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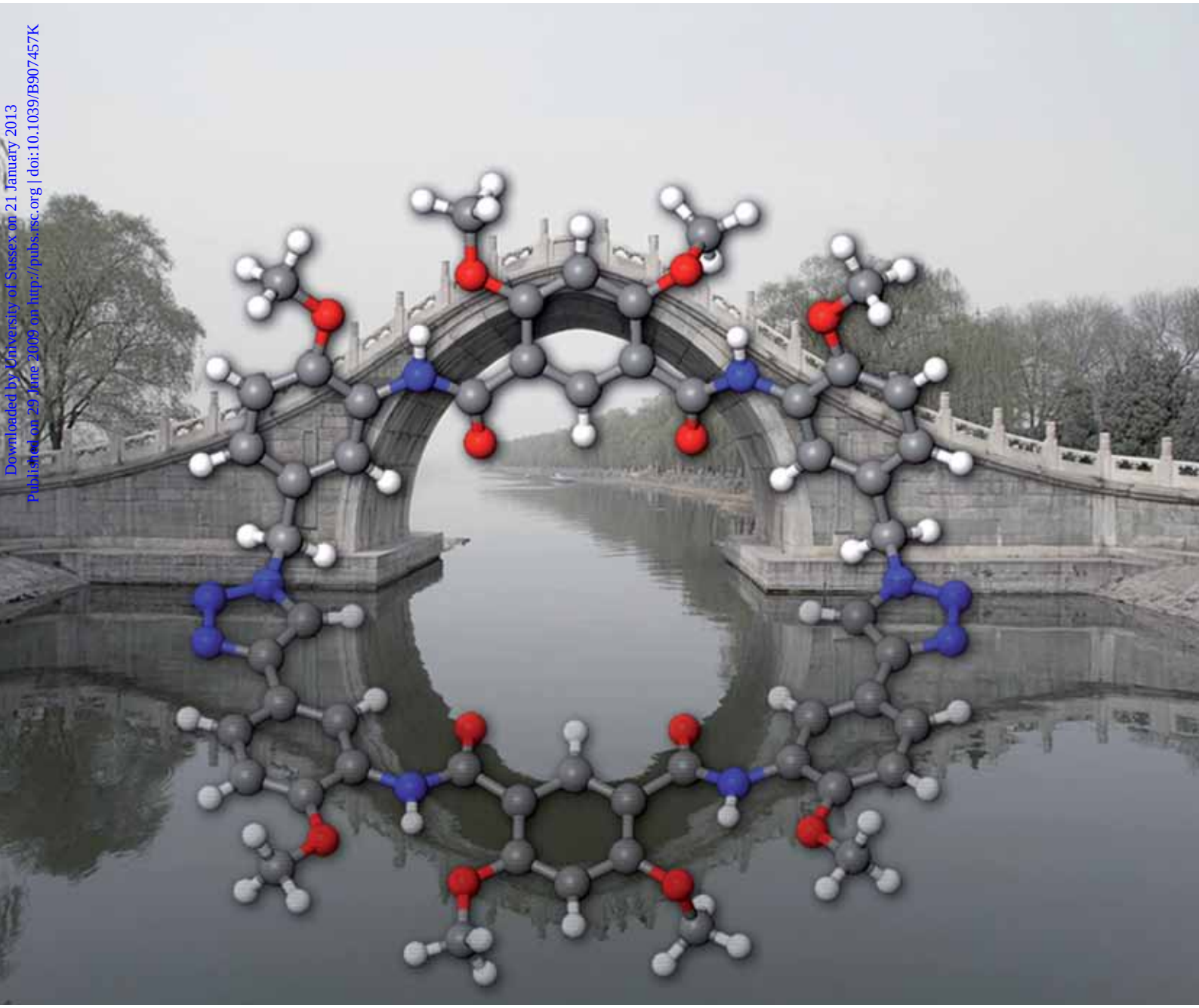

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A click chemistry approach for the synthesis of macrocycles from aryl amide-based precursors directed by hydrogen bonding†

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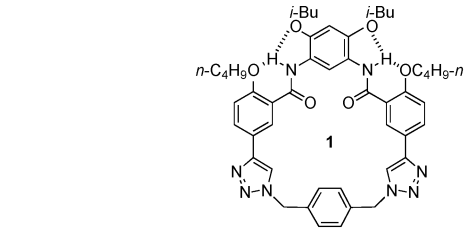
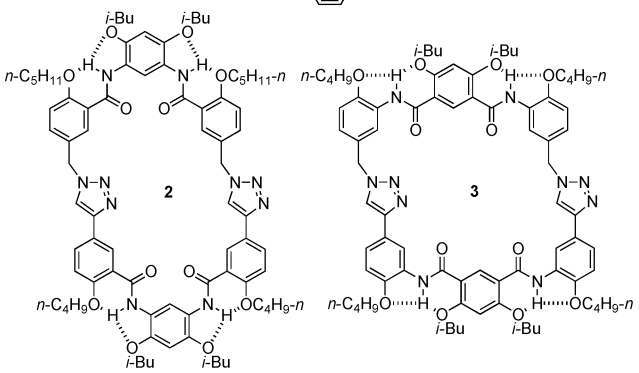
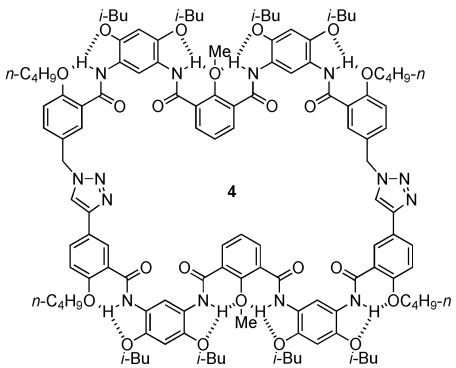
This paper describes the synthesis of four aryl amide-based macrocycles through the 1 + 1 formation of two 1,2,3-triazole units by click chemistry. Two series of aryl amide-based precursors that bear two azide or acetylene units have been prepared. Intramolecular hydrogen bonding has been utilized to induce them to adopt a U-styled conformation, which remarkably promotes the macrocyclization of two structurally matched precursors.

Introduction

In the past decade, the development of new approaches for the synthesis of shape-persistent macrocycles has received considerable attention due to their usefulness in molecular recognition, sensing and advanced materials.[1] One family of such rigid architectures consists of repeated or separated aryl amide segments, which have traditionally been synthesized stepwise or by one-step, multi-component macrocyclizations.[2] Recent advances in hydrogen bonding-driven foldamers of aryl amide-based backbones have allowed for the development of new preorganized precursors or intermediates,[3] which are capable of forming macrocyclic products in remarkably high or even quantitative yields.[4,5] With the increasing applications of "click" chemistry in the synthesis of discrete macrocyclic systems,[6–9] we became interested in constructing well-defined aryl amide-based macrocycles by making use of this approach. We herein report the synthesis and characterization of four such macrocyclic molecules, *i.e.*, **1–4**.







Results and discussion

To synthesize the above macrocycles, we have designed precursors **5–10**, which bear two ethynyl or azido units. Their aromatic backbones have been established to adopt the preorganized U-shaped conformation, which are stabilized by intramolecular hydrogen bonding.[10] These frameworks have been used to assemble several molecular tweezers for binding discrete guests.[11] The azidomethyl group is flexible, which should avoid any large tension generated due to the intramolecular hydrogen bonding for the target molecules.

For the synthesis of precursor **5** (Scheme 1), **11**[10] was first iodized with iodine in the presence of silver sulfate in ethanol to give **12** quantitatively. The ester was then hydrolyzed with lithium hydroxide to give **13**. With **13** being available, **14**[12] was reacted with *iso*-butanol in triethylamine to afford **15**,[13] which was further hydrogenated to give **16**. This diamine was instable in the air and, without purification, reacted with two equiv of the acyl chloride of **13** to give compound **17** in 95% yield. Palladium-catalyzed coupling of **17** with ethynyltrimethylsilane in triethylamine and THF generated **18** in 90% yield. Compound **5** was then obtained in 95% yield by treating **18** with tetrabutylammonium fluoride (TBAF) in dichloromethane and methanol. The 1 + 1 cycloaddition of **5** to **19**[14] in the presence of DIPEA and cupric iodide in chloroform was then performed, which generated **1** in 20% yield.

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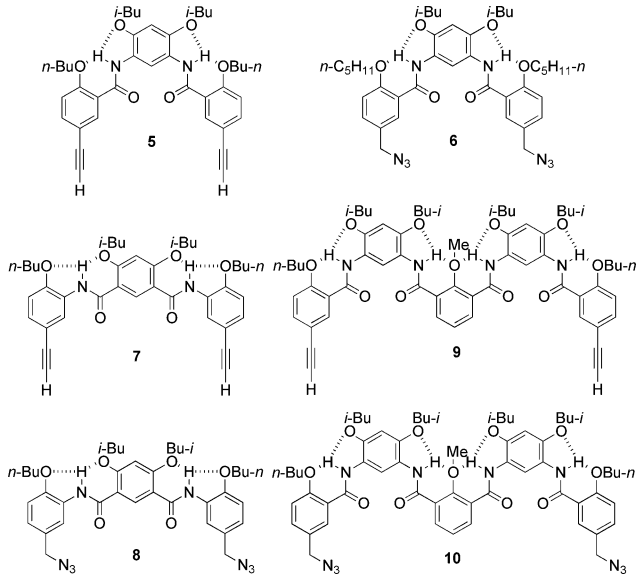
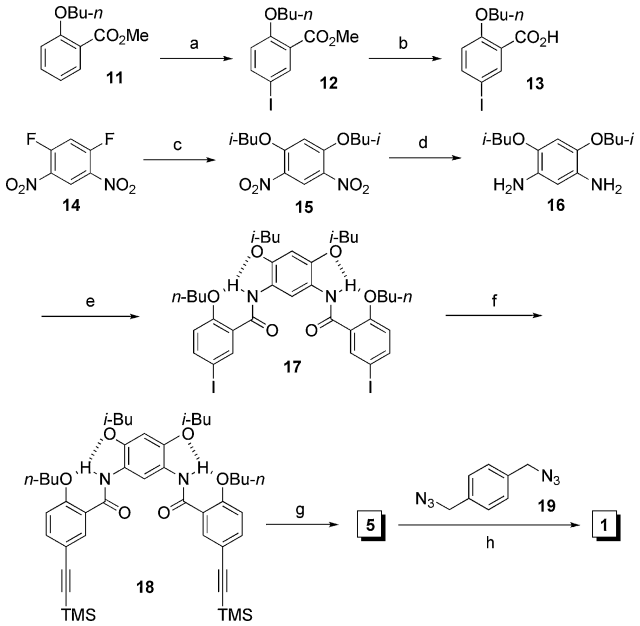
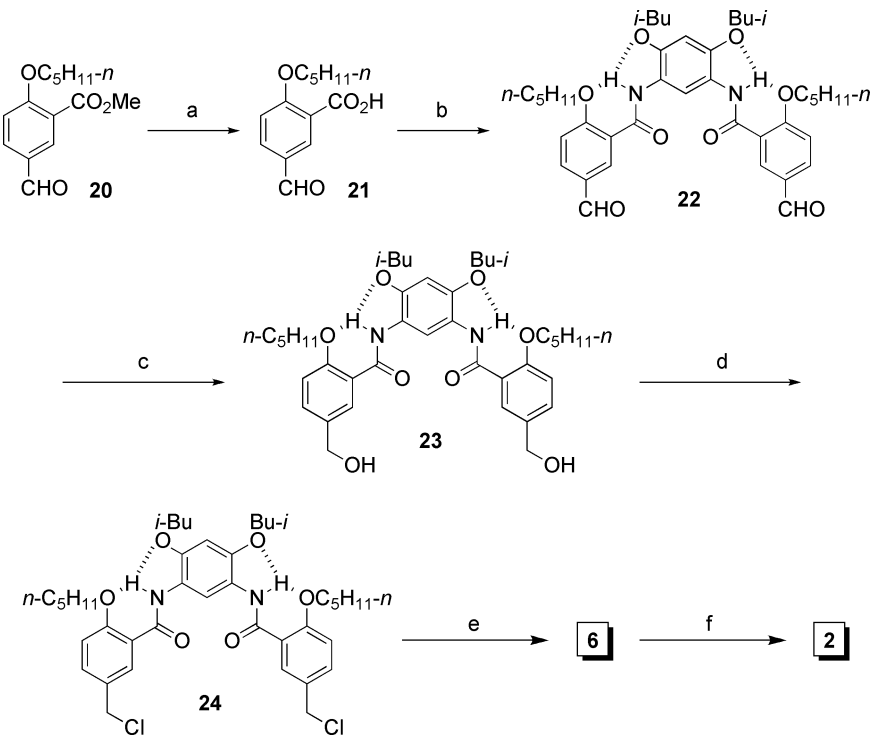




Scheme 1 *Reagents and conditions*: (a) I_2, Ag_2SO_4, EtOH, r.t., 3 h, 100%; (b) $LiOH{\cdot}H_2O$, H_2O/MeOH/THF, r.t., 12 h, 100%; (c) *i*-BuOH, Et_3N, r.t., 12 h, 100%; (d) H_2 (60 atm), Pd-C (10%), THF, 6 h, 100%; (e) **13**, $(COCl)_2$, DMF (cat), THF, 30 min; then NEt_3, THF, 0 °C to r.t., 95%; (f) ethynyltrimethylsilane, $PdCl_2(PPh_3)_2$, CuI, THF/Et_3N, 40 °C, 4 h, 90%; (g) *t*-Bu_4NF, CH_2Cl_2, 0.5 h, 95%. (h) CuI, DIPEA, $CHCl_3$, r.t., 24 h, 20%.

The synthetic route for **6** is shown in Scheme 2. Ester **20**[11a] was first prepared according to the reported method and then hydrolyzed with sodium hydroxide to give **21** in 95% yield. The acid was then coupled with **16** to produce **22** in 91% yield. This reaction needed a long time because imine derivatives might also be formed, which took time to be converted to the amide due to its reversible feature. The dialdehyde was then reduced with sodium borohydride to diol **23** in 90% yield, which was further treated with thionyl chloride at 0 °C to give **24** in 95% yield. Finally, **6** was prepared quantitatively from the reaction of **24** with sodium azide in hot DMF. The macrocyclization reaction of **5** and **6** in chloroform in the presence of DIPEA and cupric iodide was then carried out at 10 mM to give compound **2** in 82% yield, which is remarkably higher than that for compound **1**, although **1** is much smaller than **2**. This result clearly illustrates the efficiency of the

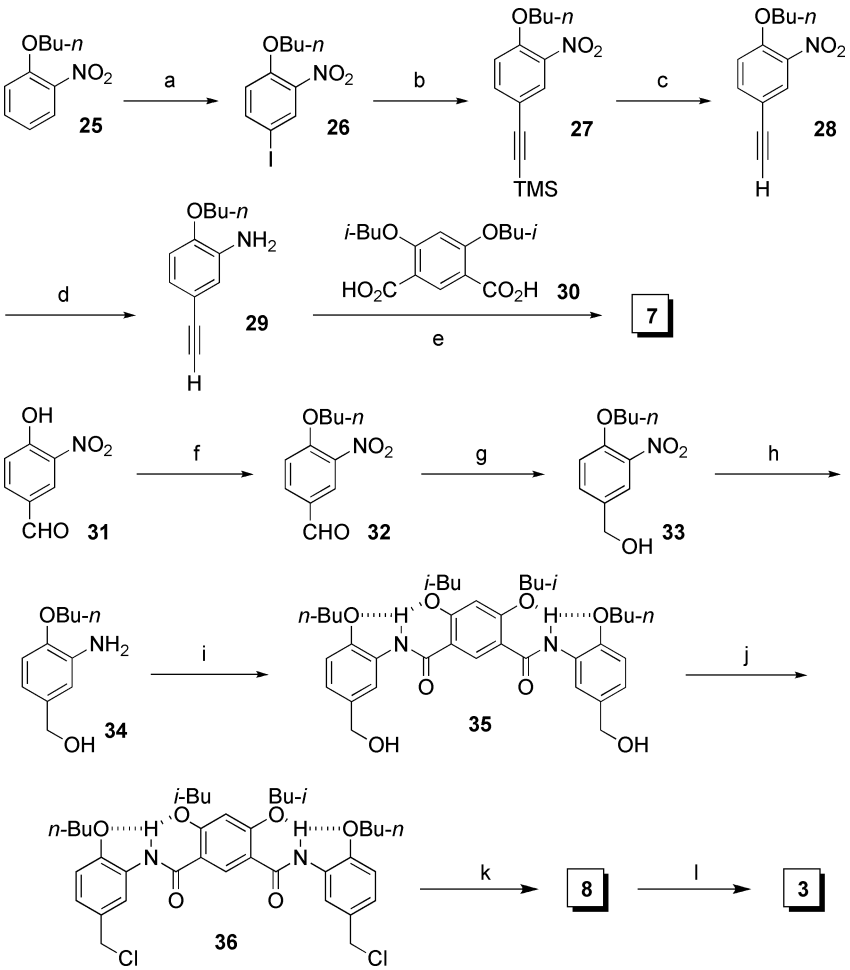


Scheme 2 *Reagents and conditions*: (a) NaOH, THF/H_2O/MeOH, r.t., 12 h, 95%; (b) **16**, $ClCO_2Pr$-*i*, Et_3N, $CHCl_3$, r.t., 24 h, 91%; (c) $NaBH_4$, THF/MeOH, 12 h, 90%; (d) $SOCl_2$, CH_2Cl_2, 0 °C, 2 h, 95%; (e) NaN_3, DMF, 80 °C, 4 h, 100%; (f) **5**, CuI, DIPEA, $CHCl_3$, 48 h, 82%.

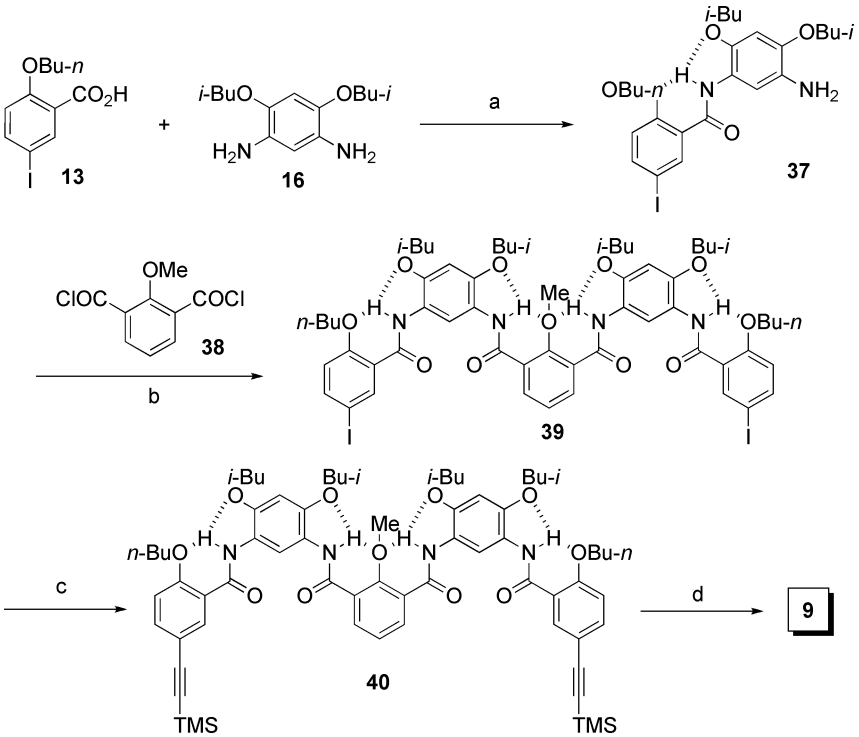
hydrogen bonding-induced preorganization of the precursors for macrocyclization.

Encouraged by the high yield of **2** from the reaction of **5** and **6**, we further prepared precursors **7** and **8**. The synthetic routes are shown in Scheme 3. The preparation of **7** started from the iodation of **25** with iodine and silver sulfate, which afforded **26** in 94% yield. Palladium-catalyzed coupling of **26** with an excess of ethynyltrimethylsilane gave **27** quantitatively, which was treated with TBAF in THF at 0 °C to yield **28** also quantitatively. Compound **28** was then selectively reduced to **29** with iron and ammonium chloride in refluxing aqueous solution of ethanol and THF. Under this reaction condition, the ethynyl group was not reduced. Compound **7** was then obtained in 90% yield by coupling **29** with **30**[13] through the related diacyl chloride. With **7** being available, phenol **31**[15] was reacted with butyl bromide with potassium carbonate as base to give **32** in 90% yield, which was reduced in THF and methanol by sodium borohydride to **33** in 95% yield. This intermediate was further reduced with iron and ammonium chloride in refluxing aqueous ethanol to afford **34** quantitatively. The aniline was then coupled with **30** in DMF in the presence of HATU and DIPEA to diol **35** in 85% yield, which was then treated with thionyl chloride in chloroform at 0 °C to afford **36** in 95% yield. Finally, compound **8** was prepared quantitatively from the reaction of **36** with sodium azide in hot DMF. Compounds **7** and **8** (1:1, 5 mM) reacted in chloroform and acetonitrile in the presence of cupric iodide and DIPEA to afford macrocycle **3** in 85% yield. The reaction could also be carried out in pure chloroform but took a much longer time. Acetonitrile might facilitate the reaction by increasing the solubility of catalyst cupric iodide. The formation of **3** in such a high yield should again be attributed to the preorganization of the two precursors.

To investigate the scope of this new approach, we also prepared two even larger precursors **9** and **10**. The synthetic route for **9** is shown in Scheme 4. Thus, **37** was first prepared in 89% yield from the coupling reaction of **13** and **16**. The reaction condition was identical to that for the preparation of **17**, but the starting materials were controlled at the 1:1 ratio. In this way, **37** could be prepared in high yield, because **37** is much less reactive than **16** for acylation. Compound **39** was then prepared in 90% yield by treating **37** with **38**[16] in THF. The diiodide was further coupled with ethynyltrimethylsilane under the catalysis of palladium in THF to produce **40** in 95% yield, which was then treated with TBAF in THF to give **9** in 95% yield.



Scheme 3 *Reagents and conditions*: (a) I_2, Ag_2SO_4, MeOH, reflux, 20 h, 94%; (b) ethynyltrimethylsilane, $PdCl_2(PPh_3)_2$, CuI, THF/Et_3N, r.t., 12 h, 100%; (c) TBAF, THF, 0 °C, 5 min, 100%; (d) Fe, NH_4Cl, EtOH/THF/H_2O, reflux, 2 h, 100%; (e) $(COCl)_2$, DMF (cat), THF, 30 min; then Et_3N, THF, 0 °C to r.t., 90%; (f) *n*-C_4H_9Br, K_2CO_3, KI (cat), DMF, 80 °C, 24 h, 90%; (g) $NaBH_4$, THF/MeOH, r.t., 1 h, 95%; (h) Fe, NH_4Cl, EtOH/H_2O, reflux, 4 h, 100%; (i) **30**, HATU, DIPEA, DMF, r.t., 85%; (j) $SOCl_2$, $CHCl_3$, 0 °C, 2 h, 95%; (k) NaN_3, DMF, 80 °C, 4 h, 100%. (l) CuI, DIPEA, $CHCl_3/CH_3CN$, 24 h, 85%.



Scheme 4 *Reagents and conditions*: (a) $(COCl)_2$, DMF (cat), THF, 0 °C, 30 min; then Et_3N, THF, 0 °C to r.t., 2 h, 89%; (b) NEt_3, THF, 0 °C to r.t., 2 h, 90%; (c) ethynyltrimethylsilane, $PdCl_2(PPh_3)_2$, CuI, NEt_3, THF, 40 °C, 12 h, 95%; (d) TBAF, THF, 0 °C, 30 min, 95%.

For the synthesis of **10** (Scheme 5), **42** was first prepared in 95% yield from the reaction of **41** and n-butyl bromide in hot DMF with potassium carbonate as base and then hydrolyzed with sodium hydroxide to acid **43** in 95% yield in aqueous methanol and THF. With **43** being available, compound **44** was prepared in 55% yield by treating **38** with two equiv of **16** in THF and further coupled with **43**, which was activated with isopropyl chloroformate, to produce **45** in 79% yield. The dialdehyde was then reduced with sodium borohydride to diol **46** in 95% yield, which was further reacted with thionyl chloride to afford **47** quantitatively. Finally, treatment of **47** with sodium azide in DMF produced **10** in quantitatively. The reaction of **9** and **10** (1:1, 5 mM) was then carried out in chloroform and acetonitrile in the presence of cupric iodide and DIPEA to afford macrocycle **4** in 25% yield.

When the reaction of **47** with sodium azide was performed at 80 °C in DMF in the presence of 1% water, compound **10** was not obtained. Instead, the reaction afforded **48** exclusively. The reaction did not occur in the absence of sodium azide, which implied that sodium azide promoted the hydrolysis of the anisole of **47** or **10**. The reaction of **48** with **9** was also performed under the reaction condition used for the preparation of **4**. MALDI-FT mass spectrum displayed the ion peak of the corresponding macrocycle **49**. However, no pure sample could be separated due to the low yield. The result again shows the importance of the conformational preorganization of the precursors for the macrocyclizations.

Conclusion

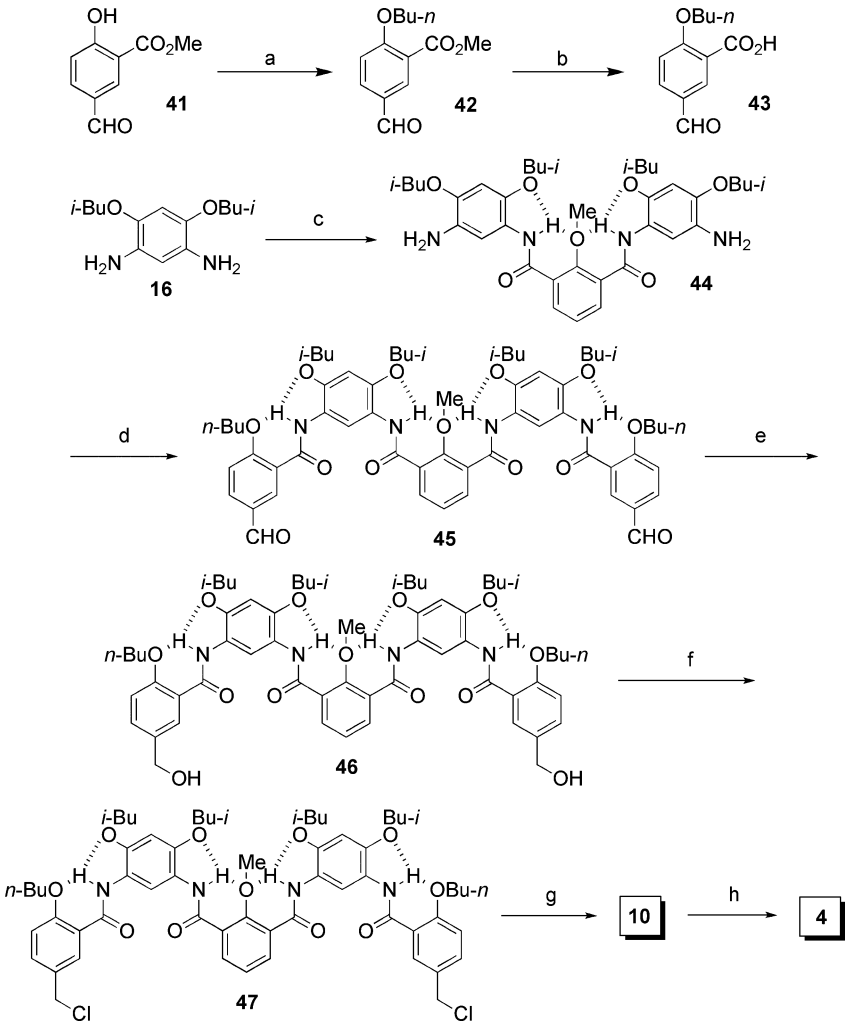
In conclusion, we have demonstrated that macrocyclic architectures can be constructed in modest to high yields through click chemistry by making use of the hydrogen bonding-induced preorganization of aromatic amide-based precursors. Considering that triazole-based macrocycles and foldamers are good receptors for anions[8,17] and their analogues are good hydrogen bonding acceptors, the new macrocycles may find applications in studies in molecular recognition. Compared to the fully hydrogen bonded macrocycles,[4,5] the new macrocycles consist of two rigid segments which are connected with two flexible methylene units. The two rigid segments of these macrocycles may oscillate or fold. Therefore, they may also display new interesting stacking properties.[18]

Experimental section

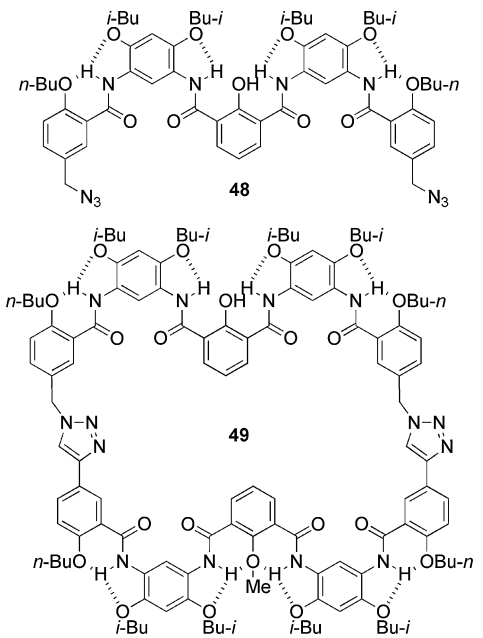
Unless otherwise indicated, all reactions were carried out under a nitrogen atmosphere. Starting materials were obtained from commercial suppliers and used without further purification. The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (chloroform: δ 7.26 ppm; DMSO: δ 2.49 ppm). MALDI-TOF spectra were obtained on Voyager-DE STR or IonSpec 4.7 Tesla FTMS spectrometer.

Compound 12

To a solution of **11** (1.81 g, 8.70 mmol) in ethanol (45 mL) were added silver sulfate (2.73 g, 8.70 mmol) and iodine (2.21 g, 8.70 mmol). The mixture was then stirred for 3 h and then the solid filtered off. The filtrate was concentrated under reduced pressure and the resulting slurry triturated with AcOEt (30 mL). The solution was washed with water (30 mL) and brine (30 mL) and dried over sodium sulfate. After the solvent was removed under



Scheme 5 *Reagents and conditions*: (a) *n*-C_4H_9Br, K_2CO_3, KI (cat), DMF, 80 °C, 5 h, 95%; (b) NaOH, H_2O/MeOH/THF, r.t., 12 h, then HCl, 95%; (c) **38**, NEt_3, THF, 0 °C to r.t., 2 h, 55%; (d) $ClCO_2Pr$-*i*, NEt_3, $CHCl_3$, r.t., 24 h, 79%; (e) $NaBH_4$, MeOH/THF, r.t., 6 h, 95%; (f) $SOCl_2$, CH_2Cl_2, 0 °C, 2 h, 100%; (g) NaN_3, DMF, r.t., 12 h, 100%; (h) CuI, DIPEA, $CHCl_3$, CH_3CN, 24 h, 25%.



reduced pressure, the resulting residue was subjected to column chromatography (PE/EA, 20:1) to give **12** as a solid (2.90 g, 100%). ^{1}H NMR ($CDCl_3$): δ 8.05 (d, J = 2.4 Hz, 1 H), 7.69 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1 H), 6.73 (d, J = 9.0 Hz, 1 H), 4.00 (t, J = 6.6 Hz, 2 H), 3.87 (s, 3 H), 1.84–1.75 (m, 2 H), 1.57–1.44 (m, 2 H), 0.97 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 158.5, 141.8, 139.9, 122.4, 115.3, 81.4, 68.8, 52.1, 31.0, 19.1, 13.8. MS (ESI): m/z 389.0 $[M + K]^+$. Anal. Calcd. for $C_{12}H_{15}IO_3$: C, 43.13; H, 4.52. Found: C, 43.44; H, 4.67.

Compound 13

A solution of **12** (0.67 g, 2.00 mmol) and lithium hydroxide monohydrate (0.17 g, 4.00 mmol) in water (10 mL), THF (6 mL) and methanol (4 mL) was stirred for 12 h and then concentrated to 10 mL. The resulting residue was acidified with diluted hydrochloric acid (5%) to pH = 3. The formed precipitate was filtrated off and washed with cold water to give **13** as a white solid (0.64 g, 100%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.00 (d, J = 2.4 Hz, 1 H), 7.77 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1 H), 6.94 (d, J = 9.0 Hz, 1 H), 4.08 (t, J = 6.3 Hz, 2 H), 1.86–1.77 (m, 2 H),

1.61–1.49 (m, 2 H), 1.01 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ 167.4, 157.9, 141.4, 139.2, 123.6, 115.3, 80.8, 68.6, 30.8, 18.8, 12.7. MS (ESI): m/z 343.0 $[M + Na]^+$. Anal. Calcd. for $C_{11}H_{13}IO_3$: C, 41.27; H, 4.09. Found: C, 41.34; H, 4.00.

Compound 16

A suspension of **15** (0.62 g, 2.00 mmol) and Pd-C (60 mg, 10%) in THF (30 mL) was stirred under 60 atm of hydrogen for 12 h and then filtrated. The filtrate was concentrated to afford compound **16** as a yellowish oil, which was unstable in air and used for the next reaction without further purification.

Compound 17

To a solution of **13** (1.28 g, 4.00 mmol) in THF (10 mL) and DMF (0.05 mL) was added oxalyl chloride (1.60 mL, 20.0 mmol) in 30 min. The solution was stirred for 30 min and then concentrated. The resulting residue was dissolved in THF (10 mL). To this solution, cooled in an ice-bath, were added triethylamine (0.60 mL, 4.40 mmol) and the above diamine **16**. The solution was stirred for 1 hour and then concentrated under reduced pressure. The resulting residue was washed with methanol thoroughly to give **17** as a yellowish solid (1.63 g, 95%). ^{1}H NMR ($CDCl_3$): δ 9.78 (s, 2 H), 9.24 (s, 1 H), 8.60 (d, $J = 2.4$ Hz, 2 H), 7.69 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, 2 H), 6.78 (d, $J = 8.7$ Hz, 2 H), 6.53 (s, 1 H), 4.18 (t, $J = 6.9$ Hz, 4 H), 3.79 (d, $J = 6.9$ Hz, 4 H), 2.15–2.06 (m, 2 H), 1.90–1.80 (m, 4 H), 1.51–1.41 (m, 4 H), 1.01 (d, $J = 6.9$ Hz, 12 H), 0.94 (t, $J = 7.5$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 161.5, 156.5, 146.3, 141.2, 141.0, 124.9, 120.8, 117.5, 115.2, 98.3, 83.7, 75.8, 69.6, 30.8, 28.3, 19.3, 19.0, 13.8. MS (MALDI-TOF): m/z 879.5 $[M + Na]^+$. Anal. Calcd. for $C_{36}H_{46}I_2N_2O_6$: C, 50.48; H, 5.41, N, 3.27. Found: C, 50.50; H, 5.49; N, 3.20.

Compound 18

To a solution of **17** (0.43 g, 0.50 mmol), $PdCl_2(PPh_3)_2$ (37 mg, 0.05 mmol) and CuI (11.5 mg, 0.05 mmol) in THF (10 mL) and triethylamine (5.00 mL) was added ethynyltrimethylsilane (0.21 g, 1.50 mmol). The solution was stirred at 40 °C for 4 h and then the solid filtrated off. The filtrate was concentrated and the resulting slurry triturated with CH_2Cl_2 (5 mL). The solution was washed with water (5 mL) and brine (5 mL) and dried over sodium sulfate. Upon removal of the solvent, the resulting residue was subjected to column chromatography (PE/CH_2Cl_2 2:1) to afford **18** as a white solid (0.36 g, 90%). ^{1}H NMR ($CDCl_3$): δ 9.74 (s, 1 H), 9.17 (s, 1 H), 8.43 (d, $J = 2.4$ Hz, 2 H), 7.51 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, 2 H), 6.94 (d, $J = 8.7$ Hz, 2 H), 6.54 (s, 1 H), 4.20 (t, $J = 6.6$ Hz, 4 H), 3.79 (d, $J = 6.6$ Hz, 4 H), 2.15–2.06 (m, 2 H), 1.91–1.82 (m, 4 H), 1.52–1.40 (m, 4 H), 1.00 (d, $J = 6.6$ Hz, 12 H), 0.95 (t, $J = 7.5$ Hz, 6 H), 0.24 (s, 18 H). ^{13}C NMR ($CDCl_3$): δ 162.1, 156.6, 146.5, 136.8, 135.6, 122.8, 120.8, 117.9, 116.2, 112.6, 104.3, 98.4, 93.3, 75.8, 69.4, 30.8, 28.2, 19.2, 19.0, 13.7, –0.1. MS (MALDI-TOF): m/z 797.8 $[M + H]^+$. Anal. Calcd. for $C_{46}H_{64}N_2O_6Si_2$: C, 69.31; H, 8.09, N, 3.51. Found: C, 69.14; H, 8.38; N, 3.55.

Compound 5

A solution of **18** (0.36 g, 0.45 mmol) and TBAF (0.13 g, 0.50 mmol) in CH_2Cl_2 (25 mL) was stirred for 30 min and then washed with water (15 mL × 2) and brine (15 mL × 2), and dried over sodium sulfate. The solvent was then distilled with a rotavapor and the resulting residue washed with cold MeOH to afford **5** as a yellowish solid (0.28 g, 95%). ^{1}H NMR ($CDCl_3$): δ 9.75 (s, 2 H), 9.18 (s, 1 H), 8.44 (d, $J = 1.8$ Hz, 2 H), 7.54 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, 2 H), 6.96 (d, $J = 8.7$ Hz, 2 H), 6.54 (s, 1 H), 4.21 (t, $J = 7.2$ Hz, 4 H), 3.79 (d, $J = 6.6$ Hz, 4 H), 3.01 (s, 2 H), 2.17–2.04 (m, 2 H), 1.92-1.82 (m, 4 H), 1.52–1.40 (m, 4 H), 1.01 (d, $J = 6.3$ Hz, 12 H), 0.95 (t, $J = 7.5$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.1, 156.9, 146.6, 136.8, 136.1, 123.0, 120.8, 117.9, 115.1, 112.8, 98.4, 82.8, 76.4, 75.9, 69.5, 30.9, 28.2, 19.3, 19.1, 13.7. MS (MALDI-TOF): m/z 675.1 $[M + Na]^+$. Anal. Calcd. for $C_{40}H_{48}N_2O_6$: C, 73.59; H, 7.41, N, 4.29. Found: C, 73.30; H, 7.32; N, 4.08.

Compound 1

A suspension of **5** (65 mg, 0.10 mmol), **19** (19 mg, 0.10 mmol), CuI (4 mg, 0.02 mmol) and DIPEA (28 mg, 0.20 mmol) in chloroform (10 mL) was stirred for 24 h. The solid was filtrated off and the filtrate concentrated in vacuo. The resulting residue was subjected to column chromatography (CH_2Cl_2/PE 2:1) to give **1** as a white solid (17 mg, 20%) ^{1}H NMR ($CDCl_3$): δ 9.17 (s, 2 H), 8.65 (s, 1 H), 8.29 (s, 2 H), 8.20 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.1$ Hz, 2 H), 7.79 (s, 2 H), 7.44 (s, 4 H), 7.06 (d, $J = 8.7$ Hz, 2 H), 6.45 (s, 1 H), 5.60 (s, 4 H), 4.22 (t, $J = 7.2$ Hz, 4 H), 3.80 (d, $J = 6.6$ Hz, 4 H), 2.20–2.11 (m, 2 H), 2.16 (s, 2 H), 1.96–1.87 (m, 4 H), 1.56–1.42 (m, 4 H), 1.06 (d, $J = 6.6$ Hz, 12 H), 0.99 (t, $J = 7.5$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 164.7, 155.7, 147.8, 147.4, 134.9, 131.3, 130.0, 129.0, 123.7, 123.3, 119.6, 112.8, 97.6, 75.5, 69.1, 53.9, 30.9, 28.2, 19.3, 19.0, 13.8. MS (MALDI-TOF): m/z 841.9 $[M + H]^+$. HRMS (MALDI-FT): Calcd. for $C_{48}H_{57}N_8O_6$: 841.4396. Found: 841.4370.

Compound 6

A solution of **24** (0.15 g, 0.20 mmol) and sodium azide (39 mg, 0.60 mmol) in DMF (4 mL) was stirred at 80 °C for 4 h and then concentrated with a rotavapor. The resulting slurry was triturated with chloroform (30 mL) and the solution washed with water (15 mL × 3) and brine (15 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by flash chromatography (PE/EA 3:1) to give **6** as a white solid (0.15 g, 100%). ^{1}H NMR ($CDCl_3$): δ 9.87 (s, 2 H), 9.28 (s, 1 H), 8.27 (d, $J = 2.7$ Hz, 2 H), 7.41 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.1$ Hz, 2 H), 7.03 (d, $J = 8.4$ Hz, 2 H), 6.55 (s, 1 H), 4.34 (s, 4 H), 4.21 (t, $J = 6.9$ Hz, 4 H), 3.80 (d, $J = 6.9$ Hz, 4 H), 2.16–2.07 (m, 2 H), 1.94–1.85 (m, 4 H), 1.47–1.29 (m, 8 H), 1.02 (d, $J = 6.6$ Hz, 12 H), 0.88 (t, $J = 7.2$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.5, 156.7, 146.2, 132.7, 132.4, 128.2, 123.0, 121.0, 117.3, 113.4, 98.3, 75.9, 69.8, 54.1, 28.6, 28.3, 27.9, 22.3, 19.2, 13.9. MS (MALDI-TOF): m/z 781.2 $[M + K]^+$. HRMS (MALDI-FT): Calcd. for $C_{40}H_{54}N_8O_6Na$ $[M + Na]^+$: 765.4058. Found: 765.4040.

Compound 2

A suspension of **5** (0.13 g, 0.20 mmol), **6** (0.15 g, 0.20 mmol), CuI (8 mg, 0.04 mmol) and DIPEA (56 mg, 80 μL, 0.20 mmol) in chloroform (20 mL) was stirred for 48 h and then concentrated with a rotavapor. After workup, the crude product was purified by flash chromatography (CH_2Cl_2/EA 1:3) to give **2** as a white solid (0.23 g, 82%). ^{1}H NMR ($CDCl_3$): δ 10.04 (s, 2 H), 9.89 (s, 2 H),

9.53 (br, 2 H), 8.48 (s, 2 H), 8.43 (s, 2 H), 8.26 (d, $J = 8.5$ Hz, 2 H), 7.90 (br, 2 H), 7.53 (d, $J = 8.4$ Hz, 2 H), 7.08 (d, $J = 8.7$ Hz, 2 H), 6.99 (d, $J = 8.0$ Hz, 2 H), 6.55 (s, 1 H), 6.52 (s, 1 H), 5.56 (s, 4 H), 4.23 (t, $J = 6.9$ Hz, 4 H), 4.19 (t, $J = 6.6$ Hz, 4 H), 3.80 (d, $J = 6.1$ Hz, 4 H), 3.79 (d, $J = 5.7$ Hz, 4 H), 2.15–2.08 (m, 4 H), 1.88–1.85 (m, 8 H), 1.46–1.30 (m, 12 H), 1.01 (d, $J = 6$ Hz, 12 H), 1.00 (d, $J = 6$ Hz, 12 H), 0.93 (t, $J = 7.0$ Hz, 6 H), 0.86 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.2, 156.9, 156.4, 147.4, 145.7, 145.1, 133.2, 133.0, 129.7, 129.6, 127.8, 124.1, 123.0, 121.6, 121.1, 119.5, 117.0, 115.6, 113.9, 113.6, 98.5, 98.2, 76.1, 75.9, 69.9, 69.6, 53.8, 30.9, 28.5, 28.2, 27.8, 22.3, 19.2, 19.0, 13.9, 13.7. MS (MALDI-FT): m/z 1417.8 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{80}H_{103}N_{10}O_{12}$: 1395.7752. Found: 1395.7771.

Compound 7

Compound **7** was prepared as a white solid (90%) from the reaction of **29** and **30** according to a procedure similar to that for **17**. ^{1}H NMR ($CDCl_3$): δ 9.66 (s, 2 H), 9.02 (s, 1 H), 8.75 (d, $J = 1.5$ Hz, 2 H), 7.16 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz, 2 H), 6.80 (d, $J = 8.4$ Hz, 2 H), 6.51 (s, 1 H), 4.07 (t, $J = 6.9$ Hz, 4 H), 4.01 (d, $J = 6.6$ Hz, 4 H), 2.97 (s, 2 H), 2.31–2.22 (m, 2 H), 1.83–1.73 (m, 4 H), 1.51–1.38 (m, 4 H), 1.04 (d, $J = 6.9$ Hz, 12 H), 0.96 (t, $J = 7.5$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.5, 160.1, 148.3, 137.5, 128.3, 127.8, 124.8, 116.3, 114.4, 111.0, 97.2, 84.0, 76.3, 75.6, 68.6, 31.1, 28.0, 19.3, 19.1, 13.9. MS (MALDI-TOF): m/z 653.7 $[M + H]^+$. Anal. Calcd. for $C_{40}H_{48}N_2O_6$: C, 73.59; H, 7.41; N, 4.29. Found: C, 74.07; H, 7.43; N, 4.19.

Compound 8

Compound **8** was prepared as a white solid (100%) from the reaction of **36** and sodium azide according to a procedure similar to that for **6**. ^{1}H NMR ($CDCl_3$): δ 9.75 (s, 2 H), 9.06 (s, 1 H), 8.60 (s, 2 H), 7.02 ($J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 2 H), 6.91 (d, $J = 8.4$ Hz, 2 H), 6.56 (s, 1 H), 4.33 (s, 4 H), 4.09 (t, $J = 6.9$ Hz, 4 H), 4.02 (d, $J = 6.9$ Hz, 4 H), 2.34–2.25 (m, 2 H), 1.84–1.74 (m, 4 H), 1.53–1.40 (m, 4 H), 1.06 (d, $J = 6.3$ Hz, 12 H), 0.97 (t, $J = 7.5$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.5, 160.1, 147.7, 137.4, 128.7, 127.9, 123.4, 121.4, 116.7, 111.4, 97.3, 76.4, 68.7, 54.7, 31.2, 28.0, 19.3, 19.1, 13.8. MS (MALDI-TOF): m/z 715.4 $[M + H]^+$. HRMS (MALDI-FT): Calcd. for $C_{38}H_{51}N_8O_6$: 715.3926. Found: 715.3912. Anal. Calcd. for $C_{38}H_{50}N_8O_6$: C, 63.85; H, 7.05; N, 15.68. Found: C, 63.50; H, 7.04; N, 15.63.

Compound 3

A suspension of **8** (0.49 g, 0.68 mmol), **7** (0.45 g, 0.68 mmol), CuI (26 mg, 0.14 mmol) and DIPEA (0.26 mL, 1.30 mmol) in $CHCl_3$ (68 mL) and CH_3CN (68 mL) was stirred for 24 h and then concentrated. The resulting slurry was triturated with CH_2Cl_2 (50 mL) and the solution washed with saturated $NaHCO_3$ solution (25 mL), water (25 mL) and brine (25 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by flash chromatography (CH_2Cl_2/EA 2:3) to give **3** as a white solid (0.79 g, 85%). ^{1}H NMR ($CDCl_3$): δ 9.93 (s, 2 H), 9.86 (s, 2 H), 9.23 (s, 1 H), 9.06 (s, 1 H), 8.90 (s, 2 H), 8.80 (s, 2 H), 8.02 (s, 2 H), 7.84 (d, $J = 8.4$ Hz, 2 H), 7.10 (d, $J = 8.1$ Hz, 2 H), 6.92 (d, $J = 8.7$ Hz, 2 H), 6.85 (d, $J = 8.4$ Hz, 2 H), 6.53 (s, 1 H), 6.51 (s, 1 H), 5.50 (s, 4 H), 4.08-3.98 (m, 16 H), 2.31–2.22 (m, 4 H), 1.80–1.70 (m, 8 H), 1.48–1.36 (m, 8 H), 1.02 (d, $J = 6.9$ Hz, 12 H), 0.99 (d, $J = 7.2$ Hz, 12 H), 0.92 (t, $J = 7.5$ Hz, 12 H). ^{13}C NMR ($CDCl_3$): δ 162.4, 162.1, 160.0, 159.9, 147.7, 147.3, 138.0, 137.5, 128.8, 128.7, 127.3, 124.0, 121.7, 117.9, 116.5, 116.4, 111.9, 111.6, 97.5, 97.1, 77.2, 76.4, 76.3, 68.6, 54.5, 31.1, 31.0, 27.9, 27.8, 19.2, 19.1, 18.9, 13.8, 13.7. MS (MALDI-TOF): m/z 1389.5 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{78}H_{99}N_{10}O_{12}$: 1367.7438. Found: 1367.7451.

Compound 9

A solution of **40** (0.41 g, 0.34 mmol) and TBAF (89 mg, 0.34 mmol) in THF (35 mL) was stirred in an ice-bath for 30 min and then concentrated. The resulting slurry was dissolved in CH_2Cl_2 (30 mL) and the solution washed with water (15 mL) and brine (15 mL) and dried over sodium sulfate. The solvent was then removed and the crude product subjected to flash chromatography (CH_2Cl_2/EA 7:1 to 5:1) to give **9** as a pale yellow solid (0.34 g, 95%). ^{1}H NMR ($CDCl_3$): δ 9.81 (s, 2 H), 9.46 (s, 2 H), 9.26 (s, 2 H), 8.46 (d, $J = 1.5$ Hz, 2 H), 8.26 (d, $J = 7.5$ Hz, 2 H), 7.56 (dd, $J_1 = 8.7$ Hz, $J_2 = 1.5$ Hz, 2 H), 7.38 (t, $J = 7.5$ Hz, 1 H), 6.97 (d, $J = 8.4$ Hz, 2 H), 6.56 (s, 2 H), 4.23 (t, $J = 6.9$ Hz, 4 H), 4.07 (s, 3 H), 3.83–3.79 (m, 8 H), 3.03 (s, 2 H), 2.17–2.07 (m, 4 H), 1.93–1.83 (m, 4 H), 1.51–1.44 (m, 4 H), 1.02 (d, $J = 6.3$ Hz, 24 H), 0.96 (t, $J = 7.5$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.4, 162.0, 156.7, 155.8, 146.4, 146.1, 136.4, 136.1, 134.8, 128.2, 125.1, 122.6, 120.5, 120.0, 116.8, 115.0, 112.8, 97.6, 82.6, 76.4, 75.7, 75.4, 69.4, 64.2, 30.7, 28.1, 28.1, 19.1, 19.1, 18.9, 13.6. MS (MALDI-TOF): m/z 1088.4 $[M + Na]^+$.

Compound 10

Compound **10** was prepared quantitatively as a white solid from the reaction of **47** and NaN_3 according to a procedure similar to that for **6**. ^{1}H NMR ($CDCl_3$): δ 9.94 (s, 2 H), 9.48 (s, 2 H), 9.30 (s, 2 H), 8.28 (s, 2 H), 8.26 (d, $J = 7.8$ Hz, 2 H), 7.44–7.38 (m, 3 H), 7.05 (d, $J = 8.7$ Hz, 2 H), 6.56 (s, 2 H), 4.34 (s, 4 H), 4.23 (t, $J = 6.6$ Hz, 4 H), 4.06 (s, 3 H), 3.83–3.79 (m, 8 H), 2.17–2.11 (m, 4 H), 1.91–1.84 (m, 4 H), 1.51–1.44 (m, 4 H), 1.03 (d, $J = 6.6$ Hz, 12 H), 1.02 (d, $J = 6.3$ Hz, 12 H), 0.96 (t, $J = 7.2$ Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.4, 162.3, 156.5, 155.7, 146.3, 146.0, 134.7, 132.5, 132.3, 128.2, 128.0, 125.0, 122.6, 120.6, 120.0, 116.8, 113.2, 97.6, 75.6, 75.3, 69.3, 64.1, 53.8, 30.7, 28.1, 28.1, 19.1, 19.0, 18.9, 13.6. MS (MALDI-FT): m/z 1149.6 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{61}H_{78}N_{10}O_{11}Na$ $[M + Na]^+$: 1149.5744. Found: 1149.5745.

Compound 4

Compound **4** was prepared as a white solid (25%) from the reaction of **9** and **10** according to a procedure similar to that for **3**. ^{1}H NMR ($CDCl_3$): δ 10.00 (s, 2 H), 9.95 (s, 2 H), 9.48 (s, 2 H), 9.44 (s, 2 H), 9.39 (s, 2 H), 9.26 (s, 2 H), 8.45 (br, 4 H), 8.20 (br, 6 H), 7.87 (br, 2 H), 7.50 (d, $J = 8.1$ Hz, 2 H), 7.10 (d, $J = 7.8$ Hz, 2 H), 7.03 (d, $J = 8.4$ Hz, 2 H), 6.55 (s, 2 H), 6.54 (s, 2 H), 5.55 (s, 4 H), 4.27–4.20 (m, 8 H), 3.56 (s, 3 H), 3.21 (s, 3 H), 2.14–2.09 (m, 8 H), 1.90–1.85 (m, 8 H), 1.50–1.42 (m, 8 H), 1.02–0.92 (m, 60 H). ^{13}C NMR ($CDCl_3$): δ 162.8, 162.6, 162.5, 157.3, 156.6, 156.0, 156.0, 146.8, 146.1, 146.0, 135.2, 135.2, 133.3, 130.2, 130.0, 129.7, 128.4, 128.3, 127.5, 125.3, 124.0, 123.1, 122.9, 121.2, 120.8, 120.3, 120.1, 117.6,

116.8, 114.1, 113.6, 97.9, 97.8, 76.0, 75.9, 75.6, 75.6, 64.5, 54.0, 31.0, 31.0, 28.4, 28.4, 19.4, 19.4, 19.2, 13.9, 13.9. MS (MALDI-FT): *m/z* 2214.1 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{124}H_{154}N_{14}O_{22}Na$ $[M + Na]^+$: 2214.1254. Found: 2214.1266.

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