Construction of 6-Triazole-Linked Mannopyranosyl Serine and Threonine as Novel Sugar Amino Acid Mimics

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Received December 29, 2009, Accepted January 27, 2010

Key Words: Sugar amino acid, Click chemistry, Propargyl amino acid, Glycomimic

Glycopeptides, or being named more succinctly: the sugar amino acids (SAA), are a range of pivotal building blocks that could be ubiquitously found in Nature.1 They play many central roles in living organisms governing myriad vital processes such as signal transportation, metabolic intermediary and intercellular recognition.2 Consequently, the design and synthesis of their mimics by assembling two most fundamental natural elements, i.e., carbohydrates and amino acids via various chemical or bio-methods has received explosive attention.3 One of the most efficiently potent tools to construct such nonnatural mimics shall be the 1,3-dipolar cycloaddition (or “Click Chemistry”)4 of organic azides with terminal alkynes.5 In the meanwhile, serine and threonine residues are identified on an enormous amount of nuclear and cytoplasmic proteins, which could generate in vivo glycosylation with sugars leading to numerous essential biological processes.9 Therefore, we decided to construct a new type of SAA mimics comprising both mannosyl scaffold and serine/threonine fragments via click chemistry. As shown in Figure 1, other than the previously described comparable samples where the amino acid moieties were conventionally settled on the anomeric carbon of saccharides (1-position, A),6,10 we would install in this report the serine/threonine precursors onto the 6-position of the mannosyl scaffold (B) for variation. Noteworthy, to the best of our knowledge, this is the first time for synthesizing such 6-distributed mannosyl serine or threonine as SAA mimics via click chemistry.

Experimental

Solvents were purified by standard procedures.1H and 13C NMR spectra were recorded on a Bruker 400 spectrometer in CDCl3 or DMSO-d6 solutions. Optical rotations were measured using a SG WZZ-2A polarimeter at room temperature and a 10-cm 1-mL cell. Column chromatography was performed on E. Merck Silica Gel 60 (230 ~ 400 mesh). Analytical thin-layer chromatography was performed on E. Merck aluminum percolated plates of Silica Gel 60F-254 with detection by UV and by spraying with 6 N H2SO4 and heating at 300 °C. High resolution mass spectra (HRMS) were recorded on a KE465 LCT Premier/XE instrument using standard conditions (ESI, 70 eV).

Preparation of N-tert-butyloxycarbonyl-O-propargyl-l-threonine benzyl ester (2). To a solution of N-tert-butyloxycarbonyl-l-threonine (2.09 g, 9.5 mmol) in DMF (15 mL) at 0 °C, was carefully added NaH (60%, 1.1 g, 28.6 mmol), stirring for 30 min. Propargyl bromide (1.6 mL, 19.1 mmol) was then added. The mixture was stirred for 30 min at 0 °C followed by 12 h

Figure 1. Previously reported SAA analogs (A) and new SAA mimics (B) presented in this paper via click chemistry.
stirring at rt. After completion of the reaction monitored by TLC, the mixture was poured into brine and extracted with EtOAc. The combined organic layers were dried over MgSO₄, evaporated to give a liquid which was directly dissolved in DMF (10 mL). NaHCO₃ (1.97 g, 21.7 mmol) and BnBr (1.4 mL, 11.4 mmol) were then added, stirring for 12 h. The mixture was successively washed with brine and water, extracted with ether, dried over MgSO₄ and concentrated. The residue was purified by column chromatography (petroleum ether/ EtOAc; 1:1) to give 2 (1.53 g, 46.1%) as a viscous oil. TLC: Rf = 0.65 (petroleum ether/EtOAc: 5:1); [α]D = +6.5 (c = 2.5, MeOH); 1H NMR (400 MHz, CDCl₃) δ 7.39-7.28 (m, 5H), 5.27 (t, 1H, J = 4.8 Hz), 5.22 (d, 1H, J = 8.0 Hz), 5.17 (d, 1H, J = 8.4 Hz), 4.36 (d, 1H, J = 9.6 Hz), 4.32-4.28 (m, 1H), 4.08-3.98 (m, 2H), 2.33 (brs, 1H), 1.46 (s, 9H), 1.25 (d, 3H, J = 6.4 Hz); 13C NMR (100 MHz, CDCl₃) δ 170.7, 156.1, 135.5, 128.5, 128.3, 79.8, 79.3, 74.6, 74.1, 67.1, 58.3, 55.9, 28.3, 15.9.

General procedure for click reaction (4 and 5). Azide 3 (1 equiv.) and the amino acid alkyne (1 equiv.) were dissolved in a mixture of CH₂Cl₂ (10 mL) and water (10 mL). With vigorous stirring, sodium ascorbate (6 equiv.) was added followed by methyl)-1 methyl)-1H-[1,2,3-triazol-4-yl)methoxy)-3-(benzyl-4-yl) butanoate benzyl ether (4): From 1 (300.0 mg, 0.89 mmol) and 3 (483.4 mg, 0.89 mmol), column chromatography (petroleum ether/EtOAc, 5:1 to 1:1) afforded 4 as a colorless syrup (646.2 mg, 87.5%). [α]D = +52.8 (c = 0.6, MeOH); TLC: Rf = 0.11 (Water/AcOH; 1:1); 1H NMR (400 MHz, DMSO-d₆) δ 8.44 (s, 3H), 8.12 (s, 1H), 4.75 (dd, 1H, J = 2.0, 14.0 Hz), 4.63 (dd, 1H, J = 12.4 Hz), 4.58 (dd, 1H, J = 12.4 Hz), 4.47 (brs, 1H), 4.41 (dd, 1H, J = 8.8, 14.0 Hz), 4.17 (brs, 1H), 3.84 (dd, 1H, J = 4.4, 10.4 Hz), 3.81 (dd, 1H, J = 3.2, 10.4 Hz), 3.64 (dd, 1H, J = 2.0, 9.2 Hz), 3.61-3.60 (m, 1H), 3.47 (dd, 1H, J = 3.2, 9.2 Hz), 3.39 (t, 1H, J = 9.2 Hz), 2.94 (s, 3H), 13C NMR (100 MHz, DMSO-d₆) δ 168.9, 142.8, 125.2, 101.0, 71.6, 70.7, 70.0, 68.0, 67.1, 63.8, 53.8, 52.3, 51.0; HRMS: calcd for C₁₅H₁₃N₃O₆: M+Na = 385.1335, found: 385.1334.

(2R)-2-Amino-3-([(2R,3S,4S,5S,6S)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-yl)methyl]-1H-1,2,3-triazol-4-yl)methoxy)propanoic acid (6): From 4 (190.0 mg, 0.23 mmol) afforded 6 as a yellow powder (81.4 mg, 97.3%). [α]D = +52.8 (c = 0.6, MeOH); TLC: Rf = 0.17 (Water/AcOH; 1:1); 1H NMR (400 MHz, DMSO-d₆) δ 8.44 (s, 3H), 8.12 (s, 1H), 4.75 (dd, 1H, J = 2.0, 14.0 Hz), 4.63 (dd, 1H, J = 12.4 Hz), 4.58 (dd, 1H, J = 12.4 Hz), 4.47 (brs, 1H), 4.41 (dd, 1H, J = 8.8, 14.0 Hz), 4.17 (brs, 1H), 3.84 (dd, 1H, J = 4.4, 10.4 Hz), 3.81 (dd, 1H, J = 3.2, 10.4 Hz), 3.64 (dd, 1H, J = 2.0, 9.2 Hz), 3.61-3.60 (m, 1H), 3.47 (dd, 1H, J = 3.2, 9.2 Hz), 3.39 (t, 1H, J = 9.2 Hz), 2.69 (s, 3H), 13C NMR (100 MHz, DMSO-d₆) δ 168.9, 142.8, 125.2, 101.0, 71.6, 70.7, 70.0, 68.0, 67.1, 63.8, 53.8, 52.3, 51.0; HRMS: calcd for C₁₇H₂₃N₃O₆: M+Na = 385.1335, found: 385.1334.

Result and Discussion

In order to obtain the desired amino acid alkynes (Scheme 1), commercially available Boc-Ser (a) and Boc-Thr (b) were employed as starting materials. According to the known literature procedure,¹ they were facilely converted to the corresponding O-Propargyl Boc-Ser-OBn (1) and O-Propargyl Boc-Thr-OBn (2) in one pot with 68.4% and 46.1% yields, respectively. The azido-mannoside could be readily prepared from norternoside and azide (3) in hand, we...
subsequently studied the 1,3-dipolar cycloaddition. The click reaction was proceeded in the presence of CuSO₄·5H₂O (3 equiv.) and sodium ascorbate (6 equiv.) in a mixture of dichloromethane and water. At room temperature, both reactions were completed in 10 h with considerable yields (87.5% for 4, 86.8% for 5). Deprotection of the click products was then easily realized. Hydrogenolysis step was conducted separately to uniquely remove the Boc group. Eventually, the desired sugar amino acids were successfully obtained with excellent yields of 97.3% and 94.3%, respectively.

In summary, we have effectively synthesized two novel sugar amino acid mimics bearing either a serine or a threonine precursor at C-6 position of the mannopyranosyl scaffold via click chemistry. It is believed that with the assist of such simply accessible method, various other SAA mimics of this category could be abundantly disclosed in the near future. Indeed, such work together with the evaluation of biological applications toward these nonnatural but nature-like structures is currently underway by us and our co-workers.

Acknowledgments. This work was supported by National Natural Science Foundation of China (Grant No.20876045).

Reference and Notes