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Synthesis of triazole cages containing C_3-symmetric α-cyclic tripeptide scaffold

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ABSTRACT

Two water-soluble C_3-symmetric 1,2,3-triazole cages containing α-cyclic tripeptide were efficiently synthesized. The key steps include a click reaction to incorporate L-glutamic or L-aspartic acids to a tripodal linker and a unique one-pot cyclotrimerization.

Cyclic peptides are important biomolecules,[1] because of their broad-ranging biological applications. Its rigid peptide backbone reduces the entropic penalty to help it act as a biological receptor.[2] The presence of optically pure amino acids allows cyclic peptides to form a chiral scaffold. Among them, C_3-symmetrical systems have wide applications in several areas, such as molecular receptors,[3] dendrimers,[4] organometallic ligands,[5] and asymmetric catalysis.[6] The synthesis of cage like macromolecular structures with well defined 3D sizes and shapes derived from constrained cyclic peptide scaffolds[7] is a promising research topic.[8] The 3D geometrical constraints produced by the cage molecules make them extremely useful in the field of supramolecular chemistry.[9] Cyclic hexapeptides are in general, relatively flexible compared to cyclic tripeptide; to make the backbone rigid, heterocyclic rings were usually incorporated.[7a,b]

All reported cyclic peptide cages were synthesized from naturally occurring thiazole- and oxazole-containing cyclic hexapeptide alkaloids as scaffolds (derived from serine, threonine, and cysteine amino acids).[10] Positively-charged triazolium cages are known for sensing halides, fluorides, chlorides, and oxoanions.[11] Triazole cage[12] with α-cyclic tripeptide is remained unreported because synthetic difficulties of cyclic nine-member ring synthesis. Cyclic tripeptides are the most rigid member of the cyclic peptide family and require all *cis* amide bonds[13] to synthesize it. In cyclic state, it stays in crown[14] form that helps cyclic tripeptides to act as unique receptors.

We constructed two new C_3-symmetric cages (**1** and **2**) that contain either L-glutamyl or L-aspartyl cyclic tripeptide scaffolds with a unique nine-member backbone structure. Synthesis was achieved via a tripodal compound, which controlled its self-assembly and cyclooligomerization during cyclization.

We took Boc-L-glutamic acid γ-benzyl ester **3** as a building block to construct cage **1**. The α-acid of compound **3** was protected with methyl group by reacting with dimethyl sulfate in the presence of potassium carbonate in acetone to give Boc-L-glutamyl-α-(OMe)-γ-benzyl ester **4**. Liberation of carboxylic acid in side chain of **4** with Pd/C-catalyzed hydrogenolysis, followed by coupling with propargylamine in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC), hydroxybenzotriazol (HOBt), and triethylamine (TEA) in dichloromethane resulted in a propargylamine modified compound **6** with a 90% yield. Alternatively, compound **5** can be directly prepared from Boc-L-glutamic acid enzymatically with a 90% yield[15] (Scheme 1).

We choose tris 2-azidoethyl amine **9** as tripodal linker instead of tris-carboxylic acid to avoid the formation of diastereomer cages.[16] Tris 2-azidoethyl amine **9** was prepared from tris 2-chloroethyl amine hydrochloride[17] **8** using reported procedure[18] (see Supporting information).

Side chain Boc-L-glutamyl-α(OMe) propargyl amide **6** was attached with tripodal linker **9** via click reaction.[19] Mixing lutidine, *N,N*-diisopropylethylamine (DIPEA), and Cu(I) iodide in degassed acetonitrile gave glutamyl-tripodal methyl ester **10** with a 90%

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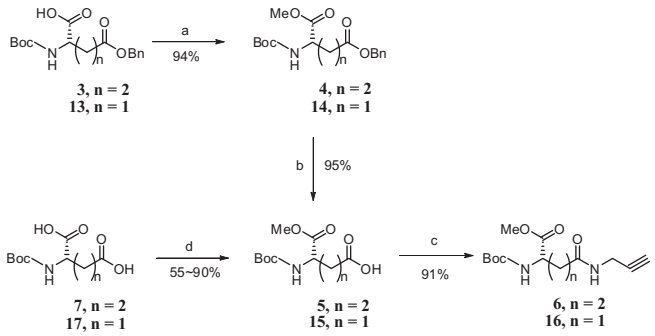
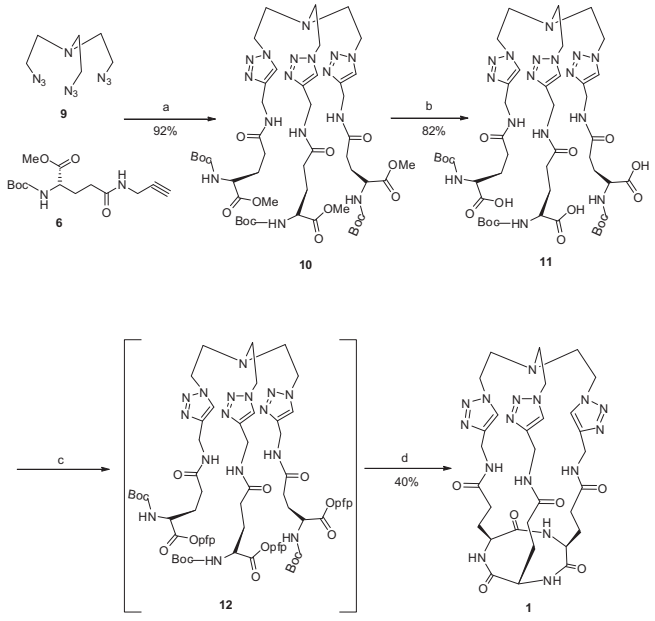


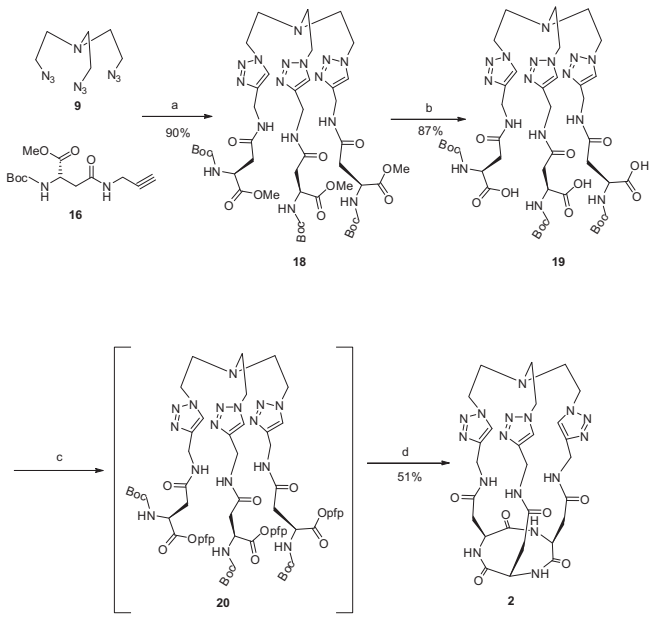
Scheme 1. *Reagents and conditions*: (a) dimethyl sulfate, K_2CO_3, acetone; (b) Pd/C, H_2, MeOH; (c) DCC, HOBt, TEA, propargylamine, 0 °C ~ rt; (d) Papain, pH 4.2, MeOH.

yield. Three α-methyl esters on tripodal **10** were removed by saponification in 1 N NaOH/methanol (1:1), followed by coupling with pentafluorophenol, which led to form a glutamyl-tripodal activated ester **12**. This tripodal **12** was treated with TFA to effect the cleavage of Boc group and was, then, subjected to macrocyclization in pyridine at high dilution (2 mM) to provide water-soluble cyclotriglutamyl cage **1**[20] with a 40% yield (Scheme 2). An attempt was made to directly cyclize fully deprotected tripodal amino acids by PyBOP and DIPEA in DMF at high dilution. However, it ended up with cyclooligomer as the major product. Formation of monomeric compound was confirmed from mass spectrometry. The NMR spectroscopic data for **1** were consistent with those expected for C_3-symmetric cyclotriglutamyl cage. Two singlet peaks at δ 2.89 and δ 4.16 were observed in ^{1}H NMR spectrum for the corresponding two –CH_2 groups of tripodal linker. NMR signals were also observed for α-protons (δ 4.21–4.24) within the cyclotripeptide ring and –CH protons (δ 7.34–7.56) of triazole rings. ^{13}C spectrum showed only one set of carbon peaks and directly supported the formation of a C_3-symmetric cage.

After successful synthesis of cyclotriglutamyl cage, we attempted to synthesize cyclotriaspartyl cage and extend our study to know the effect of a shortened side chain amino acid on the



Scheme 2. *Reagents and conditions*: (a) lutidine, DIPEA, CuI, acetonitrile; (b) 1 N NaOH/MeOH; (c) DCC, pentafluorophenol, DCM; (d) (i) TFA/DCM (1:1), 0 °C, (ii) pyridine, high dilution, rt.



Scheme 3. *Reagents and conditions*: (a) lutidine, DIPEA, CuI, acetonitrile; (b) 1 N NaOH/MeOH; (c) DCC, pentafluorophenol, DCM; (d) (i) TFA/DCM (1:1), 0 °C, (ii) pyridine, high dilution, rt.

construction of cyclic tripeptide cage. As previously noted, we modified the aspartic acid side chain. The side chain propargylamine modified Boc-L-Asp(OMe) **16** was synthesized with a 91% yield from Boc-L-aspartic acid-γ-(OBn) **13** via α-methyl esterification, followed by removal of γ-benzyl ester and coupling with propargylamine by DCC in dichloromethane (Scheme 1).

Modified aspartic acid **16** was attached with a tripodal linker **9** (3:1 ratio) via click reaction to obtain aspartyl-tripodal methyl ester **18** with a 90% yield. Methyl esters were removed by basic hydrolysis and followed by esterification with pentafluorophenol gave aspartyl-tripodal activated ester **20**. It was further treated with TFA to remove the Boc protecting group and subjected to cyclization in pyridine at high dilution to obtain water-soluble cyclotriaspartyl cage **2**[21] with a 51% yield (Scheme 3). An 11% increase in yield indicates that chain length may play a vital role in cyclization step. Tripodal with longer chain lengths is probably more flexible at reducing the chances of cyclization. As a result, a short chain length tripodal will convert more to the corresponding cage. Mass spectroscopy also confirmed the formation of the desired monomer. Furthermore, C_3-symmetric structure of **2** was confirmed by ^{1}H NMR spectra which showed two triplet peaks at δ 2.85, δ 4.10 for tripodal linker and one singlet peak at δ 7.49 for triazole ring. The presence of only one set of carbon peaks in ^{13}C NMR supports the presence of symmetry.

Two novel cryptand like cages **1** and **2** based with α-cyclic tripeptide scaffold were synthesized in good yields. This is the first synthesis of cages that contain nine-member cyclic tripeptide ring. We synthesized cyclic scaffold and cages simultaneously via controlled assembly using a tertiary nitrogen linker. This cyclization technique can be used to overcome synthetic barriers for the formation of rigid 9-member cyclic tripeptides with polar side chain. Applications for water-soluble triazole hosts[11c] to be used as a potential 3D carrier to enhance dissolution rate for poor water-soluble guests are currently in progress.

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Supplementary data

Supplementary data (experimental details and spectroscopic characterization of all compounds along with ^{1}H, ^{13}C NMR, IR and mass spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.089.

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20. *Data for* ***1***: $[\alpha]_D^{21}$ 8 (*c* 0.1, MeOH); ^{1}H NMR: (D_2O, 400 MHz) 1.87–1.92 (m, 2H), 2.00–2.01 (m, 2H), 2.28 (t, 6H, *J* = 8.08 Hz), 2.35–2.45 (m, 2H), 2.89 (s, 6H), 4.16 (s, 6H), 4.21–4.24 (m, 3H), 4.32 (s, 2H), 4.38 (s, 4H), 7.34–7.56 (m, 3H); ^{13}C NMR: (D_2O, 100 MHz) 25.1, 29.2, 34.4, 48.4, 53.1, 57.0, 123.8, 144.2, 174.7, 182.2. IR (KBr) 3410, 2956, 2108, 1678, 1550, 1436, 1390, 1253, 1152, 1120, 1059, 770, 667 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{30}H_{43}N_{16}O_6$ $[M+H]^+$ 723.3547; found 723.3622.
21. *Data for* ***2***: $[\alpha]_D^{21}$ −11 (*c* 0.1, $CHCl_3$); ^{1}H NMR: (D_2O, 400 MHz) 2.45 (dd, 3H, *J* = 5.53 Hz, *J* = 18.29 Hz), 2.85 (t, 6H, *J* = 6.24 Hz), 3.03 (q, 3H), 3.87 (q, 3H), 4.10 (t, 6H, *J* = 5.78 Hz), 4.65 (s, 6H), 7.49 (s, 3H); ^{13}C NMR: (D_2O, 100 MHz) 33.4, 36.6, 48.6, 49.8, 53.2, 124.4, 141.7, 177.5, 180.9; IR (KBr) 3429, 2926, 2854, 1707, 1666, 1546, 1434, 1406, 1338, 1226, 1170, 1057, 617, 579 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{37}N_{16}O_6$ $[M+H]^+$ 681.3076; found 681.3125.