Synthesis of Macrocycles with Anthracene Units and Amide Bonds; Potential Building Blocks for 1D and 2D Constructions

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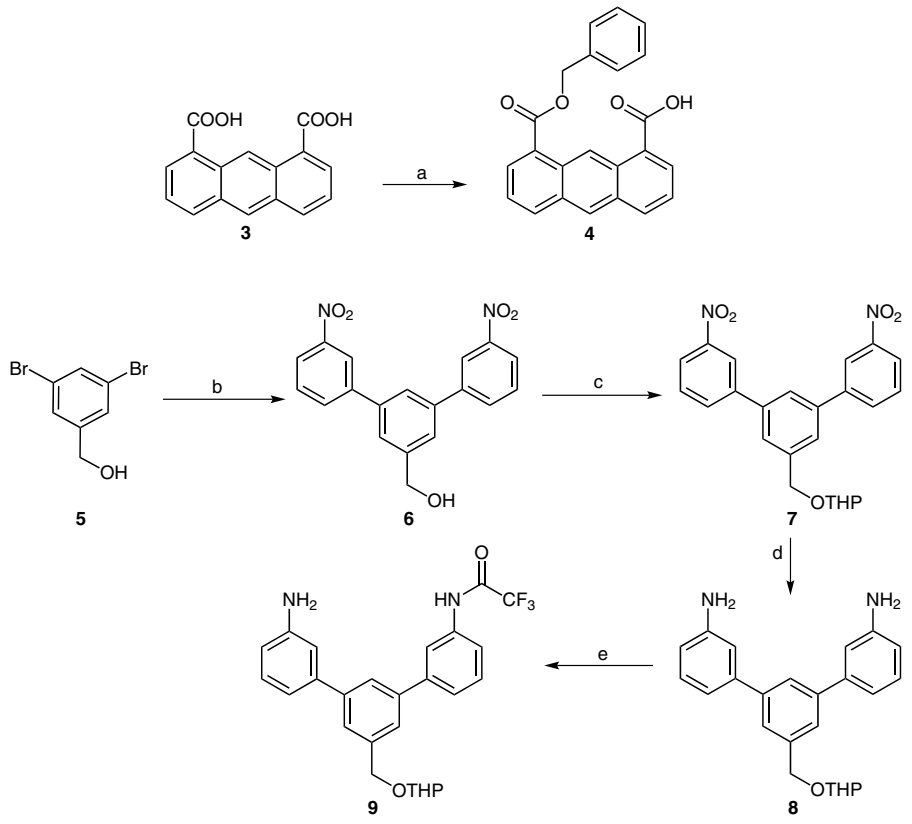
Abstract: A collection of novel *m*-terphenyl and mixed *m*-terphenyl-anthracene building blocks were synthesised on scales between several 100 mg and a few grams. Proper connection of some of these building blocks utilising amide coupling chemistry afforded macrocycles containing two and three anthracene units. These macrocycles were obtained as virtually pure compounds on 14 and 24 mg scales, respectively. Their UV/Vis and fluorescence spectra are reminiscent of the parent anthracene, which renders them potential candidates for various applications including sensing and molecular constructions.

Key words: macrocycles, anthracene, amides, photochemistry, polymers

Macrocycles have the potential to serve as versatile building blocks in the construction of large supramolecular/macromolecular architectures.[1] For example, when stacked on top of each other 1D tubular assemblies result,[2] but when arranged laterally the same macrocycle can instead form a 2D porous structure.[3] In order to promote the formation of such well-defined supramolecular entities, it is desirable to involve strong (yet reversible) directional interactions.[2–4] In addition, it can be an attractive further option to covalently fix the obtained supramolecular assembly by subsequent treatment in order to convert it into a non-equilibrium structure.[5]

In the present study, two new macrocycles were designed in which three or two sets of *m*-terphenylene and 1,8-



Scheme 1 Synthetic route used for the preparation of the symmetric (**3** and **8**) and unsymmetric (**4** and **9**) building blocks. *Reagents and conditions*: (a) BnBr, DIPEA, DMF, 40%; (b) $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$, Na_2CO_3, benzene–EtOH–H_2O, 98%; (c) 3,4-dihydro-2*H*-pyran, $TsOH\cdot H_2O$, DMF, 95%; (d) $Pd(OH)_2/C$, H_2, CH_2Cl_2–EtOH, 90%; (e) CF_3CO_2Et, Et_3N, MeOH, 45%.

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anthrylene units[6] are alternatively connected to each other through amide bonds (**1** and **2**, respectively, Figure 1a). These macrocycles have a semi-rigid molecular structure that can adopt two extreme conformations, a more or less flat form and a cylindrical form. The ratio between the two forms can be influenced by several measures, which

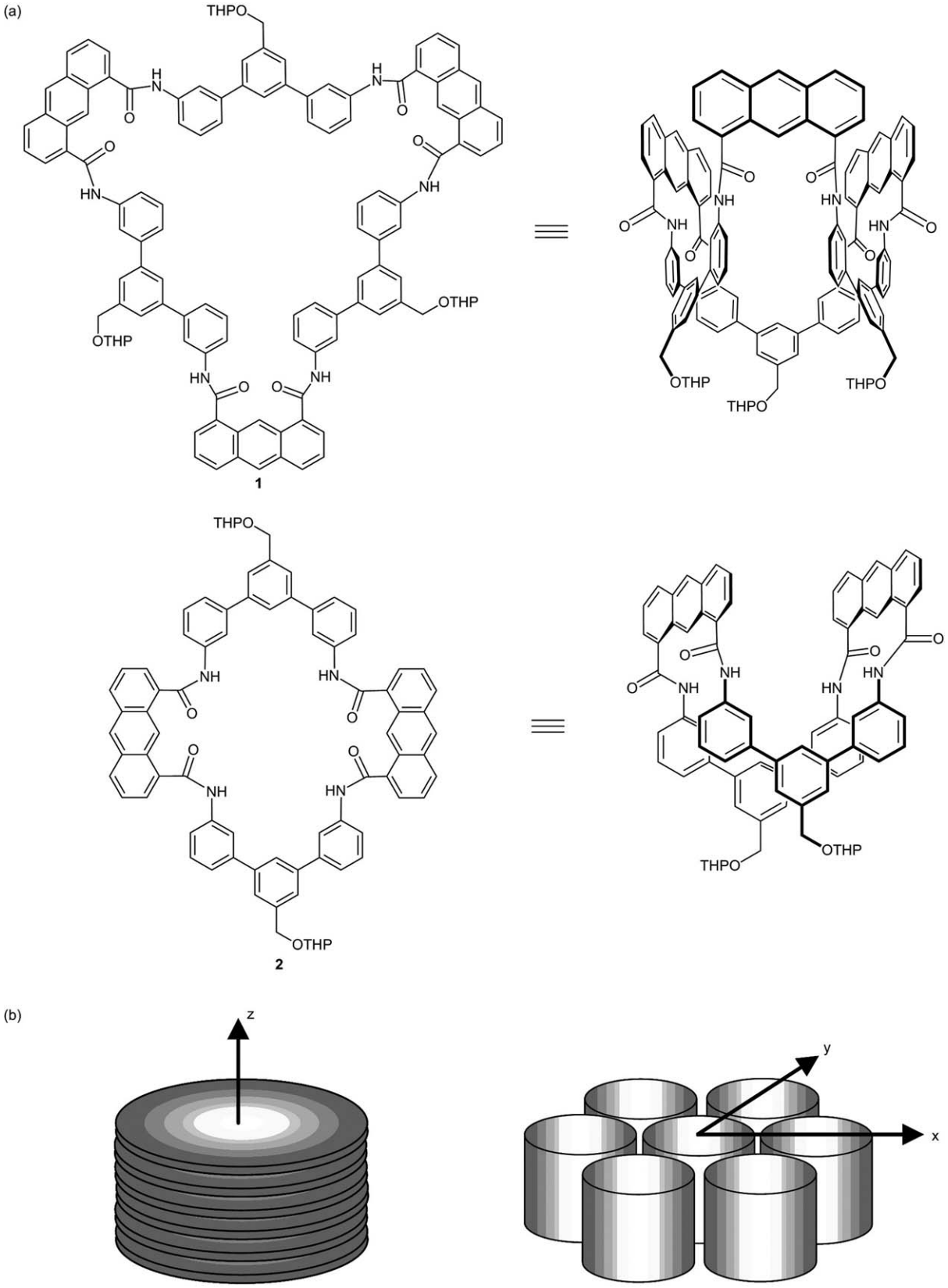


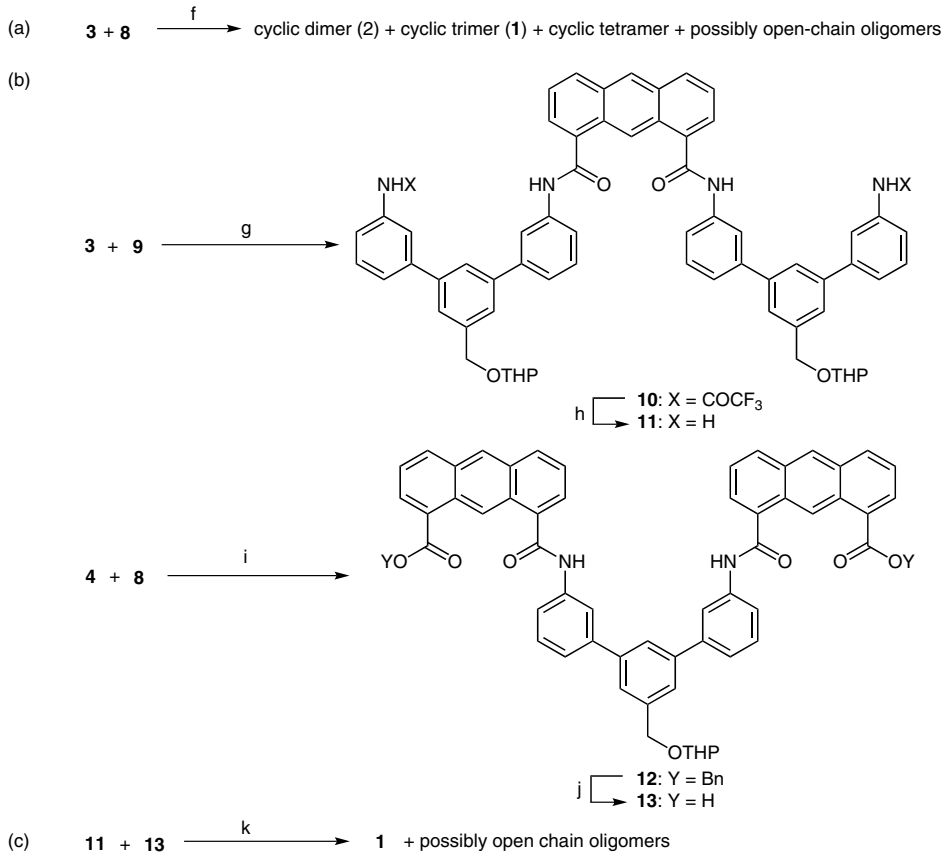
Figure 1 (a) Chemical structures of macrocycles **1** and **2**; flat (left) and cylindrical (right). (b) The conformations may allow the macrocycles to be used as building blocks for 1D and 2D constructions, respectively.

can go as far as to favour one conformation completely over the other. This can be achieved by chemical modification,[7] temperature,[8] pressure,[9] solvophobic effects,[10,11] and guest uptake.[6,12] Moreover, because of the orientation of the amide bonds and the aromatic planes in **1** and **2**, the macrocycles may be directed into 1D and 2D assemblies when adopting the flat and the cylindrical conformation, respectively (Figure 1b).[13]

Photophysical and -chemical properties arising from the anthracene moieties of our compounds make them attractive for various applications.[14] Once 1D or 2D assemblies form, these active moieties may arrange themselves with controlled mutual distances and orientations.[11] This may allow, for example, efficient energy transfer between them or covalent stabilization of the assembly structure by subsequent photo-treatment. Furthermore, hydroxymethyl groups are introduced at the periphery of the macrocycle that are protected with tetrahydropyranyl (THP) groups during the synthesis but can be subsequently modified with chemical entities of various sorts; this is expected to lead to the formation of a regular array on the resultant assembly surface.

We followed two different synthetic strategies to **1** and **2**. For this purpose a collection of small anthracene (**3** and **4**) and terphenylene-based building blocks (**8** and **9**) was needed; their syntheses are shown in Scheme 1.

Scheme 2 (a) describes the random oligomerization between the symmetric building blocks **3** and **8**, Scheme 2 (b) shows the sequences used to obtain the more extended building blocks **11** and **13**, which are required as direct precursors for **1**; Scheme 2 (c) depicts the final assembly of the target cycle **1** from **11** and **13**. In Scheme 1, 1,8-anthracene dicarboxylic acid (**3**), was synthesised in three steps from commercially available 1,8-dichloroanthraquinone following a published procedure.[15] Compound **3** was obtained on a 25 gram scale. The statistical protection to generate **4** was performed with benzyl bromide and afforded the required intermediate in 40% yield. The terphenylene building block **9** was synthesised starting from the known dibromide **5**,[16] which was converted into dinitroterphenylene **6** by Suzuki–Miyaura cross-coupling chemistry[17] employing 3-nitrobenzene boronic acid. Simple tetrahydropyran (THP) protection of the alcohol of **6** gave **7**, which could be smoothly reduced with H_2 over $Pd(OH)_2/C$. Subsequent statistical protection of one of the amino functions of **8** with trifluoroacetyl was performed with ethyl trifluoroacetate to give **9** in a yield of 45%. The oligomerisation between the bifunctional compounds **3** and **8** afforded, as expected, a rather complex product mixture containing cyclic and open-chain oligomers of various molar masses. This mixture was analysed by MALDI-TOF mass spectrometry using DCTB/Ag^+ as a



Scheme 2 Synthetic route used for the preparation of (a) macrocycle **2**, (b) extended building blocks for **1**, and (c) macrocycle **1**. *Reagents and conditions*: (f) EDC·HCl, HOBt, DMAP, DIPEA, DMF–CH_2Cl_2, 2%; (g) EDC·HCl, HOBt, DMAP, DIPEA, DMF–CH_2Cl_2, 83%; (h) NaOH, H_2O, DMF, 95%; (i) EDC·HCl, HOBt, DMAP, DIPEA, DMF–CH_2Cl_2, 89%; (j) NaOH, H_2O, DMF, 81%; (k) EDC·HCl, HOBt, DMAP, DIPEA, DMF–CH_2Cl_2, 5%.

matrix (see the Supporting Information, Figure S23). The spectrum showed the molecular ions of the dimeric **2**, trimeric **1**, and tetrameric cyclic species; the open-chain oligomers, which were presumably also formed, could not be detected.[18] The product mixture did not dissolve in chloroform and methanol but a partial separation could be accomplished on Sephadex LH-20 with DMF as an eluent. This afforded **2** in a low yield of 2%. Nevertheless, it was obtained on a few mg scale (14 mg) allowing for its full characterization. Compound **1** and the larger cyclic species could not be isolated from the complex mixture. Although repeated chromatography over Sephadex LH-20 gave fractions enriched in **1**, we could not find conditions that would allow its isolation.

This was a motivation to start the systematic sequence shown in Scheme 2 (b), leading to the immediate cyclisation precursors **11** and **13**. Standard amide coupling reactions between **3** and **9** as well as **4** and **8** afforded the key building blocks **10** and **12**, respectively, in yields of more than 80%. These compounds were prepared on a 2.5 gram scale. Deprotection of **10** was conventional. Whereas deprotection of **12** (NaOH, H_2O–DMF) was straightforward, its purification was found to be laborious in that the free carboxylic acid turned out to stick to the silica gel column. We therefore used it directly for the next reaction without chromatographic purification. The obtained crude material **13** was then repeatedly washed with water followed by methanol to remove the formed benzyl alcohol and other unwanted components. This procedure was rather successful in terms of obtaining pure **13**, as the clean NMR spectrum provided in the Supporting Information shows.

Scheme 2 (c) depicts the final cyclization of **11** and **13**. This was performed under moderately high dilution conditions (final concentration 1 mM) starting from **11** (259 mg) and **13** (230 mg). As in the above case, eventually, open-chain oligomers did not show in the MALDI-TOF mass spectrum of the product mixture, resulting in a spectrum that basically contained the molecular ion of **1**, however, NMR spectroscopy indicated that there were in fact some open-chain oligomers present. Isolation of **1** was successful on Sephadex LH-20 with DMF as eluent, followed by reverse-phase chromatography (C18 as stationary phase; MeOH–DMF, 9:1) and gave **1** in low yield (24 mg, 5%).[19]

The UV/Vis and fluorescence spectra of **1**, together with model compound **14**, are depicted in Figure 2. It is noted

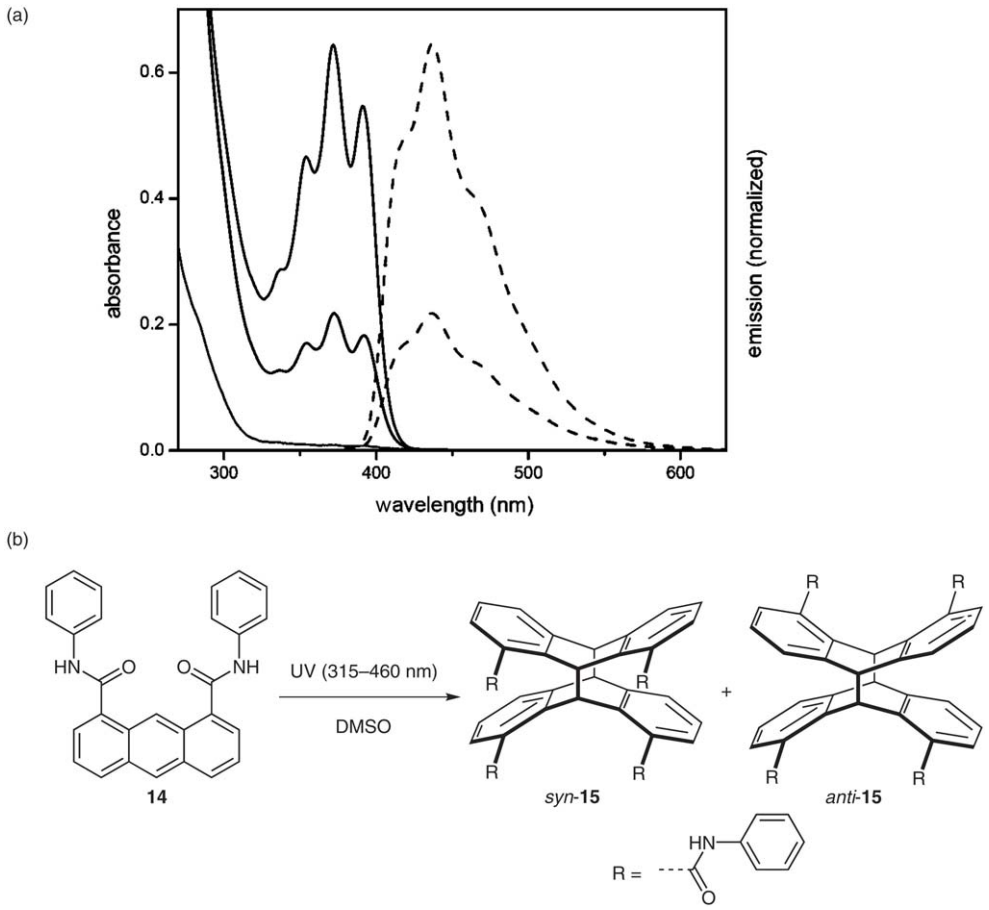


Figure 2 UV absorption and emission spectra of model compound **14** and monomer **1** together with UV spectrum of the dimer *syn*-**15** in DMSO. Black, dark-gray, and light-gray lines correspond to the spectra of **1**, **14** and **15**, respectively. Solid and broken lines are used for the absorption and emission spectra, respectively. Concentrations: Absorption: 20, 7 and 10 μM for **14**, **1**, and **15**, respectively. Emission: 2 and 0.7 μM for **14** and **1**, respectively. As expected, the absorption of the dimer in the range of λ = 350–400 nm is virtually absent, which should allow selective excitation of the macrocycle.

that the macrocycle shows characteristic signatures of its three anthracene units, which are completely unaltered as compared to those of the model compound. This is a clear sign that they do not form any intramolecular excimers and that there is no interaction between them and other parts of the compound either in the ground or the excited states. Model compound **14** underwent photoinduced [4+4] cycloaddition dimerisation, which is well known for anthracenes.[14] This supports our view that the macrocycles can, in fact, be used for similar reactions involving anthracene dimerisation, leading to extended covalent structures. The photochemical dimerisation of model **14** afforded both *syn*-**15** and *anti*-**15** dimers. In contrast to many other 1,8-disubstituted anthracenes, for which the *anti*-dimer is largely favoured,[6] in this case, the *syn*/*anti* ratio was 55:45 after standing in DMSO at 21 °C for three days. The conversion reached 50% with remaining **14** being unchanged. Preliminary results indicate that this ratio can be shifted even further towards the *syn* dimer, which is considered an indication of possible hydrogen bond involvement in the stereochemistry determining step of the dimerisation.

In conclusion, macrocycles with two and three anthracene units were obtained through amide coupling chemistry in virtually pure form (as judged by NMR spectroscopic analysis). The relatively small scale in which these two targets were obtained is mainly attributed to the low efficiency of the final cyclisation step. Nevertheless, the cyclisations can easily be repeated in order to provide amounts that are sufficient for subsequent studies. UV/Vis absorption and fluorescence spectroscopic analyses of the obtained macrocycles as well as photoreactions of a model compound indicate that the anthracenes in both macrocycles are not only independent from one another but also do not show signs of interaction with other parts of the compound. This is a key prerequisite for these macrocycles to be good starting compounds for self-assembly and subsequent photophysical and -chemical studies. This self-assembly may be followed at interfaces, in solution or in bulk.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) Open-chain oligomers are likely to be present because the ^{1}H NMR spectra of crude mixtures showed signals that did not belong to cycles but absorbed at similar chemical shifts. No attempts were made to isolate non-cyclic products.
(19) **Synthesis of macrocycle 1 from 11 and 13**: Compounds **11** (258.6 mg, 0.26 mmol) and **13** (230.0 mg, 0.26 mmol) was dissolved in a mixture of anhydrous DMF (500 mL) and anhydrous CH_2Cl_2 (28 mL). HOBt (356.0 mg, 2.64 mmol), DMAP (3.2 mg, 0.026 mmol), and DIPEA (853.0 mg, 6.6 mmol) were added successively under N_2 and the mixture was cooled to 0 °C. EDC·HCl (506.0 mg, 2.64 mmol) was added and the mixture was warmed to r.t. overnight. The reaction was then stirred at r.t. under N_2 for 21 d. After the reaction was over, solvent was removed under reduced pressure. The crude reaction mixture was purified by using Sephadex LH-20 as packing material and DMF as the eluent, and finally by reverse-phase chromatography (C18 as stationary phase; MeOH–DMF, 9:1) to give **1** (24.0 mg, 5%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 50 °C): δ = 10.54 (s, 6 H, NH), 9.33 (s, 3 H), 8.72 (s, 3 H), 8.21 (d, *J* = 8.5 Hz, 6 H), 7.96 (s, 6 H), 7.72 (d, *J* =

6.0 Hz, 6 H), 7.52 (t, J = 7.0 Hz, 6 H), 7.43 (s, 9 H), 7.23–7.12 (m, 18 H), 4.70–4.65 (m, 6 H, benzyl and THP), 4.47 (d, J = 12.0 Hz, 3 H, benzyl), 3.80–3.77 (m, 3 H, THP), 3.44–3.42 (m, 3 H, THP), 1.71–1.42 (m, 18 H, THP). ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ = 167.1, 140.7, 140.4, 139.7, 139.49, 139.42, 135.0, 131.0, 130.4, 129.0, 128.0, 127.3, 125.8, 125.0, 124.9, 124.0, 122.2, 119.2, 118.4, 97.3, 68.0, 61.3, 30.1, 24.9, 19.0. HRMS (FT-MALDI, DCTB): *m/z* [M + Na]$^+$ calcd for $C_{120}H_{96}N_6O_{12}$: 1835.6978; found: 1835.6990.

