JOC Notes

C_2-Symmetric Macrocyclic Carbohydrate/Amino Acid Hybrids through Copper(I)-Catalyzed Formation of 1,2,3-Triazoles

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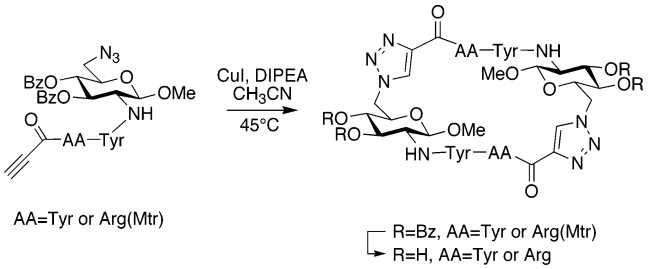

An efficient method was developed for the preparation of macrocyclic carbohydrate/amino acid hybrids by macrocyclization with copper(I)-catalyzed 1,2,3-triazole formation. Methyl 2-amino-6-azido-3,4-di-*O*-benzoyl-2,6-dideoxy-β-D-glucopyranoside was prepared and coupled to two different *N*-propiolyl dipeptides (propiolyl-Tyr-Tyr-OH and propiolyl-Arg(Mtr)-Tyr-OH) to obtain bifunctional molecules carrying one azido group and one terminal alkyne. These bifunctional molecules were cyclodimerized using Cu(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes to form macrocycles containing two 1,2,3-triazoles. Various cyclization methods were evaluated, and the most efficient conditions were found to be CuI and *N,N*-diisopropylethylamine in CH_3CN.

Macrocycles containing amino acids are important as conformationally constrained peptidomimetics and have as such found use as pharmaceuticals, e.g., antibiotics.[1] Furthermore, macrocycles have been synthesized from amino acids in combination with other building blocks, such as carbohydrates.[2] Such macrocycles constitute promising candidates as artificial receptors[3] for small biomolecules as they can contain functionalities that allow for most types of intermolecular interactions and can be designed to be water-soluble and conformationally constrained. Hence, development of methods for efficient synthesis of macrocycles containing amino acids is an important area of research. In our ongoing search for artificial receptors, we have recently prepared macrocyclic carbohydrate/amino acids hybrids with both C_2 and C_3 symmetry[4,5] by cyclization of linear peptides containing sugar amino acids. However, these macrocyclic carbohydrate/amino acid hybrids adopted relatively compact conformations with only small cavities and displayed only moderate affinities toward various guest biomolecules. Hence, we decided to explore alternative chemistries toward conformationally more open macrocycles presenting topologically different cavities for more efficient guest molecule binding. Within this context, copper(I)-catalyzed addition of azides to alkynes to form 1,2,3-triazoles[6] appeared attractive as its efficiency in macrocyclizations was recently demonstrated in the preparation of cyclodextrin analogues[7] and in peptide cyclizations.[8] We decided to exploit this reaction to prepare C_2-symmetric carbohydrate/amino acid macrocycles with the expectation that it would lead not only to an expedient synthesis but also to more rigid macrocycles with more open structures that would be interesting for evaluation as artificial receptors.

The synthetic strategy involved the coupling of an azidoaminoglucopyranoside to dipeptide propiolamides to obtain bifunctional molecules that carried one azido group and one terminal alkyne and thus could be cyclodimerized to C_2-symmetric macrocycles by copper(I)-catalyzed 1,2,3-triazole formation. Accordingly, the first task was to prepare the azidoaminoglucopyranoside derivative (Scheme 1). Compound **1**[4,9,10] was protected with Boc_2O to afford **2** in 95% yield after crystallization. The protected sugar **2** was deacetylated under Zemplén conditions, and the crude product was dissolved in CH_2Cl_2 and pyridine and treated with TsCl overnight followed

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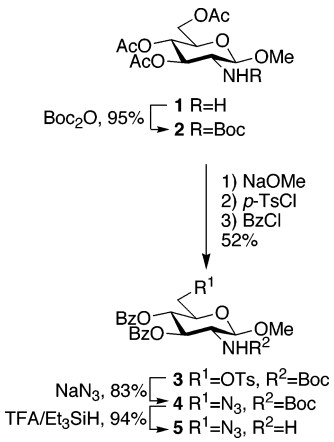
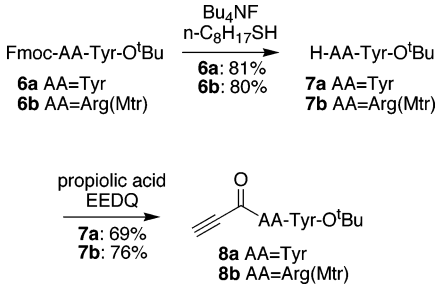
SCHEME 1. Synthesis of Methyl 2-Amino-6-azido-3,4-di-*O*-benzoyl-2,6-dideoxy-β-D-glucopyranoside 5



SCHEME 2. Synthesis of Dipeptide Propiolamides 8a,b



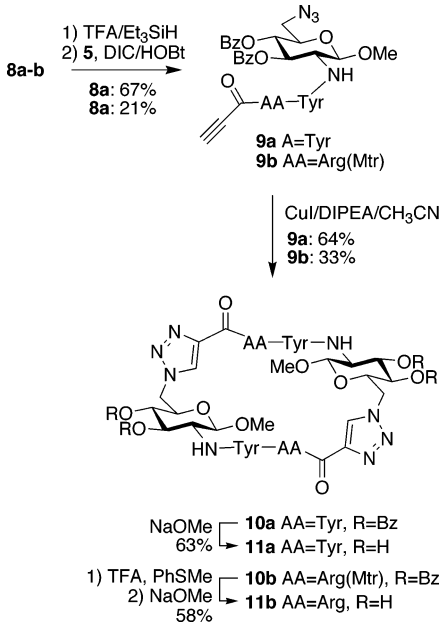
by BzCl to afford **3** in 52% yield. The tosyl group in **3** was then substituted with an azido group to give **4** in 83% yield, and finally the Boc group was cleaved using TFA and Et_3SiH in CH_2Cl_2[11] in 94% yield to afford the azidoaminosugar **5**.

The two propiolamides were prepared from dipeptides **6a,b**[4] (Scheme 2). The Fmoc groups of **6a,b** were cleaved using Bu_4NF in THF with 1-octanethiol as a scavenger[12] to obtain **7a** and previously reported compound **7b**.[4] The N-deprotected dipeptides were then coupled to propiolic acid with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) as activating agent to afford **8a,b** in good yields.

The *tert*-butyl ester of **8a** was cleanly cleaved with 33% TFA and Et_3SiH in CH_2Cl_2,[11] and the crude free acid was directly coupled to **5** using *N,N*′-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) to produce compound **9a** in 67% yield (Scheme 3). It has been reported previously by us[4] and others[2f] that the 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr) group is stable under these or similar conditions, but when the *tert*-butyl ester of **8b** was cleaved, partial cleavage of the Mtr group occurred. Nevertheless, the free acid was purified and coupled to **5** to afford **9b** in 21% over both steps.

The cyclodimerization of **9a** to **10a** was attempted under various conditions (Table 1). The previously reported conditions with CuI and DBU in toluene were sluggish with **9a** at low temperatures and failed to give product at higher temperatures. The same result was

SCHEME 3. Synthesis of Macrocycles 11a,b



obtained when *N,N*-diisopropylethylamine (DIPEA) was used instead of DBU. Compound **9a** was only partially soluble in toluene, and the cyclization was attempted in THF instead. The reaction was slow, but after 7 days the starting material **9a** had been consumed and cyclodimerized product **10a** was obtained in 16% yield along with an insoluble compound that appeared to be polymerized starting material.

Although an encouraging result, the reaction conditions needed to be optimized further. The reaction was repeated at 10 times more dilute conditions, which gave **10a** in 45% yield after 28 days. The reaction could be improved further by using acetonitrile as a solvent, which resulted in a faster reaction and a better yield. Again, the yield was better at more dilute conditions, and 64% of **10a** could be obtained after 3 days. It has previously been noted that the reaction works best in the presence of acetonitrile when the catalyst is added in the form of a copper(I) salt,[6a] and it has been proposed that the reason for this is that complexation with acetonitrile prevents oxidation of copper(I) to copper(II).[13] The reaction was also attempted with $CuSO_4$ and sodium ascorbate,[6a] which resulted in a very sluggish reaction at room temperature and only a low yield of **10a** at 70 °C.

Optimal cyclization conditions were thus concluded to be CuI and DIPEA in acetonitrile under dilute conditions. Compound **9b** could also be cyclodimerized to **10b** in 33% yield under these conditions. The formation of the 1,4 regioisomers of **10a,b** was confirmed by the presence of a NOESY cross-peak between triazole H-5 and the glucose H-6 signals of **10a,b**. Macrocycle **10a** was deprotected with NaOMe in MeOH to afford **11a** in 63% yield. Macrocycle **10b** was first treated with neat TFA containing 5% thioanisol[14] to cleave the Mtr group and then with NaOMe in MeOH to give the deprotected **11b** in 58% yield.

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TABLE 1. Cyclodimerization Attempts with 9a To Give 10a

reagents	solvent	concn (mM)	temp (°C)	time	yield (%)
CuI/DBU	toluene	2.5	rt, then 85	24 h, then 16 h	0
CuI/DBU	toluene	2.5	50	16 h	0
CuI/DIPEA	toluene	2.5	45	6 days	0
CuI/DIPEA	THF	2.5	45	7 days	16
CuI/DIPEA	THF	0.25	45	28 days	45
CuI/DIPEA	CH_3CN	2.5	45	24 h	20
CuI/DIPEA	CH_3CN	0.25	45	3 days	64
$CuSO_4$/sodium ascorbate	*t*-BuOH/H_2O 4:1	2.5	rt, then 70	48 h, then 7 days	9

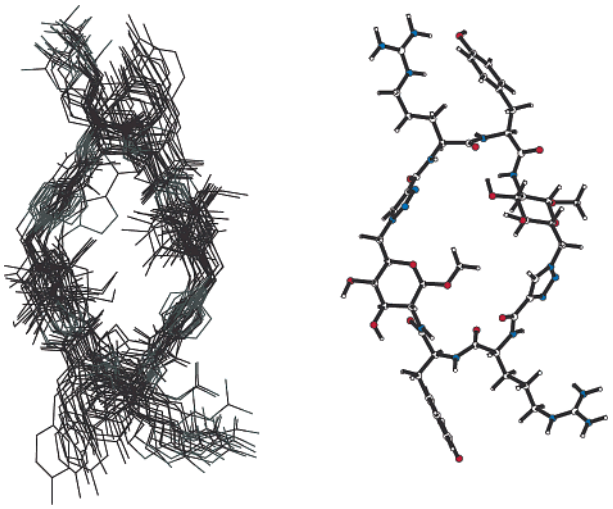

FIGURE 1. Superimposed structures of the 25 conformers with lowest energy found in the conformational search with **11b** (left) and the global minimum shown alone (right). Similar results were obtained with **11a**.

Conformational searches carried out on macrocycles **11a,b** in MacroModel 8.5 (MMFFs force field in water, all backbone torsions were selected for variation, 20 000 steps) show that the strategy to incorporate 1,2,3-triazoles into macrocyclic carbohydrate/amino acid hybrids in order to obtain more rigid macrocycles with more open structures is valid. The low-energy conformers of macrocycles **11a,b** have relatively open structures with a central cavity (Figure 1), whereas our previous macrocycles with three amino acids, instead of one 1,2,3-triazole and two amino acids, had formed collapsed structures.[4]

In conclusion, the work herein describes the first synthesis of C_2-symmetic carbohydrate/amino acid hybrid macrocycles through copper(I)-catalyzed formation of 1,2,3-triazoles. The starting material for the cyclodimerization can be prepared in a relatively small number of steps, thus making this an efficient synthesis of macrocyclic carbohydrate/amino acid hybrid molecules. The rigidity conferred by the triazole rings leads to open cleft-like macrocycles as promising candidates for artificial receptors in water.

Experimental Section

Propiolyl-Tyr-Tyr/Azidoaminosugar Hybrid (9a). Compound **8a** (279 mg, 0.615 mmol) was dissolved in CH_2Cl_2 (9.5 mL) and Et_3SiH (245 μL, 1.54 mmol) and TFA (4.7 mL) were added. The mixture was stirred for 4 h and then concentrated together with toluene. The crude free acid and compound **5** (262 mg, 0.615 mmol) were dissolved in THF (12 mL) and HOBt (83.1 mg, 0.615 mmol) and DIC (106 μL, 0.677 mmol) were added. After stirring for 16 h, MeOH (3 mL) was added and the mixture was concentrated. The product was purified with flash chromatography (toluene/EtOAc 2:5, R_f = 0.25) followed by size-exclusion chromatography to give **9a** (333 mg, 67%) as a white foam. $[\alpha]^{22}_D$ −16 (*c* 0.5, DMSO); ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.87 (m, 4H, Bz-*o*), 7.52 (m, 2H, Bz-*p*), 7.37 (m, 4H, Bz-*m*), 6.98 (d, J = 8.5 Hz, 2H, Tyr-H$^\delta$), 6.83 (d, J = 8.5 Hz, 2H, Tyr-H$^\delta$), 6.68 (d, J = 8.5 Hz, 2H, Tyr-H$^\epsilon$), 6.55 (d, J = 8.5 Hz, 2H, Tyr-H$^\epsilon$), 5.69 (dd, J = 10.6 Hz, J = 9.4 Hz, 1H, H-3), 5.37 (t, J = 9.6 Hz, 1H, H-4), 4.73 (d, J = 8.4 Hz, 1H, H-1), 4.51 (dd, J = 9.4 Hz, J = 5.2 Hz, 1H, Tyr-H$^\alpha$), 4.43 (dd, J = 9.0 Hz, J = 4.8 Hz, 1H, Tyr-H$^\alpha$), 4.18 (dd, J = 10.6 Hz, J = 8.4 Hz, 1H, H-2), 4.07 (m, 1H, H-5), 3.56 (s, 1H, CH), 3.54 (s, 3H, OMe), 3.50 (m, 1H, H-6), 3.37 (dd, J = 13.5 Hz, J = 2.6 Hz, 1H, H-6), 2.91 (dd, J = 14.1 Hz, J = 5.1 Hz, 1H, Tyr-H$^\beta$), 2.80 (dd, J = 14.1 Hz, J = 4.8 Hz, 1H, Tyr-H$^\beta$), 2.64 (dd, J = 14.2 Hz, J = 9.4 Hz, 1H, Tyr-H$^\beta$), 2.48 (dd, J = 14.1 Hz, J = 9.0 Hz, 1H, Tyr-H$^\beta$); HRMS (FAB) calcd for $C_{42}H_{40}N_6O_{11}Na$ (M + Na) 827.2653, found 827.2666.

Protected Tyr-Tyr-Containing Macrocycle (10a). Compound **9a** (50.0 mg, 62.1 μmol) was dissolved in CH_3CN (250 mL) and CuI (3.5 mg, 19 μmol) and DIPEA (11 μL, 62 μmol) were added. The mixture was stirred at 45 °C under N_2 for 72 h and then concentrated. The residue was suspended in CH_2Cl_2/MeOH 1:1 and filtered through Celite. The filtrate was concentrated and the product was purified with flash chromatography (CH_2Cl_2/MeOH 10:1, R_f = 0.18) to give **10a** (31.9 mg, 64%) as a white amorphous solid. $[\alpha]^{21}_D$ −49 (*c* 0.5, DMSO); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.09 (s, 4H, Tyr-OH), 8.58 (d, J = 9.0 Hz, 2H, NH), 8.51 (d, J = 9.0 Hz, 2H, NH), 8.41 (s, 2H, triazole), 7.92 (m, 6H, Bz-*o* + NH), 7.79 (d, J = 7.2 Hz, 4H, Bz-*o*), 7.65 (m, 4H, Bz-*p*), 7.53 (t, J = 7.7 Hz, 4H, Bz-*m*), 7.46 (t, J = 7.5 Hz, 4H, Bz-*m*), 6.82 (d, J = 8.6 Hz, 4H, Tyr-H$^\delta$), 6.79 (d, J = 8.7 Hz, 4H, Tyr-H$^\delta$), 6.52 (d, J = 8.7 Hz, 4H, Tyr-H$^\epsilon$), 6.49 (d, J = 8.6 Hz, 4H, Tyr-H$^\epsilon$), 5.45 (t, J = 9.8 Hz, 2H, H-3), 4.78 (m, 6H, H-4 + H-5 + H-6), 4.71 (d, J = 8.4 Hz, 2H, H-1), 4.50 (m, 4H, H-6 + Tyr-H$^\alpha$), 4.23 (m, 2H, Tyr-H$^\alpha$), 3.93 (m, 2H, H-2), 3.42 (s, 6H, OMe), 2.40 (m, 6H, Tyr-H$^\beta$), 2.06 (t, J = 12.3 Hz, 2H, Tyr-H$^\beta$); HRMS (FAB) calcd for $C_{84}H_{80}N_{12}O_{22}Na$ (M + Na) 1631.5408, found 1631.5408.

Deprotected Tyr-Tyr-Containing Macrocycle (11a). Compound **10a** (20.2 mg, 12.5 μmol) was dissolved in MeOH (5 mL) and NaOMe in MeOH (1.0 M, 50 μL) was added. The solution was stirred for 24 h, then neutralized with AcOH and concentrated. The product was purified using preparative HPLC (C_{18} column, 0 → 30% B in A over 60 min, A = H_2O + 0.1% TFA, B = CH_3CN + 0.1% TFA, t_R = 35 min) to afford **11a** (9.5 mg, 63%) as a fluffy white powder after lyophilization. $[\alpha]^{21}_D$ −55 (*c* 0.3, DMSO); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.12 (s, 2H, Tyr-OH), 9.10 (s, 2H, Tyr-OH), 8.66 (d, J = 8.1 Hz, 2H, NH), 8.32 (s, 2H, triazole), 7.91 (d, J = 9.0 Hz, 2H, NH), 7.78 (d, J = 8.9 Hz, 2H, NH), 7.05 (d, J = 8.4 Hz, 4H, Tyr-H$^\delta$), 6.89 (d, J = 8.2 Hz, 4H, Tyr-H$^\delta$), 6.62 (d, J = 8.3 Hz, 4H, Tyr-H$^\epsilon$), 6.57 (d, J = 8.3 Hz, 4H, Tyr-H$^\epsilon$), 5.39 (d, J = 5.1 Hz, 2H, OH-4), 4.87 (d, J = 5.3 Hz, 2H, OH-3), 4.65 (m, 4H, H-6), 4.46 (m, 2H, Tyr-H$^\alpha$), 4.36 (m, 2H, Tyr-H$^\alpha$), 4.15 (d, J = 8.1 Hz, 2H, H-1), 3.56 (m, 2H, H-5), 3.30 (m, 4H, H-2+H-3), 3.03 (m, 8H, H-4, OMe), 2.94 (dd, J = 13.9 Hz, J = 4.2 Hz, 2H, Tyr-H$^\beta$), 2.69 (m, 6H, Tyr-H$^\beta$); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.8 (Tyr-C′), 170.6 (Tyr-C′), 159.5 (triazole-C′), 155.70 (Tyr-C$^\xi$), 155.68 (Tyr-C$^\xi$), 142.0 (triazole-C^4), 130.4 (Tyr-C$^\delta$), 129.7 (Tyr-C$^\delta$), 127.9, 127.7, 127.4 (Tyr-C$^\gamma$, Tyr-C$^\gamma$, triazole-C^5), 115.0 (Tyr-C$^\epsilon$), 114.7 (Tyr-C$^\epsilon$), 101.7 (SAA-C^1), 73.9 (SAA-C^3), 72.9 (SAA-C^5), 71.0 (SAA-C^4), 56.0 (Tyr-C$^\alpha$),

55.6 (SAA-OMe), 54.8 (SAA-C^2), 53.8 (Tyr-C^α), 50.3 (SAA-C^6), 37.0 (Tyr-C^β), 36.8 (Tyr-C^β); HRMS (FAB) calcd for $C_{56}H_{64}N_{12}O_{18}$-Na (M + Na) 1215.4359, found 1215.4340.

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Supporting Information Available: General experimental methods, experimental procedures and physical data for compounds **2**−**8** and **9b**−**11b**, ^{1}H NMR spectra for all new compounds, ^{13}C NMR spectra for compounds **11a,b**, and tables of atom coordinates and pdb files for minimized **11a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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