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An efficient and convergent route towards water-soluble, chiral and amphiphilic macrocycles

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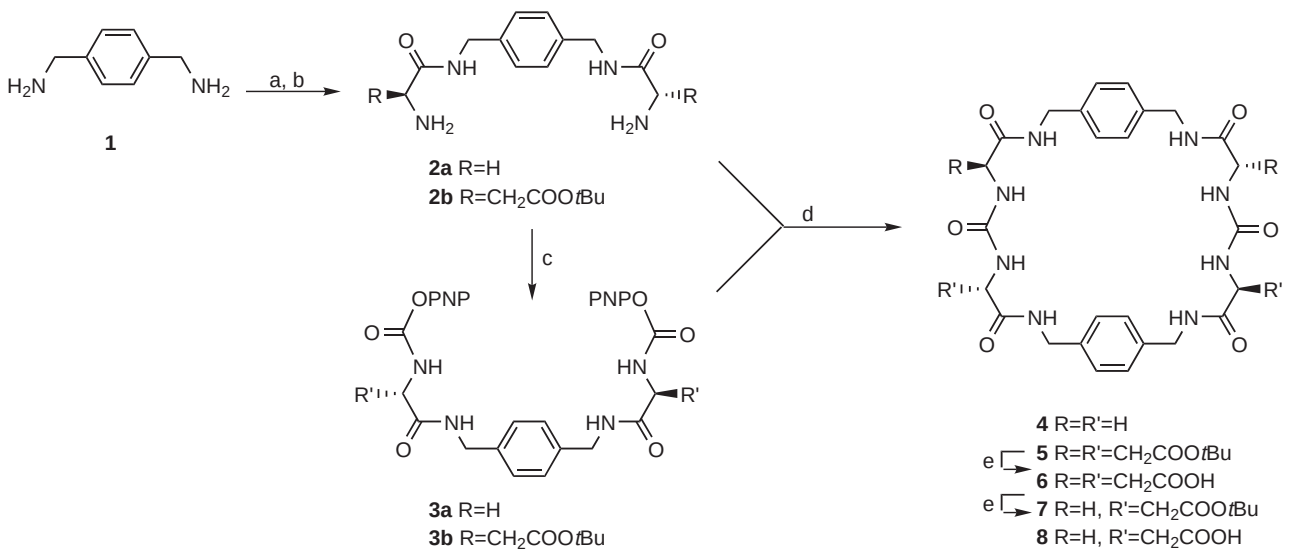
Abstract—A practical procedure for the synthesis of water-soluble, chiral and amphiphilic macrocyclic molecules is described. Acylation of *p*-xylylene diamine with Fmoc-protected glycine and aspartic acid, followed by removal of the Fmoc moiety afforded amino acid:*p*-xylene conjugates as free diamines. These diamines were converted to symmetrical and unsymmetrical macrocycles via stepwise urea formation using *p*-nitrophenyl chloroformate. © 2001 Elsevier Science Ltd. All rights reserved.

Macrocyclic structures have received much attention in the search for artificial receptors, mainly because of their inherent reduced flexibility and higher degree of pre-organization as compared to their acyclic counterparts. Consequently, several elegant and efficient macrocyclic receptors for biomolecules in organic solvents, as well as some in aqueous environment, have been reported.[1,2] Within our ongoing research activities towards receptors for biomolecules, we sought a straightforward, yet flexible, method for the synthesis of water-soluble and chiral macrocyclic structures displaying diverse functionalities capable of taking part in different types of intermolecular interactions (hydrogen bonds, charge–charge, van der Waals, hydrophobic, etc.). In this respect, macrocyclizations based on urea formation between diamines appeared to be an attractive approach. Syntheses of achiral,[3–10] as well as chiral,[11,12] macrocyclic ureas have been reported and some have been shown to function as receptors for cations[3–7] or anions.[10,12]



Scheme 1. (a) Fmoc-amino acid, DIC, HOBt, THF. (b) Piperidine, DMF. (c) *p*-Nitrophenyl chloroformate, pyridine, DMF. (d) **2a**+**3a**→**4**, **2b**+**3b**→**5** or **2a**+**3b**→**7** pyridine, DMAP, DMF. (e) TFA, H_2O.

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In this letter we describe a simple synthetic route towards water-soluble and chiral macrocyclic amphiphiles, using predictable and high-yielding amide and urea bond forming reactions between amino acids and a diamino-functionalized hydrophobic scaffold. The amide and urea moieties are expected to induce rigidity in the final products, as well as providing sites for hydrogen bonding. In addition, the use of amino acids as building blocks allows for convenient introduction of charged and polar functionalities, which promotes water-solubility and provides sites for charge–charge or hydrogen bonding interactions. The methodology is demonstrated with the synthesis of three macrocycles based on the amino acids glycine and L-aspartic acid.

As a building block for the hydrophobic part of the amphiphilic macrocycles, the readily available *p*-xylylene diamine **1** was selected (Scheme 1). Carbodiimide/hydroxybenzotriazole-promoted acylation with Fmoc-protected amino acids, followed by Fmoc-cleavage, afforded the bis-glycine and aspartic acid derivatives **2a** and **2b** in 95 and 90% yields, respectively.[13] The choice of an amino-reactive cross-linking reagent for macrocyclizations of **2a** and **2b** fell on *p*-nitrophenyl chloroformate, because it allows selective reaction with one amine component at a time via an intermediate *p*-nitrophenyl carbamate. Thus, treatment of **2a** and **2b** with an excess of *p*-nitrophenyl chloroformate yielded the *p*-nitrophenyl carbamates **3a** and **3b** in 50 and 67% yields.

Macrocyclizations were accomplished under high dilution conditions (1.4 mM) with amines **2**, *p*-nitrophenyl carbamates **3**, pyridine and DMAP in *N*,*N*-dimethylformamide over 12 h. The macrocyclic compounds **4**, **5** and **7** precipitated as the major products (38, 53 and 28%, respectively).[14] *t*-Butyl esters in compounds **5** and **7** were removed with trifluoroacetic acid to give the final macrocycles **6** and **8** in 80 and 75% in purities of >95% according to NMR spectroscopy. The glycine-based macrocycle **4** was insoluble in PBS buffer (pH 7.2), while the L-aspartate-containing compounds **6** and **8** proved to be highly soluble, thus fulfilling a fundamental prerequisite for biomimetic receptors.

In summary, we have developed a simple and high-yielding procedure for the synthesis of water-soluble and chiral amphiphilic macrocycles. A particularly attractive feature of our simple and flexible procedure is that it is amenable for diversification of the amino acid and/or the hydrophobic diamine components, which would give rapid access to libraries of water-soluble and chiral amphiphilic macrocycles.

Acknowledgements

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13. All compounds were characterized by ^{1}H NMR (1D and 2D), MALDI-TOF MS, and FAB-HRMS: **2a**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.27 (s, 4H, ArH), 4.40 (bs, 4H, $ArCH_2$), (d, 4H, *J* 1.6 Hz, CH_2CO); MALDI-TOF-MS *m*/*z* calcd for $C_{12}H_{18}N_4NaO_2$ (M+Na): 273.1, found 274.0; FAB-HRMS *m*/*z* calcd for $C_{12}H_{19}N_4O_2$ (M+H): 251.1508, found 251.1459. **2b**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.26 (s, 4H, ArH), 4.37 (d, 4H, *J* 4.4 Hz, $ArCH_2$), 3.64 (t, 2H, *J* 6.0 Hz, CHCO), 2.67 (dd, 2H, *J* 5.7, 16.3 Hz, CH_2CO), 2.55 (dd, 2H, *J* 6.8, 16.3 Hz, CH_2CO), 1.45 (s, 18H, CH_3); MALDI-TOF-MS *m*/*z* calcd for $C_{24}H_{38}N_4NaO_6$ (M+Na): 501.3, found 501.7; FAB-HRMS *m*/*z* calcd for $C_{24}H_{39}N_4O_6$ (M+H): 479.2870, found 479.2874. **3a**: ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.55 (t, 2H, *J* 5.6 Hz, $ArCH_2N\mathit{H}$), 8.27 (d, 4H, *J* 9.0 Hz, ArH), 7.42 (d, 4H, *J* 9.0 Hz, ArH), 7.22 (s, 4H, ArH), 4.27 (d, 4H, *J* 5.5 Hz, $ArCH_2$), 3.75 (d, 4H, *J* 5.8 Hz, CH_2CO). **3b**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.65 (t, 2H, *J* 5.4 Hz, $CH_2N\mathit{H}$), 8.26 (d, 4H, *J* 9.2 Hz, ArH), 7.37 (d, 4H, *J* 9.2 Hz, ArH), 7.26 (s, 4H, ArH), 4.57 (m, 2H, CHCO), 4.40 (m, 4H $ArCH_2$), 2.87 (dd, 2H, *J* 5.6, 16.2 Hz, CH_2CO), 2.68 (dd, 2H, *J* 8.1, 16.2 Hz, CH_2CO), 1.46 (s, 18H, CH_3). **4**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.49 and 8.42 (2s, 2H each, $ArCH_2N\mathit{H}$), 7.29 (s, 8H, ArH), 6.60 (bs, 4H, $COCH_2N\mathit{H}$), 4.35 (bs, 8H, $ArCH_2$), 3.77 (d, 8H, *J* 15.8 Hz, CH_2CO); MALDI-TOF-MS *m*/*z* calcd for $C_{26}H_{32}N_8NaO_6$ (M+Na): 575.2, found 575.8. **5**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.16 (s, 4H, $ArCH_2N\mathit{H}$), 7.12 (s, 8H, ArH), 6.55 (bs, 4H, $CHN\mathit{H}$), 4.10–4.42 (m, 10H, $ArCH_2$, $C\mathit{H}$), 1.37 (s, 36H, CH_3); MALDI-TOF-MS *m*/*z* calcd for $C_{50}H_{72}N_8NaO_{14}$ (M+Na): 1031.5, found 1031.2. **6**: ^{1}H NMR (400 MHz, *d*-PBS, pD 7.2) δ 7.17 (s, 8H, ArH), 4.27 (ABq, 8H, *J* 15.9, 22.2 Hz, $ArC\mathit{H}_2$), 4.24 (dd, 4H, *J* 4.6, 8.3 Hz,

C*H*CH_2), 2.56 (dd, 4H, *J* 4.6, 16.0 Hz, CHC*H*$_2$), 2.47 (dd, 4H, *J* 8.3, 16.0 Hz, CHC*H*$_2$); MALDI-TOF-MS *m*/*z* calcd for $C_{34}H_{41}N_8O_{14}$ (M+H): 785.3, found 784.0. **7**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.32 (bs, 4H, $ArCH_2NH$), 7.14 (s, 4H, ArH), 7.12 (s, 4H, ArH), 6.52 (dd, 2H, *J* 8.2, 14.4 Hz, N*H*COCH), 6.43 (t, 2H, *J* 7.0 Hz, N*H*COCH$_2$), 4.41 (dd, 2H, *J* 8.2, 14.4 Hz, CH), 4.16–4.32 (m, 8H, $ArCH_2$), 3.78 (dd, 2H, *J* 6.9, 16.7 Hz, $COCH_2NH$), 3.44 (dd, 2H, *J* 16.1 Hz, $COCH_2NH$), 2.59–2.63 (m, 4H, CHC*H*$_2$), 1.36 (s, 18H, CH_3); MALDI-TOF-MS *m*/*z* calcd for $C_{30}H_{37}N_8O_{10}$ (M+H): 669.3, found 669.8. **8**: ^{1}H NMR (400 MHz, *d*-PBS, pD 7.2) δ 7.05 (s, 4H, ArH), 7.01 (s, 4H, ArH), 4.35 (dd, 2H, *J* 4.6, 8.6 Hz, C*H*CH_2), 4.27 (d, 2H, *J* 15.7 Hz, ArC*H*$_2$), 4.17 (d, 2H, *J* 15.5 Hz, ArC*H*$_2$), 4.15 (d, 2H, *J* 15.7 Hz, ArC*H*$_2$), 4.10 (d, 2H, *J* 15.5 Hz, ArC*H*$_2$), 3.90 (d, 2H, *J* 17.5 Hz, C*H*$_2$CO), 3.62 (d, 2H, *J* 17.5 Hz, C*H*$_2$CO), 2.58 (dd, 2H, *J* 4.6, 15.7 Hz, CHC*H*$_2$), 2.46 (dd, 2H, *J* 8.6, 15.7 Hz, CHC*H*$_2$); MALDI-TOF-MS *m*/*z* calcd for $C_{30}H_{37}N_8O_{10}$ (M+H): 669.3, found 669.6; FAB-HRMS *m*/*z* calcd for $C_{30}H_{37}N_8O_{10}$ (M+H): 669.2633, found 669.2647.

14. Typical procedure for macrocyclization: To a solution of pyridine (8.6 μL) and DMAP (1 mg) in DMF was added **2a** (27.5 mg, 110 μmol) and **3a** (63.8 mg, 110 μmol). After 12 h, the white precipitate formed was filtered off and washed with DMF and MeOH to give **4** (23 mg, 38%).