanes has been outlined. It is envis-



Scheme 1

SYNLETT 2009, No. 12, pp 1949–1950
Advanced online publication: 01.07.2009
DOI: 10.1055/s-0029-1217534; Art ID: D08409ST

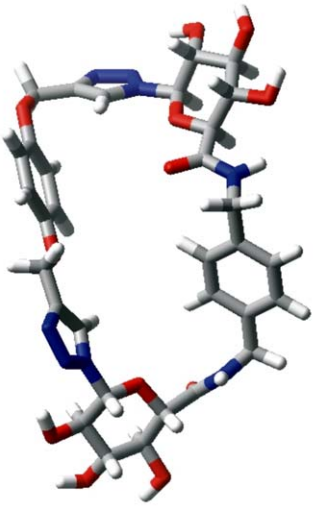


Figure 1 A low-energy structure of **5** (macromodel)

aged that a variety of novel chiral cyclophane[16] derivatives could be generated by the concise approach described herein.

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(14) **Preparation of 3 and 5**

To ice-cold **1** (0.95 g, 2.75 mmol) in CH_2Cl_2 (anhyd, 20 mL) was added oxalyl chloride (0.25 mL, 3.03 mmol), followed by DMF (0.005 mL) under N_2 and the mixture stirred for 0.5 h. *p*-Xylenediamine (0.169 mg, 1.24 mmol) and DIPEA (0.48 mL, 2.75 mmol) were stirred together in the presence of 4 Å MS in CH_2Cl_2 (anhyd, 10 mL) until complete dissolution of the amine. The solution containing the acid chloride was added, and the mixture was stirred for a further 2 h at 0 °C. The mixture was extracted with CH_2Cl_2 (20 mL), washed with $NaHCO_3$ (2 × 15 mL), HCl (2 × 15 mL), brine (2 × 15 mL), H_2O (2 × 15 mL), dried (Na_2SO_4), filtered, and the solvent removed to give a pale brown foam. Silica gel chromatography (EtOAc–Cy, gradient elution, 1:1 to 2:1) gave the protected diamide as a white foam (0.359 g, 37%). This diamide (74.9 mg, 0.095 mmol) was dissolved in MeOH–CH_2Cl_2 (3.5 mL, 6:1) to which was added NaOMe in MeOH (0.1 mL of 1.09 M) and the mixture left to stir for 3 h at r.t. The solvent was removed and the residue dissolved in H_2O. Lyophilization gave **3** as an off-white powder (51 mg, quant.); $[\alpha]_D$ –30.81 (*c* 0.37 g, H_2O). ^{1}H NMR (500 MHz, D_2O): δ = 7.24 (s, 4 H, ArH), 4.73 (d, *J* = 8.8 Hz, 2 H, H-1), 4.37 (s, 4 H, $PhCH_2$), 3.93 (d, *J* = 9.3 Hz, 2 H, H-5), 3.55–3.46 (m, 4 H, overlapping of H-3, H-4), 3.25 (m, 2 H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2 (CONH), 136.9 (ArC), 127.7 (CH), 90.4, 77.1, 75.6, 72.6, 71.3 (each CH), 42.7 ($NHCH_2Ph$). LRMS: *m/z* found: 561.1 $[M + Na]^+$, 537.2 $[M - H]^-$. HRMS (ES): *m/z* calcd for $C_{20}H_{27}O_{10}N_8$: 539.1850; found: 539.1865 $[M + H]^+$.

The bisazide **3** (60 mg, 0.111 mmol) was dissolved in a solution of MeCN–H_2O (1:1, 4.5 mL) to which was added alkyne **4** (20 mg, 0.111 mmol) and the reactants stirred before the addition of sodium ascorbate (2 mg, 0.011 mmol) followed by $CuSO_4 \cdot 5H_2O$ (0.55 mL of a 0.01 M solution, 0.0055 mmol) and then stirred for a further 13 h. The resulting precipitate was **5** (45 mg, 56%). ^{1}H NMR (300 MHz, DMSO–HOD, 9:1): δ = 8.38 (s, 2 H, C=CHN), 7.13 (s, 4 H, ArH), 6.95 (s, 4 H, ArH), 5.58 (d, *J* = 9.3 Hz, 2 H, H-1), 5.04 (s, 4 H, $PhOCH_2$), 4.20 (s, 4 H, $PhCH_2$), 3.92 (d, *J* = 9.7 Hz, 2 H, H-5), 3.85 (dd, *J* = 9.9, 8.1 Hz, 2 H, H-2), 3.55–3.51 (m, 2 H, H-4), 3.41 (dd, *J* = 9.5, 8.7 Hz, 2 H, H-2). LRMS: *m/z* found: 747.1 $[M + Na]^+$, 723.2 $[M - H]^-$. HRMS (ES): *m/z* calcd for $C_{32}H_{37}O_{12}N_8$: 725.2531; found: 725.2549 $[M + H]^+$.

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