DOI: 10.1002/chem.200900309

Hydrogen-Bonding-Mediated Dynamic Covalent Synthesis of Macrocycles and Capsules: New Receptors for Aliphatic Ammonium Ions and the Formation of Pseudo[3]rotaxanes

Xiao-Na Xu, Lu Wang, Gui-Tao Wang, Jian-Bin Lin, Guang-Yu Li, Xi-Kui Jiang, and Zhan-Ting Li*[a]

Abstract: This paper describes a novel, highly efficient approach to the self-assembly of monomacrocycles and two-layered capsules by using dynamic covalent chemistry. Intramolecular hydrogen-bonding was used to preorganize aromatic amide-based monomers that contain aldehyde and *tert*-butoxycarbonylamino units. As a result, in the presence of an excess of trifluoroacetic acid (TFA), four monomers could self-couple to produce macrocycles selectively through the formation of three imine or hydrazone bonds. Three dipodal precursors were also prepared by connecting two hydrogen-bonded segments with a flexible linker. In the presence of TFA, these precursors could also self-couple, leading to the exclusive formation of two-layered capsules. As a result of intramolecular hydrogen-bonding, all the macrocycles and capsules were stable in solution and could be purified by simple recrystallization. The new capsules were able to form complexes with linear propylenediammonium derivatives to give unique two-layered pseudo[3]rotaxanes.

Keywords: capsules · dynamic covalent chemistry · foldamers · hydrogen bonds · macrocycles · molecular recognition

Introduction

The formation of three-dimensional structures of natural peptides and proteins heavily relies on the balance of the domains of their secondary structures and flexible segments.[1] This enables them to adjust the active sites to realize sophisticated functions such as ligand-binding, catalysis, and ion transportation. To mimic natural secondary structures, chemists have constructed foldamers,[2,3] synthetic oligomers that adopt discrete compact conformation as a result of noncovalent forces. More recently, hydrogen-bonding-mediated folded segments have been utilized to promote the formation of macrocycles of aryl amides.[4] This paper demonstrates the highly efficient covalent synthesis of a new class of three-dimensional capsules by using dynamic covalent chemistry (DCC).[5]

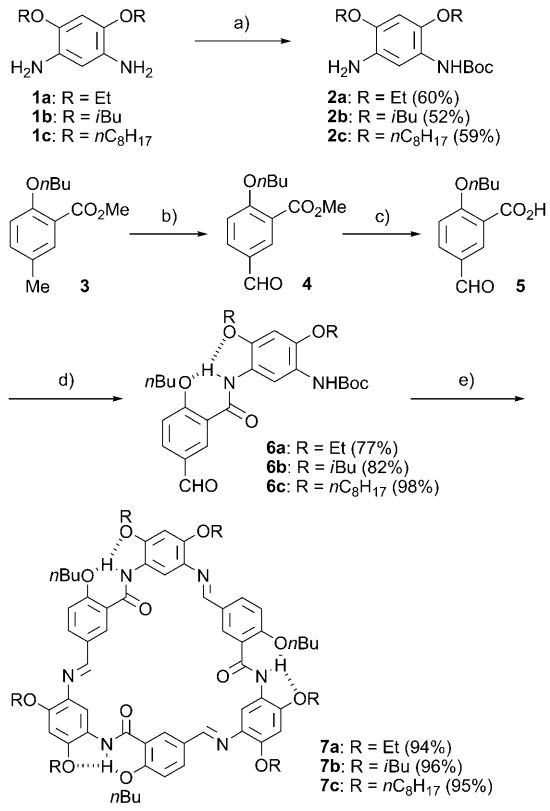
In the past two decades, spherical architectures of defined shape and size have received much attention due to their applications as nanoreactors and molecular sensors and receptors. The studies of Cram[6] and Sherman[7] and their co-workers focused on covalently linked rigid carcerands. Advances in self-assembly involving hydrogen-bonding, transition-metal coordination, and hydrophobic and electrostatic interactions have allowed the construction of nanometer-sized capsules with remarkably high efficiency.[8–11] Recently, Warmuth and co-workers utilized DCC to construct several single molecular capsules from preorganized calix[4]arene monomers.[12] Herein we show how folded segments can be used to modulate dynamic covalent synthesis.[13] By using hydrogen-bonding to preorganize simple linear aryl amide precursors we have been able to quantitatively construct two-layered capsules. These capsules form complexes with aliphatic diammonium ions, leading to the formation of unique two-layered pseudo[3]rotaxanes.

[a] X.-N. Xu, L. Wang, G.-T. Wang, J.-B. Lin, Dr. G.-Y. Li, Prof. Dr. X.-K. Jiang, Prof. Dr. Z.-T. Li
State Key Laboratory of Bio-Organic and Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
Fax: (+86) 21-6416 6128
E-mail: ztli@mail.sioc.ac.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900309.

Results and Discussion

In recent years DCC has been successfully utilized to prepare a number of imine-based macrocyclic systems.[14] We previously demonstrated that hydrogen-bonded foldamers of aryl amides are versatile frameworks for developing preorganized supramolecular synthons.[15] More recently we found that they are particularly useful for the controlled formation of planar bi- or trimacrocyclic architectures by DCC.[16] We were therefore interested in assembling three-dimensional structures from simple hydrogen-bonding-mediated segments by using DCC. In the first step we prepared compounds **6a–c** to test their capacity for forming monomacrocycles (Scheme 1). The amino groups of **6a–c** were protected with a *tert*-butoxycarbonyl (Boc) group to avoid the formation of imine bonds prior to the ring-closing process. It was envisioned that intramolecular three-centered hydrogen-bonding would induce the reaction sites,[2c–e] that is, the aldehyde and amino units, to orientate at around 60°, an angle that is ideal for the formation of macrocyclic architectures from three identical segments.[14g]



Scheme 1. Reagents and conditions: a) $(Boc)_2O$, NEt_3, THF, RT, 15 h; b) i. NBS, $(PhCO)_2O$, CCl_4, reflux, 10 h; ii. $(CH_2)_6N_4$, AcOH, 60 °C, 5 h, 30% (two steps); c) NaOH, $MeOH/H_2O$, RT, 5 h, 77%; d) **2a–c**, $ClCO_2iBu$, $CHCl_3$, NEt_3, RT, 24 h, 77–98%; e) TFA (20 equiv), $CHCl_3$, RT, 12 h.

To prepare compounds **6a–c** (Scheme 1), diamines **1a–c**[4a] were first treated with di(*tert*-butyl) dicarbonate in THF to afford **2a–c** in yields of 52–60%. Then compound **3**[15a] was treated with *N*-bromosuccinimide to give the corresponding dibromomethyl derivative, which was further treated with hexamethyleneimine to give **4** in a yield of 30% (two steps). The aldehyde was then hydrolyzed with sodium hydroxide to acid **5** in a yield of 77%. Finally, **5** was condensed with **2a–c** to afford **6a–c** in yields of 77–98%. The ^{1}H NMR spectra of **6a–c** in $CDCl_3$ exhibited signals corresponding to their amide hydrogen atoms in the downfield region (9.96–9.98 ppm), and these were concentration-independent. This indicates that the amide hydrogen atoms are strongly hydrogen-bonded to the neighboring ether oxygen atoms.[2c–e] Solutions of **6a–c** in chloroform (50 mM) were stirred in the presence of an excess of TFA, which led to the formation of the corresponding macrocycles **7a–c** in very high yields (Scheme 1). All the macrocycles were stable and the purifications thus simple. After the reactions had reached equilibrium, the solutions were neutralized, dried, and concentrated, and the pure products could be obtained by recrystallizing the crude samples from methanol and ethyl acetate. The reaction progress of **6c** was also tracked in $CDCl_3$ by ^{1}H NMR spectroscopy (Figure 1). As expected, the reaction first gave rise to discrete species, as indicated by the presence of complicated signals in the spectra. After approximately 10 h the spectrum had evolved into only one set of signals (Figure 1b–f), which could be assigned to **7c** by comparison of the spectrum of the pure sample recorded under identical conditions. This result shows that initially the reaction proceeded under dynamic control and then changed to a thermodynamically controlled reaction owing to the reversibility of the imine bond. Macrocycle **7c** was more soluble than **7a** and **7b** due to the presence of the longer octyl chains. The ^{1}H NMR spectra of **7a–c** in $CDCl_3$ at room tem-

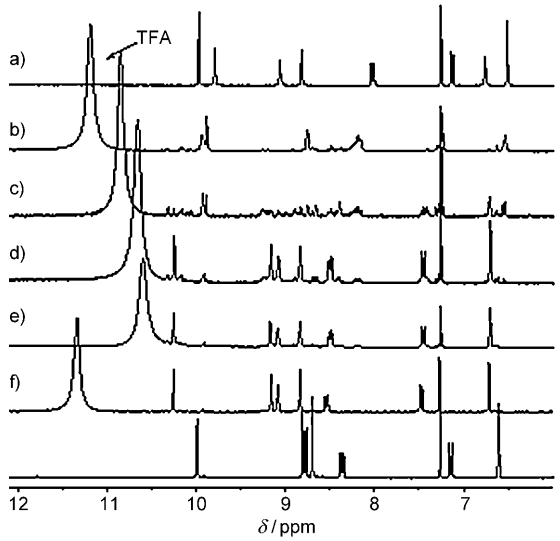
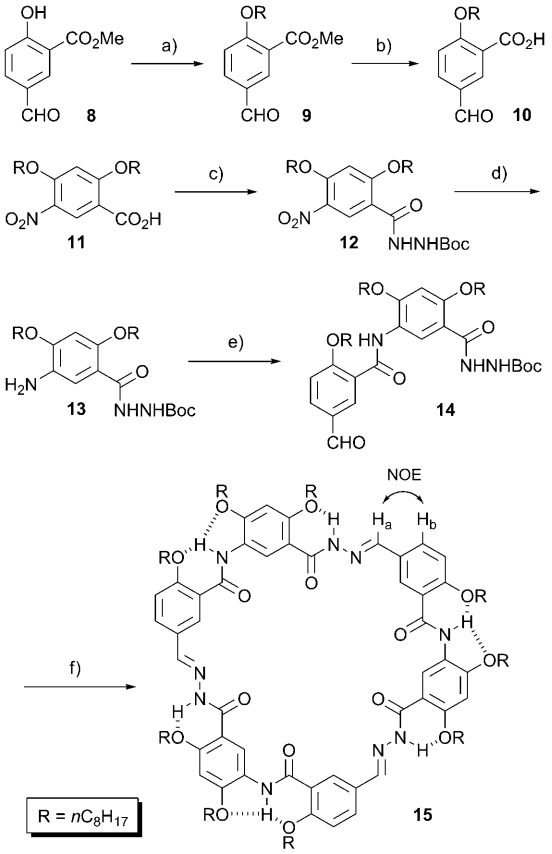


Figure 1. Partial ^{1}H NMR spectra of a) **6c**, b) **6c**+TFA (0.25 h), c) **6c**+TFA (1 h), d) **6c**+TFA (4 h), e) **6c**+TFA (10 h), f) **7c**+TFA (10 h), and g) **7c** in $CDCl_3$ ([**6c**] = 5 mM, [**7c**] = 1.7 mM, [TFA] = 20 mM).

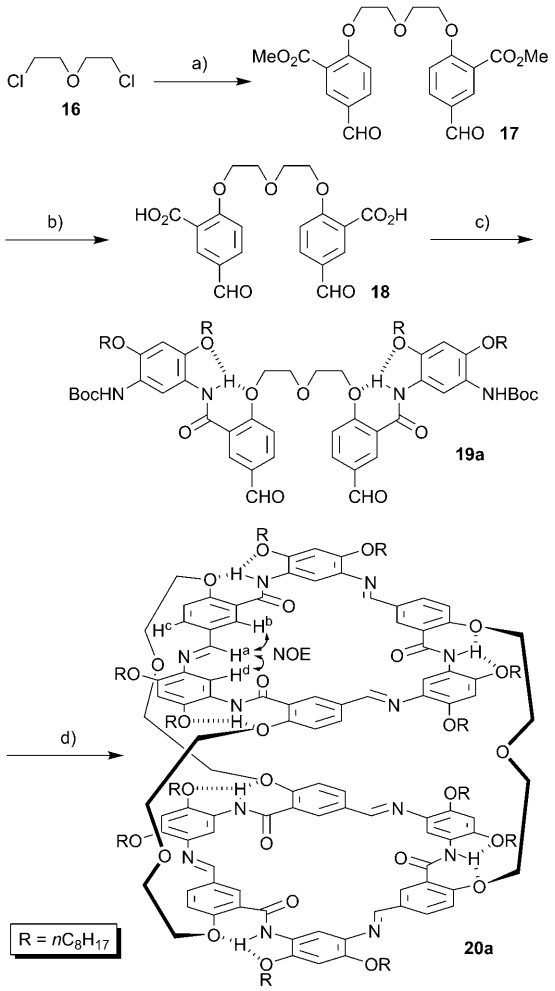
perature all exhibited a set of sharp signals, which indicates that their imine units did not undergo configurational isomerization (Figure 1g). 2D NOESY ^{1}H NMR experiments showed that their imine carbon atoms were directed away from the neighboring alkoxy group (cf. Scheme 2 below).

To extend the scope of the DCC approach, compound **14** was also prepared (Scheme 2) to construct a large macrocycle through the formation of three hydrazone bonds. Several peptides and U-shaped aryl amide derivatives bearing aldehyde and acyl hydrazide units have been reported to selectively generate macrocycles or [2]catenanes.[16,17] To prepare **14**, phenol **8**[18] was first octylated to give intermediate **9**, which was hydrolyzed with lithium hydroxide to afford the acid **10**. With this acid available, compound **12** was prepared in a yield of 91% from the coupling reaction of **11**[19] and NH_2NHBoc in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC) and then hydrogenated to **13** quantitatively. The aniline was then coupled with compound **10** to give **14** in a yield of 63%. In the presence of an excess of TFA, the Boc group of **14** was removed quickly and the resulting intermediate self-coupled to give macrocycle **15** selectively. The reaction was also tracked in $CDCl_3$ by ^{1}H NMR spectroscopy, which revealed that the original complicated signal patterns gradually evolved, after the reaction had reached equilibrium within 8 h, into one set of signals for **15**, as observed for **7a**–**c**. The solubility of the neutral sample of **15** in chloroform was low, but good in a mixture of chloroform and DMSO. Therefore, a 2D NOESY experiment was performed for **15** in binary $CDCl_3$ and [D_6]DMSO (4:1), which revealed a NOE contact between the H_a and H_b signals (Scheme 2). This observation verifies that the imine hydrogen atoms are directed outwards and that all six carbonyl groups are orientated inwards.



Scheme 2. Reagents and conditions: a) $nC_8H_{17}Br$, K_2CO_3, KI, DMF, 14 h, 73%; b) LiOH, MeOH/H_2O, RT, 4 h, 95%; c) NH_2NHBoc, DCC, DMAP, THF, RT, 12 h, 91%; d) H_2, Pd/C, MeOH/THF, 8 h, 100%; e) **10**, $ClCO_2iBu$, NEt_3, $CHCl_3$, 48 h, 63%; f) TFA, $CHCl_3$, RT, 8 h, 95%.

Encouraged by the above results, we then prepared dipodal **19a** to test if a three-dimensional structure could be constructed (Scheme 3). Three octyl units were introduced, which were expected to render the target molecule soluble. The two preorganized segments were linked with a flexible chain, which we envisioned would enable the formation of two macrocyclic units without weakening the intramolecular three-center hydrogen-bonding. Compound **17** was first obtained from the reaction of compounds **8** and **16** and then



Scheme 3. Reagents and conditions: a) **8**, K_2CO_3, KI, DMF, 105°C, 18 h, 62%; b) NaOH, H_2O/MeOH, reflux, 12 h, 88%; c) **2c**, $ClCO_2iBu$, NEt_3, $CHCl_3$, RT, 24 h, 71%; d) TFA, $CHCl_3$, RT, 14 h, 95%.

hydrolyzed with sodium hydroxide to **18**. The diacid was then condensed with **2c** to afford **19a**. A solution of **19a** in chloroform was stirred in the presence of TFA (40 equiv) to give the two-layered compound **20a** exclusively. The time-dependent ^{1}H NMR spectra in $CDCl_3$ indicated that this conversion was also thermodynamically controlled and nearly quantitative (Figure 2). The reaction reached equilibrium within 2 h, which was notably shorter than that needed for **6a–c**. Considering that the reaction involved the one-step formation of six C=N bonds and that the water formed was not removed from the solution, this result was impressive and indicated that **20a** is much more stable than any other possible products. Capsule **20a** was comprehensively characterized by ^{1}H and ^{13}C NMR spectroscopy, (HR)MS spectrometry, and elemental analysis. Its amide hydrogen signals appeared at 9.91 ppm, which suggests that they maintained the intramolecular three-center hydrogen-bonding. 2D NOESY ^{1}H NMR experiment in $CDCl_3$ revealed NOE contacts between H_a and H_b and H_d, but no NOE contact between H_a and H_c (Scheme 3). This result verifies that its imine hydrogen atoms are orientated inwards. Reducing the concentration of **20a** in $CDCl_3$ to 0.5 mM did not lead to the appearance of new signals in the ^{1}H NMR spectrum, which indicates that the capsule is quite stable and does not change to other species, even in dilute solution.

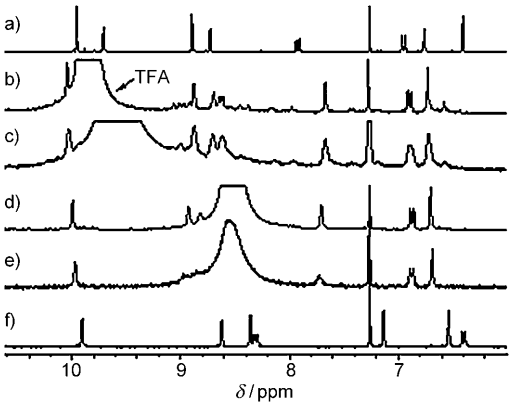
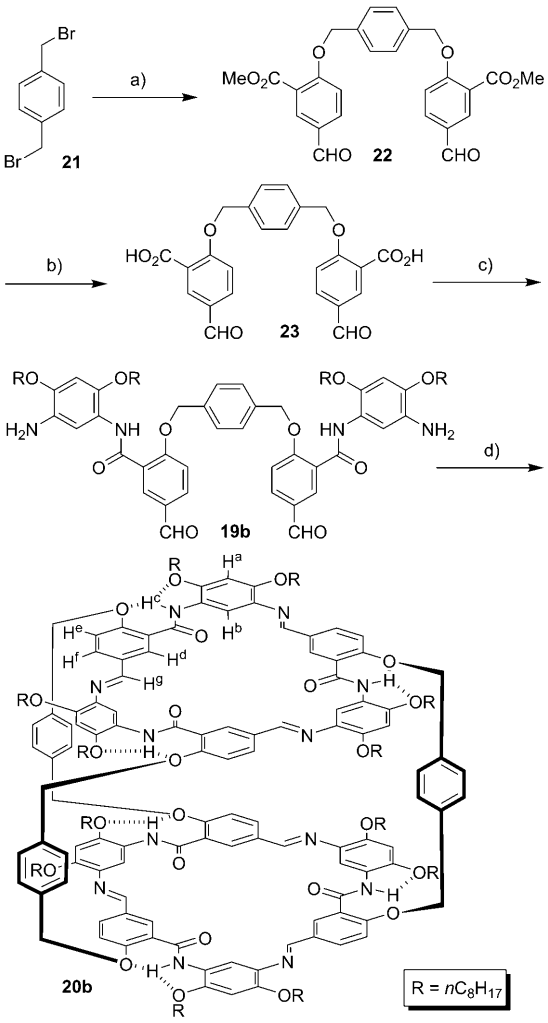


Figure 2. Partial ^{1}H NMR spectra of a) **19a** (5 mM), b) **19a** (5 mM) + TFA (1 h), c) **19a** (5 mM) + TFA (1.5 h), d) **19a** (5 mM) + TFA (2 h), e) **20a** (1.7 mM) + TFA (2 h), and f) **20a** (1.7 mM) in $CDCl_3$ ([TFA] = 0.20 M).

We then prepared dipodal **19b**, which possesses a rigid *p*-xylenene linker, to investigate its capacity for generating the three-dimensional architecture. The synthesis is shown in Scheme 4. Compound **22** was first prepared from the reaction of **8** and **21** in a yield of 84% and then hydrolyzed with lithium hydroxide to **23** in a yield of 86%. The diacid was then coupled with **2c** to give **19b** in a yield of 63%. Treatment of **19b** with an excess of TFA in chloroform produced capsule **20b** also exclusively (>95% yield). Similar to that of **20a**, its ^{1}H NMR spectrum in $CDCl_3$ also displayed a set of sharp signals. The amide hydrogen signals appeared at

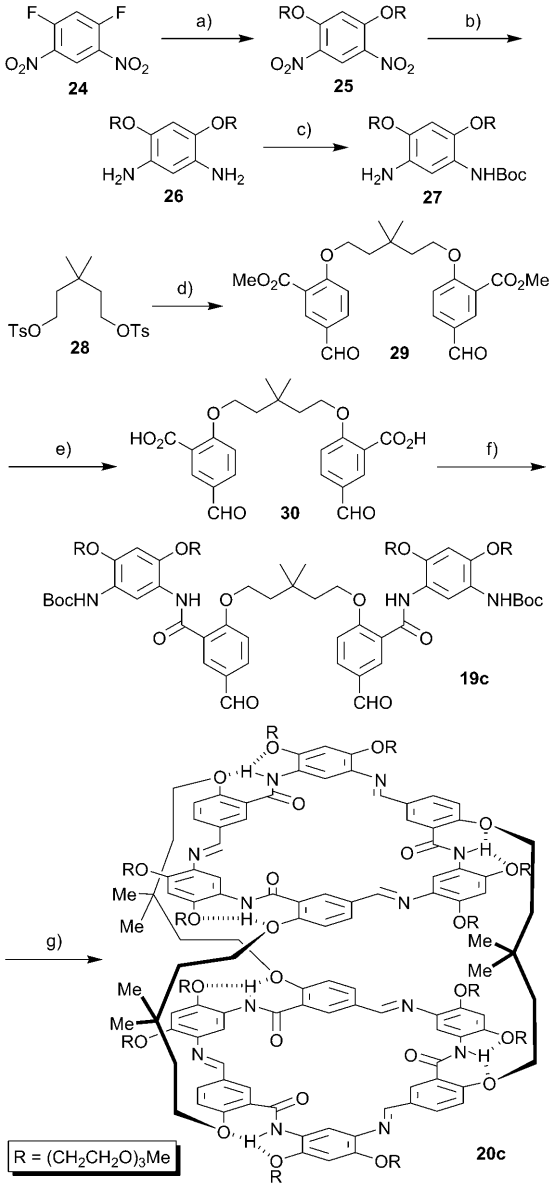


Scheme 4. Reagents and conditions: a) **8**, K_2CO_3, KI, DMF, 105 °C, 24 h, 84%; b) LiOH, THF/MeOH/H_2O, RT, 20 h, 86%; c) **2c**, $ClCO_2iBu$, NEt_3, $CHCl_3$, RT, 24 h, 63%; d) TFA, $CHCl_3$, RT, 12 h, 95%.

10.01 ppm, which indicates that they are also involved in intramolecular three-centered hydrogen-bonding.

In principle, the two cyclophane moieties of the above capsules might adopt two different orientations, that is, parallel or opposite arrangements. Their ^{1}H NMR spectra showed that only one isomer was formed, but did not differentiate between them. To address this issue, we also prepared dipodal **19c**, which possesses a 3,3-dimethylpentylene linker and four tri(ethylene glycol) chains. This new chain was designed not only to render the corresponding capsule soluble, but also to avoid any possible signal overlap with signals of the methyl units on the linkers in the upfield area of the ^{1}H NMR spectrum. It was expected that the ^{1}H NMR spectrum of the parallel-arranged isomer would exhibit two discrete singlets for the hydrogen atoms of the two methyl units on the linker, whereas the corresponding atoms of the opposite-arranged isomer would give rise to one singlet. The synthetic route to **19c** is shown in Scheme 5. Compound **24**[20] was first treated with 2-[2-(2-methoxyethoxy)ethoxy]e-

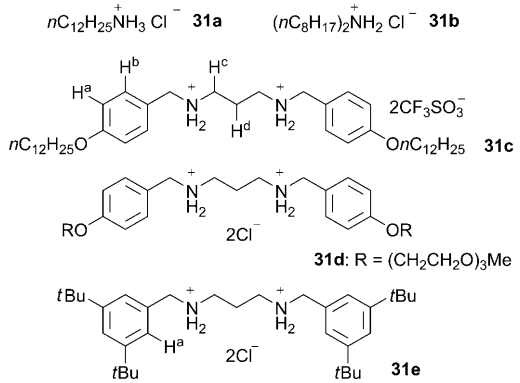
thanol in DMF to give **25** in a yield of 85%. This intermediate was then hydrogenated to give **26** quantitatively and this diamine was then treated with di(*tert*-butyl) dicarbonate to afford **27** in a yield of 63%. With this intermediate available, **8** was treated with ditosylate **28**[21] in DMF to produce diester **29** in a yield of 74%. Diacid **30** was then prepared by hydrolyzing **29** and then coupled with **27** to afford compound **19c**. The TFA-catalyzed reaction of **19c** was then performed in chloroform to afford an oily product that formed only one spot on TLC plates. The ^{1}H NMR spectrum of the product in $CDCl_3$ showed that capsule **20c** was formed as the major product, but some minor byproducts



Scheme 5. Reagents and conditions: a) $Me(OCH_2CH_2)_3OH$, K_2CO_3, DMF, RT, 11 h, 85%; b) H_2 (50 atm), Pd/C, THF, RT, 7 h, 100%; c) $(Boc)_2O$, NEt_3, THF, RT, 14 h, 63%; d) **8**, K_2CO_3, DMF, 60 °C, 40 h, 74%; e) NaOH, THF/MeOH/H_2O, reflux, 4 h, 76%; f) **27**, $ClCO_2iBu$, NEt_3, $CHCl_3$, RT, 24 h, 71%; g) TFA, $CHCl_3$, RT, 35 h, 82%.

were also generated (see the Supporting Information), which could not be removed by low-temperature recrystallization, as shown by ^{1}H NMR spectroscopy.[22] However, the signals of **20c** in the upfield area could be assigned on the basis of the 2D NOESY ^{1}H NMR spectrum. The ^{1}H NMR spectrum exhibited only one strong singlet at 1.13 ppm for the hydrogen atoms of the methyl units on the linker, which shows that the two cyclophane moieties are arranged oppositely.

The C=O oxygen atoms of **7a–c** and **20a–c** are all directed inwards. Several hydrogen-bonding-mediated aryl amide based foldamers and macrocycles have already been shown to bind aliphatic ammonium or guanidinium cations through intermolecular C=O···H–N hydrogen-bonding.[23,24] Therefore we investigated the binding ability of **7c**, **20a**, and **20b** towards **31a–e**. Compounds **31c–e** were prepared in high yields from the reactions of aldehydes **32–35**[25–27] with **33**, followed by reduction of the corresponding diimine intermediates with sodium borohydride, and acidification of the resulting diamines. Mixing **7c** or **20a** with **31a–c** (1:1, 3 mM) in $CDCl_3$ caused a notable shift of their signals in the ^{1}H NMR spectra.[28] For example, the signals of the ammonium hydrogen atoms of **31a** and **31b** were shifted upfield by 0.02 and 0.03 ppm in the presence of 1 equiv of **7c**. Upon mixing **20b** with **31c**, the signals of the inward-directed H_b, H_d, and H_g of **20b** were shifted upfield by 0.03, 0.02, and 0.01 ppm, respectively, whereas those of H_a–H_d of **31c** were shifted by −0.14, −0.07, 0.12, and 0.04 ppm, respectively (see the structures for numbering). In contrast, the outward-directed hydrogen atoms of **20b** did not exhibit any observable shifting of their signals. A ^{1}H NMR DOSY experiment was also performed for the solution of **20b** and **31c** (1:1, 3 mM) in $CDCl_3$[4d,29] and revealed that the diffusion coefficients obtained from all the assignable signals of both molecules were significantly lower (see the Supporting Information for detailed results). All these results indicate that the ammonium guests bind to the mono- and two-layered macrocycles in the cavity.

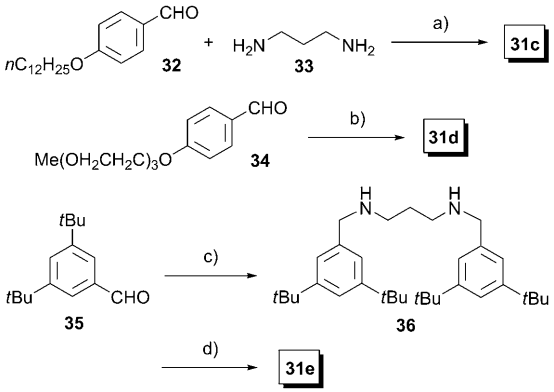


The fluorescence of **7c**, **20a**, and **20b** was notably enhanced in the presence of the ammonium guests. Therefore quantitative fluorescent titrations were performed in chloro-

form (see the Supporting Information) and the Benesi–Hildebrand[30] equation was applied to the resulting data. The association constants (K_{assoc}) of the complexes **7c·31a**, **7c·31b**, **20a·31c**, **20a·31d**, **20b·31c**, and **20b·31d** were thus determined to be 540, 240, 630, 590, 1500, and 970 M^{-1}, respectively.

ESI mass spectrometry was also used to investigate the binding patterns of the new complexes. Because **31b** possesses a larger steric hindrance and less hydrogen atoms are involved in the intermolecular hydrogen-bonding than **31a**, **7c·31b** is less stable than **7c·31a**. However, the ESI mass spectrum of a 1:1 mixture of **7c** and **31b** showed the ion peak of complex **7c·31b** to be the base peak ($[M-Cl]^+$: $m/z=1894.1$). In contrast, a 1:1 mixture of **7c** and **31a** only exhibited a weak ion peak for complex **7c·31a** ($[M-Cl]^+$: $m/z=$ 1837.6; see the Supporting Information). These results suggest for **7c·31b** that the two *n*-octyl chains of **31b** are not simply located on the same side of **7c**. Instead the molecule is threaded through the cavity of **7c** to form a pseudo[2]rotaxane, which would take longer to decompose.

ESI and MALDI-TOF experiments were also performed on mixtures of **20a** and **20b** with **31a–d**. These experiments failed to produce the ion peaks of the corresponding complexes. To gain an insight into the binding patterns of the capsular molecules with the linear guests we prepared **31e** (Scheme 6), which bears two large 3,5-di(*tert*-butyl)phenyl units. It was expected that if its linear propylenediammonium segment was threaded through the two cyclophane units of the capsules, the dethreading process would take even longer. In fact this was the case. The MALDI-TOF mass spectrum of a 1:1 mixture of **20a** and **31e** displayed a very strong ion peak (base peak) for the complex **20a·31e** ($[M-2Cl]^+$: $m/z=3660.2$). In contrast, the MALDI-TOF mass spectrum of a 2:1 mixture of **7c** and **31e** only exhibited a very weak ion peak for the complex **7c·31e** ($[M-Cl]^+$: $m/z=2131.3$; see the Supporting Information). These results strongly suggest that the complex **20a·31e** possesses the structure of a pseudo[3]rotaxanes with the linear guest



Scheme 6. Reagents and conditions: a) i. toluene, reflux, 4 h; ii. $NaBH_4$, MeOH/THF, RT, 12 h; iii. CF_3SO_3H, MeOH, 86% (three steps); b) i. **33**, toluene, reflux, 5 h; ii. $NaBH_4$, MeOH/THF, RT, 12 h; iii. HCl, MeOH, 94% (three steps); c) i. **33**, toluene, reflux, 6 h; ii. $NaBH_4$, MeOH/THF, RT, 9 h, 94% (two steps); d) HCl, MeOH, 93%.

threaded through the two cyclophane units of the capsule, as shown in Figure 3a. On the basis that the complex of **20a** and **31d** is more stable, it would be reasonable to propose that a similar structure is also formed for **20a·31d** (Figure 3b). However, its decomposition should be much quicker due to the lack of the large stoppers. Further evidence for the threaded structure comes from 2D NOESY ^{1}H NMR experiments. The 1:1 solution of **20a** and **31e** (3 mM) in $CDCl_3$ revealed intermolecular NOE contacts between H_a and H_b of **20a** and H_a of **31e** (see the structure for labeling and also the Supporting Information). Similar contacts were not observed with the 1:1 solution of **7c** and **31e**. This can be explained by considering the above differences in the dethreading process. The resolution of the ^{1}H NMR spectrum of the above 1:1 solution of **20a** and **31e** was reduced significantly relative to that of the solution of **20a** or **31e** alone at the same concentration, but no signal splitting was observed for either of them, even at a lower temperature (RT to 0 °C),[31] which implies that exchange between the threading and dethreading states occurs on the ^{1}H NMR timescale.

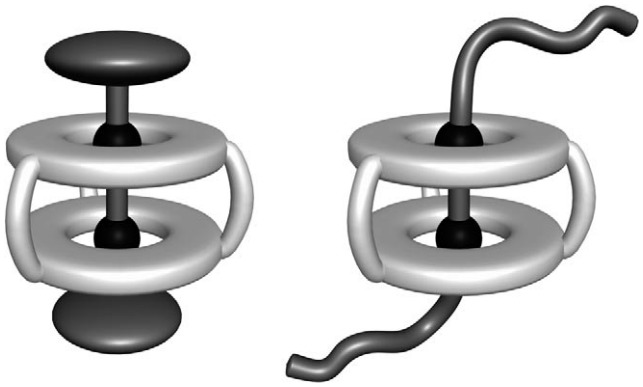


Figure 3. The pseudo[3]rotaxane structures of the complexes formed between two-layered capsule **20a** and a) **31e** and b) **31d**. The former complex is less stable but takes longer to decompose.

Conclusions

We have demonstrated that intramolecular hydrogen-bonding can be used to preorganize rationally designed molecular monomers to direct the formation of two- and three-dimensional architectures by using dynamic covalent chemistry. The fact that stable molecular capsules have been assembled in very high yields through the one-step formation of six imine bonds illustrates the robust capacity of this new DCC approach. One notable implication of this study is that partially ordered segments can be used to efficiently assemble three-dimensional systems. The formation of new unique two-layered pseudo[3]rotaxanes from the capsule and aliphatic ammonium ions bodes well for the design of new three-dimensional architectures for molecular encapsulation or catalysis. Currently, we are trying to modify the preorgan-

ized segments and/or linkers to tune the width and length of the capsules and also to introduce chiral units to assemble chiral capsules.

Experimental Section

General methods: All reactions were carried out under a dry nitrogen atmosphere. All solvents were dried before use following standard procedures. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. Analytical thin-layer chromatography (TLC) was performed on glass plates precoated with 0.2 mm silica gel 60 and the F_{254} indicator. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or 400 DPX spectrometer in the indicated solvents. Chemical shifts are expressed in parts per million (δ) and residual solvent protons were used as internal standards (^1H: chloroform: $\delta = 7.26$ ppm; DMSO: $\delta = 2.49$ ppm; ^{13}C: $CDCl_3$: $\delta = 77.2$ ppm).

Compound 2a: A solution of di(*tert*-butyl) dicarbonate (2.59 g, 11.9 mmol) in THF (10 mL) was added dropwise to a stirred solution of **1a** (2.33 g, 11.9 mmol) and triethylamine (1.75 mL, 12.7 mmol) in THF. The mixture was stirred at RT for 15 h and then concentrated with a rotavapor. The resulting residue was dissolved in chloroform (30 mL) and the solution washed with water (2×15 mL) and brine (15 mL) and dried over sodium sulfate. After the solvent had been removed with a rotavapor, the crude product was purified by column chromatography (petroleum ether/ethyl acetate, 15:1 to 10:1) to give **2a** as a reddish solid (2.10 g, 60%). ^1H NMR ($CDCl_3$): $\delta = 7.55$ (s, 1H), 6.85 (s, 1H), 6.45 (s, 1H), 4.02–3.95 (m, 4H), 3.26 (s, 2H), 1.51 (s, 9H), 1.44–1.37 ppm (m, 6H); MS (ESI): *m/z*: 319.2 $[M+Na]^+$; elemental analysis calcd (%) for $C_{15}H_{24}N_2O_4$: C 60.79, H 8.16, N 9.45; found: C 60.76, H 7.97, N 9.36.

Compound 2b: Reddish oil (52%). ^1H NMR ($CDCl_3$): $\delta = 7.52$ (s, 1H), 6.82 (s, 1H), 6.42 (d, $J = 2.1$ Hz, 1H), 3.69–3.65 (m, 4H), 3.55 (s, 2H), 2.11–2.04 (m, 2H), 1.51 (s, 9H), 1.06–0.76 ppm (m, 12H); MS (ESI): *m/z*: 375.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{32}N_2O_4$: C 64.74, H 9.15, N 7.95; found: C 64.41, H 9.34, N 7.70.

Compound 2c: Reddish oil (59%). ^1H NMR ($CDCl_3$): $\delta = 7.53$ (s, 1H), 6.84 (s, 1H), 6.44 (s, 1H), 3.92–3.88 (m, 4H), 3.25 (s, 2H), 1.79–1.72 (m, 4H),1.51–1.28 (m, 29H), 0.90–0.86 ppm (m, 6H); MS (ESI): *m/z*: 487.4 $[M+Na]^+$; elemental analysis calcd (%) for $C_{27}H_{48}N_2O_4$: C 69.79, H 10.41, N 6.03; found: C 69.50, H 10.30, N 6.01.

Compound 4: Benzoic anhydride (0.84 g, 3.50 mmol) was added to a solution of **3** (14.0 g, 63.0 mmol) and NBS (12.3 g, 69.3 mmol) in CCl_4 (100 mL). The mixture was heated under reflux for 10 h and then cooled to RT The precipitate formed was filtered off and the solution concentrated. The resulting residue was dissolved in acetic acid (90 mL) and then hexamethylenetetramine (10.6 g, 75.6 mmol) was added slowly. The mixture was stirred at RT for 10 min and then water (90 mL) added. The mixture was stirred at 60 °C for 5 h and concentrated again. The resulting residue was triturated with AcOEt (400 mL). The solution was washed with a saturated sodium bicarbonate solution (2×400 mL), water (400 mL), and brine (400 mL), and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by column chromatography (petroleum ether/AcOEt 5:1) to give **4** as a white solid (4.42 g, 30%). ^1H NMR ($CDCl_3$): $\delta = 9.84$ (s, 1H), 8.25 (dd, $J_1 = 7.9$, $J_2 = 2.3$ Hz, 1H), 7.91 (d, $J = 2.3$ Hz, 1H), 7.19 (d, $J = 7.9$ Hz, 1H), 4.07 (t, $J = 6.4$ Hz, 2H), 3.85 (s, 3H), 1.79–1.76 (m, 2H), 1.49–1.44 (m, 2H), 0.93 ppm (t, $J = 7.2$ Hz, 3H); MS (ESI): *m/z*: 237.1 $[M+H]^+$.

Compound 5: A solution of **4** (3.90 g, 16.5 mmol) and sodium hydroxide (0.80 g, 19.8 mmol) in methanol (90 mL) and water (30 mL) was stirred at RT for 5 h and then concentrated to about 30 mL. Water (50 mL) was added and the solution was extracted with AcOEt (2×40 mL). Dilute hydrochloric acid (1 M) was added to the aqueous phase to give pH 4. The precipitate formed was filtered. After recrystallization from ethanol, **5** was obtained as a white solid (2.82 g, 77%). ^1H NMR ($CDCl_3$): $\delta = 9.98$ (s, 1H), 8.67 (d, $J = 2.2$ Hz, 1H), 8.13 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.2$ Hz, 1H), 7.21 (d, $J = 8.7$ Hz, 1H), 4.35 (t, $J = 6.5$ Hz, 2H), 1.95–1.93 (m, 2H), 1.58–1.55 (m, 2H), 1.03 ppm (t, $J = 7.2$ Hz, 3H); MS (ESI): *m/z*: 221.0 $[M-H]^-$; elemental analysis calcd (%) for $C_{12}H_{14}O_4$: C 64.85, H 6.35; found: C 64.76, H 6.42.

Compound 6a: Isobutyl chloroformate (0.54 mL, 4.15 mmol) was slowly added to a stirred solution of **5** (0.38 g, 1.69 mmol) and triethylamine (0.58 mL, 4.19 mmol) in chloroform (15 mL). Stirring was continued for 30 min and then a solution of **2a** (0.50 g, 1.69 mmol) in chloroform (20 mL) was added. The solution was stirred for 24 h and then washed with a saturated sodium bicarbonate solution (20 mL), water (20 mL), and brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent, the crude product was recrystallized from methanol to give **6a** as a white solid. (0.65 g, 77%). ^1H NMR ($CDCl_3$): $\delta = 9.96$ (s, 1H), 9.84 (s, 1H), 9.11 (s, 1H), 8.83 (d, $J = 2.1$ Hz, 1H), 8.01 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.2$ Hz, 1H), 7.13 (d, $J = 8.6$ Hz, 1H), 6.78 (s, 1H), 6.51 (s, 1H), 4.32 (t, $J = 6.9$ Hz, 2H), 4.12–4.04 (m, 4H), 1.95–1.90 (m, 2H), 1.51–1.39 (m, 17H), 0.99–0.94 ppm (m, 3H); MS (ESI): *m/z*: 501.3 $[M+H]^+$, 523.3 $[M+Na]^+$; HRMS (ESI): calcd for $C_{27}H_{36}N_2O_7Na$ $[M+Na]^+$: 523.2391; found: 523.2415.

Compound 7a: TFA (0.68 mL, 8.88 mmol) was added to a stirred solution of **6a** (0.22 g, 0.44 mmol) in chloroform (12 mL). The solution was stirred at room temperature for 12 h and then a saturated sodium bicarbonate solution (10 mL) was added. After stirring for another 10 min, chloroform (50 mL) was added. The organic phase was washed with a saturated sodium bicarbonate solution (2×50 mL), water (50 mL), and brine (50 mL), and dried over sodium sulfate. The solvent was then removed with a rotavapor to give **7a** as a yellow solid (0.17 g, 100%). The product was recrystallized from methanol and ethyl acetate for analysis (94%). ^1H NMR (TFA/$CDCl_3$, 1:10): $\delta = 10.22$ (s, 3H), 9.05 (d, $J = 9.3$ Hz, 6H), 8.89 (s, 3H), 8.25 (s, 3H), 7.47 (d, $J = 8.7$ Hz, 3H), 6.67 (s, 3H), 4.57–4.52 (t, $J = 6.9$ Hz, 6H), 4.37–4.24 (m, 12H), 2.05–2.00 (m, 6H), 1.60–1.49 (m, 24H), 1.06–1.01 ppm (m, 9H); MS (MALDI-TOF): *m/z*: 1147.3 $[M+H]^+$; HRMS (MALDI-TOF): *m/z*: calcd for $C_{66}H_{80}N_6O_{12}$ $[M+H]^+$: 1147.5732; found: 1147.5751; elemental analysis calcd (%) for $C_{66}H_{78}N_6O_{12}\cdot H_2O$: C 68.02, H 6.92, N 7.21; found: C 68.14, H 7.02, N 7.09.

Compound 6b: White solid (82%). ^1H NMR ($CDCl_3$): $\delta = 9.97$ (s, 1H), 9.73 (s, 1H), 9.00 (s, 1H), 8.81 (d, $J = 2.2$ Hz, 1H), 8.02 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.3$ Hz, 1H), 7.14 (d, $J = 8.7$ Hz, 1H), 6.75 (s, 1H), 6.50 (s, 1H), 4.31 (t, $J = 6.9$ Hz, 2H), 3.78–3.73 (m, 4H), 2.13–2.08 (m, 2H), 1.91–1.84 (m, 2H), 1.52 (s, 9H), 1.06–0.96 ppm (m, 17H); ^{13}C NMR ($CDCl_3$): $\delta = 190.7$, 161.6, 161.1, 152.9, 144.8, 144.7, 137.2, 131.9, 130.1, 123.2, 121.4, 120.9, 114.2, 113.2, 98.3, 76.1, 75.6, 69.8, 30.8, 28.4, 28.3, 28.2, 19.3, 19.2, 19.0, 13.7 ppm; MS (ESI): *m/z*: 557.3 $[M+H]^+$, 579.3 $[M+Na]^+$; HRMS (MALDI-TOF): *m/z*: calcd for $C_{31}H_{44}N_2O_7Na$ $[M+Na]^+$: 579.3029; found: 579.3041.

Compound 7b: Yellow solid (96%). ^1H NMR ($CDCl_3$): $\delta = 9.99$ (s, 3H), 8.80 (s, 3H), 8.77 (d, $J = 1.8$ Hz, 3H), 8.69 (s, 3H), 8.36 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.3$ Hz, 3H), 7.14 (d, $J = 8.8$ Hz, 3H), 6.60 (s, 3H), 4.34 (t, $J = 7.2$ Hz, 6H), 3.88 (d, $J = 6.8$ Hz, 12H), 2.22–2.18 (m, 6H), 1.97–1.92 (m, 6H), 1.54–1.46 (m, 6H), 1.01–0.97 ppm (m, 45H); ^{13}C NMR ($CDCl_3$): $\delta = 190.7$, 162.6, 158.4, 157.5, 150.1, 147.9, 137.0, 134.3, 130.5, 130.1, 122.7, 122.3, 113.5, 113.0, 101.0, 75.6, 69.9, 69.6, 30.9, 30.7, 28.7, 28.5, 28.4, 28.2, 19.4, 19.3, 19.1, 13.8, 13.7 ppm; MS (MALDI-TOF): *m/z*: 1315.8 $[M+H]^+$, 1337.7 $[M+Na]^+$; HRMS (MALDI-TOF): *m/z*: calcd for $C_{78}H_{103}N_6O_{12}$ $[M+H]^+$: 1315.7646; found: 1315.7629; elemental analysis calcd (%) for $C_{78}H_{102}N_6O_{12}$: C 71.21, H 7.81, N 6.39; found: C 70.89, H 8.15, N 6.27.

Compound 6c: Pale-yellow solid (98%). ^1H NMR ($CDCl_3$): $\delta = 9.98$ (s, 1H), 9.80 (s, 1H), 9.07 (s, 1H), 8.82 (d, $J = 2.2$ Hz, 1H), 8.03 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.2$ Hz, 1H), 7.14 (d, $J = 8.6$ Hz, 1H), 6.8 (s, 1H), 6.52 (s, 1H), 4.30 (t, $J = 6.9$ Hz, 1H), 4.04–3.96 (m, 4H), 1.95–1.76 (m, 6H), 1.54 (s, 9H), 1.44–1.22 (m, 22H), 0.99–0.86 ppm (m, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 161.5$, 161.1, 152.8, 144.5, 144.4, 137.1, 131.9, 130.2, 123.3, 121.6, 121.3, 113.9, 113.2, 98.5, 80.1, 69.9, 69.8, 69.4, 31.7, 31.6, 30.8, 29.3, 29.2, 29.1, 28.4, 26.0, 25.9, 22.6, 22.5, 19.0, 14.0, 13.9, 13.6 ppm; MS (ESI): *m/z*: 669.6 $[M+H]^+$, 691.5 $[M+Na]^+$; elemental analysis calcd (%) for $C_{39}H_{60}N_2O_7$: C 70.03, H 9.04, N 4.19; found: C 69.63, H 9.36, N 3.98.

Compound 7c: Yellow solid (95%). ^{1}H NMR ($CDCl_3$): δ = 10.00 (s, 3H), 8.82 (s, 3H), 8.77 (d, J = 1.8 Hz, 3H), 8.74 (s, 3H), 8.37 (dd, J_1 = 8.7 Hz, J_2 = 1.7 Hz, 3H), 7.12 (d, J = 8.8 Hz, 3H), 6.62 (s, 3H), 4.33 (t, J = 7.1 Hz, 6H), 4.13 (t, J = 6.8 Hz, 12H), 2.00–1.84 (m, 18H), 1.56–1.26 (m, 66H), 1.25–0.92 ppm (m, 27H); ^{13}C NMR ($CDCl_3$): δ = 162.5, 158.5, 157.4, 149.9, 147.7, 137.0, 137.5, 134.2, 130.5, 130.2, 122.9, 122.2, 113.2, 112.8, 101.1, 71.4, 69.6, 69.3, 31.8, 31.7, 31.0, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 26.1, 25.9, 22.7, 22.6, 19.1, 14.1, 14.0, 13.8 ppm; MS (MALDI-TOF): m/z: 1652.1 $[M+H]^+$; elemental analysis calcd (%) for $C_{102}H_{150}N_6O_{12}$: C 74.14, H 9.15, N 5.09; found: C 74.29, H 9.23, N 5.17.

Compound 9: *n*-Octyl bromide (3.00 mL, 16.7 mmol) was added to a stirred mixture of compound **8** (2.00 g, 11.1 mmol), potassium carbonate (4.60 g, 33.3 mmol), and potassium iodide (0.20 g, 1.20 mmol) in DMF (50 mL). The mixture was stirred at 80°C for 14 h and then concentrated with a rotavapor. The resulting slurry was triturated with ethyl acetate (50 mL). The organic phase was then washed with water (2×25 mL) and brine (25 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was purified by column chromatography (petroleum ether/EtOAc, 20:1) to give compound **9** as a pale-yellow solid (2.40 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.89 (s, 1H), 8.30 (d, J = 2.1 Hz, 1H), 7.98 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 4.12 (t, J = 6.3 Hz, 2H), 3.91 (s, 3H), 188–1.81 (m, 2H), 1.51–1.47 (m, 2H), 1.31–1.22 (m, 8H), 0.87 ppm (t, J = 6.9 Hz, 3H); MS (EI): m/z: 292 $[M]^+$.

Compound 10: A solution of compound **9** (2.00 g, 6.80 mmol) and lithium hydroxide monohydrate (1.10 g, 27.2 mmol) in a mixture of THF (30 m), methanol (15 mL), and water (7.5 mL) was stirred at room temperature for 4 h and then concentrated to 5 mL in a rotavapor. The resulting slurry was diluted with hydrochloric acid (1 N) to pH 1 and the mixture extracted with ethyl acetate (40 mL). The organic phase was then washed with water (2×20 mL) and brine (25 mL), and dried over sodium sulfate. After removal of the solvent under reduced pressure, the crude product was recrystallized from ethanol to give compound **10** as a white solid (1.80 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.97 (s, 1H), 8.68 (d, J = 2.1 Hz, 1H), 8.13 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 4.35 (t, J = 6.6 Hz, 2H), 2.01–1.91 (m, 2H), 1.51–1.43 (m, 2H), 1.36–1.29 (m, 8H), 0.87 ppm (t, J = 7.2 Hz, 3H); MS (EI): m/z: 278 $[M]^+$.

Compound 12: DCC (1.10 g, 5.20 mmol) was slowly added to a stirred solution of compound **11** (2.00 g, 4.70 mmol), NH_2NHBoc (2.50 g, 18.8 mmol), and DMAP (0.20 g, 1.60 mmol) in THF (50 mL) cooled in an ice bath. The mixture was stirred at room temperature for 12 h and then filtered to remove the solid. The filtrate was concentrated with a rotavapor and the resulting residue suspended in diethyl ether (10 mL). The solid was filtered and the filtrate concentrated again. The resulting residue was purified by column chromatography (CH_2Cl_2/EtOAc, 100:1) to give compound **12** as a pale-yellow solid (2.30 g, 91%). M.p. 92–93°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.37 (s, 1H), 8.84 (s, 1H), 6.96 (s, H), 6.50 (s, 1H), 4.20 (t, J = 6.6 Hz, 2H), 4.12 (t, J = 6.6 Hz, 2H), 2.02–1.83 (m, 4H), 1.56–1.55 (m, 4H), 1.50 (s, 9H), 1.37–1.26 (m, 16H), 0.89 ppm (t, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.2, 161.4, 155.2, 133.4, 131.3, 111.9, 97.73, 81.93, 70.78, 70.38, 31.98, 31.96, 29.47, 29.43, 29.35, 29.37, 29.03, 28.38, 26.27, 26.01, 22.85, 19.37, 14.30 ppm; MS (EI): m/z: 437 $[M-Boc+H]^+$; elemental analysis calcd (%) for $C_{18}H_{18}O_6$: C 62.55, H 8.81, N 7.81; found: C 62.38, H 9.06, N 7.68.

Compound 13: A suspension of compound **12** (0.49 g, 0.90 mmol) and Pd/C (10%, 50 mg) in methanol (20 mL) and THF (5 mL) was stirred under 1 atm of hydrogen for 8 h. The solid was filtered off and the filtrate concentrated with a rotavapor to give compound **13** as a brown oil (0.46 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.62 (s, 1H), 7.52 (s, 1H), 6.88 (s, 1H), 6.40 (s, 1H), 4.06 (t, J = 6.3 Hz, 2H), 4.01 (t, J = 6.3 Hz, 2H), 3.62 (br, 2H), 1.93–1.79 (m, 4H), 1.49 (s, 13H), 1.32–1.26 (m, 16H), 0.89 ppm (t, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.9, 155.4, 151.4, 150.9, 130.5, 117.4, 111.6, 97.70, 81.33, 70.53, 68.74, 50.61, 31.98, 29.54, 29.50, 29.40, 29.36, 28.36, 26.33, 26.26, 22.83, 14.27 ppm; MS (ESI): m/z: 508 $[M+H]^+$; HRMS (MALDI-FT): m/z: calcd for $C_{28}H_{49}N_3O_5Na$ $[M+Na]^+$: 530.3564; found: 530.3562.

Compound 14: A solution of compound **10** (0.64 g, 2.30 mmol), NEt_3 (0.32 mL, 2.30 mL), and isobutyl chloroformate (0.30 mL, 2.30 mmol) in chloroform (5 mL) was stirred for 40 min and then a solution of **13** (0.97 g, 1.90 mmol) in chloroform (5 mL) was added dropwise. The solution was stirred for 48 h and then chloroform (100 mL) added. The solution was washed with water (2×50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was then removed under reduced pressure and the resulting residue purified by column chromatography (petroleum ether/EtOAc, 3:1) to give compound **14** as a pale-yellow oil (0.93 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.96 (s, 1H), 9.67 (s, 1H), 9.53 (s, 1H), 9.06 (s, 1H), 8.75 (s, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.02 (s, 1H), 6.47 (s, 1H), 4.29 (t, J = 8.6 Hz, 2H), 4.11–4.07 (m, 4H), 1.96–1.80 (m, 6H), 1.48 (s, 9H), 1.45–1.22 (m, 30H), 0.90–0.81 ppm (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.5, 163.6, 161.7, 161.0, 155.0, 154.7, 152.7, 136.7, 132.2, 130.0, 125.6, 122.8, 121.5, 113.2, 111.8, 96.71, 81.18, 70.12, 69.90, 69.14, 31.72, 31.66, 29.31, 29.29, 29.24, 29.16, 29.10, 29.04, 28.83, 28.14, 26.10, 25.78, 25.70, 22.57, 22.53, 22.53, 14.12, 14.00, 13.96 ppm; MS (ESI): m/z: 790 $[M+Na]^+$; HRMS (MALDI-FT): m/z: calcd for $C_{44}H_{69}N_3O_8Na$ $[M+Na]^+$: 790.4977; found: 790.4963.

Compound 15: A solution of compound **14** (0.12 g, 0.15 mmol) and TFA (1.10 mL, 15.0 mmol) in chloroform (15 mL) was stirred at room temperature for 8 h and then further chloroform (20 mL) was added. The solution was washed with a saturated sodium bicarbonate solution (2×20 mL), water (2×20 mL), and brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the crude product was recrystallized from methanol to give compound **15** as a yellow solid (93 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$/[D$_6$]DMSO 4:1): δ = 11.11 (s, 3H), 9.95 (s, 3H), 9.27 (s, 3H), 8.92 (s, 3H), 8.25 (s, 3H), 7.64 (d, J = 8.4 Hz, 3H), 7.18 (d, J = 8.4 Hz, 3H), 6.70 (s, 3H), 4.35 (t, J = 6.9 Hz, 6H), 4.25–4.24 (m, 12H), 1.98–1.88 (m, 18H), 1.47–1.13 (m, 90H), 0.87–0.86 ppm (m, 27H); ^{13}C NMR (125 MHz, $CDCl_3$/[D$_6$]DMSO 4:1): δ = 167.4, 167.2, 162.5, 159.1, 156.8, 137.1, 136.6, 133.0, 129.8, 127.6, 126.7, 118.6, 117.7, 102.1, 74.73, 74.14, 36.72, 36.66, 34.31, 34.28, 34.21, 34.16, 34.03, 33.92, 31.18, 30.73, 30.70, 27.52, 19.09, 5.996, 5.088 ppm; MS (MALDI-TOF): m/z: 1971 $[M+Na]^+$; HRMS (MALDI-FT): m/z: calcd for $C_{117}H_{177}N_9O_{15}Na$ $[M+Na]^+$: 1971.3256; found: 1971.3265.

Compound 17: Potassium carbonate (18.3 g, 133 mmol) and potassium iodide (2.21 g, 13 mmol) were added to a solution of compounds **8** (4.76 g, 33.0 mmol) and **16** (12.0 g, 66.0 mmol) in DMF (100 mL). The mixture was stirred at 105°C for 18 h and then concentrated. The resulting residue was triturated with AcOEt (200 mL). The organic phase was then washed with a saturated sodium bicarbonate solution (100 mL), water (100 mL), and brine (100 mL), and dried over sodium sulfate. Upon removal of the solvent, the crude product was recrystallized from methanol to give compound **17** as a yellow solid (8.84 g, 62%). ^{1}H NMR ($CDCl_3$): δ = 9.90 (s, 2H), 8.32 (d, J = 2.2 Hz, 2H), 7.99 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H), 4.32 (t, J = 4.7 Hz, 4H), 4.07 (t, J = 4.7 Hz, 4H), 3.88 ppm (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 190.0, 165.2, 162.9, 134.4, 134.3, 129.2, 120.8, 113.4, 69.7, 69.2, 52.1 ppm; MS (MALDI-TOF): m/z: 452.8 $[M+Na]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{22}H_{22}O_9Na$ $[M+Na]^+$: 453.1158; found: 453.1156.

Compound 18: A solution of compound **17** (3.22 g, 7.50 mmol) and sodium hydroxide (0.72 g, 18.0 mmol) in THF (30 mL), water (10 mL), and methanol (10 mL) was heated under reflux for 12 h and then concentrated to about 10 mL. The suspension was diluted with water (20 mL) and the solution extracted with dichloromethane (2×10 mL). The aqueous phase was then acidified with dilute hydrochloric acid (2 M) to pH 4 and then extracted with AcOEt (3×25 mL). The organic phase was then washed with water (2×30 mL) and brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the crude solid was recrystallized from methanol to give **18** as a yellow solid (2.64 g, 88%). ^{1}H NMR ([D$_6$]acetone): δ = 9.98 (s, 2H), 8.38 (d, J = 2.2 Hz, 2H), 8.07 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 4.48 (t, J = 4.6 Hz, 4H), 4.08 ppm (t, J = 4.6 Hz, 4H); ^{13}C NMR ([D$_6$]DMSO): δ = 191.0, 166.4, 161.8, 134.0, 132.5, 128.7, 122.0, 113.9, 68.9, 68.8 ppm; MS (ESI): m/z: 401.1 $[M-H]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{20}H_{18}N_9Na$ $[M+Na]^+$: 425.0832; found: 425.0843.

Compound 19a: Isobutyl chloroformate (0.2 mL, 1.54 mmol) was added to a stirred solution of compound **18** (0.11 g, 0.27 mmol) and triethylamine (0.3 mL, 2.17 mmol) in chloroform (15 mL), cooled in an ice-bath.

The solution was stirred for 30 min and then **2c** (0.26 g, 0.55 mmol) was added. After stirring for 24 h, the solution was concentrated. The resulting residue was recrystallized from methanol to give compound **19a** as a yellowish solid (0.24 g, 71%). ^{1}H NMR ($CDCl_3$): δ = 9.96 (s, 2H), 9.72 (s, 2H), 8.90 (s, 2H), 8.73 (d, J = 2.2 Hz, 2H), 7.92 (dd, J_1 = 8.6, J_2 = 2.2 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 6.76 (s, 2H), 6.41 (s, 2H), 4.27–4.23 (m, 4H), 3.93–3.88 (m, 12H), 1.81–1.64 (m, 8H), 1.55 (s, 18H), 1.45–0.83 ppm (m, 52H); ^{13}C NMR ($CDCl_3$): δ = 190.4, 161.4, 160.5, 152.6, 144.8, 144.5, 136.4, 131.9, 130.5, 123.5, 121.6, 120.7, 113.9, 98.6, 70.1, 69.2, 69.1, 68.8, 31.7, 31.6, 29.3, 29.3, 29.2, 29.1, 28.3, 25.9, 25.7, 22.5, 22.4, 14.0, 14.9 ppm; MS (MALDI-TOF): m/z: 1318.0 $[M+Na]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{74}H_{110}N_4O_{15}Na$ $[M+Na]^+$: 1317.7861; found: 1317.7860.

Compound 20a: A solution of compound **19a** (0.17 g, 0.13 mmol) and TFA (0.2 mL, 2.61 mmol) in chloroform (10 mL) was stirred at RT for 14 h and then a saturated sodium bicarbonate solution (10 mL) was added. After stirring for 10 min, the organic phase was separated and washed with water (10 mL) and brine (10 mL), and dried over sodium sulfate. Upon removal of the solvent, the resulting solid was recrystallized from ethyl acetate and dichloromethane 10:1 to give compound **20a** as a yellow solid (0.12 g, 95%). ^{1}H NMR ($CDCl_3$): δ = 9.91 (s, 6H), 8.61 (d, J = 1.8 Hz, 6H), 8.36 (s, 6H), 8.28 (dd, J_1 = 8.7 Hz, J_2 = 1.7 Hz, 6H), 7.13 (s, 6H), 6.54 (s, 6H), 6.38 (d, J = 8.8 Hz, 6H), 4.22–4.04 (m, 12H), 4.01–3.88 (m, 36H), 1.89–1.75 (m, 24H), 1.47–1.22 (m, 120H), 0.87–0.83 ppm (m, 36H); ^{13}C NMR ($CDCl_3$): δ = 162.2, 158.6, 150.5, 150.2, 148.9, 137.4, 135.5, 130.8, 129.9, 122.5, 121.2, 115.0, 112.8, 102.5, 71.6, 70.6, 67.9, 67.4, 31.8, 31.7, 29.7, 29.4, 29.3 (d), 29.2, 26.0, 25.8, 22.6, 22.6, 14.1, 14.0 ppm; MS (MALDI-TOF): m/z: 3178.7 $[M+H]^+$, 3199.8 $[M+Na]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{192}H_{270}N_{12}O_{27}Na$ $[M+Na]^+$: 3199.0100; found: 3199.0016; elemental analysis calcd (%) for $C_{192}H_{270}N_{12}O_{27}\cdot H_2O$: C 72.15, H 8.58, N 5.26; found: C 71.88, H 8.38, N 4.91.

Compound 22: A suspension of compounds **8** (4.00 g, 22.2 mmol) and **21** (2.85 g, 10.8 mmol), K_2CO_3 (6.09 g, 44.2 mmol), and KI (1.31 g, 7.88 mmol) in DMF (100 mL) was stirred at 105 °C for 24 h and then concentrated. After work-up, the crude product was recrystallized from methanol to give compound **22** as a white solid (4.17 g, 84%). ^{1}H NMR ($CDCl_3$): δ = 9.92 (s, 2H), 8.37 (d, J = 2.2 Hz, 2H), 7.99 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 2H), 7.54 (s, 4H), 7.14 (d, J = 8.7 Hz, 2H), 5.30 (s, 4H), 3.94 ppm (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 190.0, 165.4, 162.5, 135.7, 134.5, 134.3, 129.4, 127.2, 121.1, 113.7, 70.5, 52.3 ppm; MS (MALDI-TOF): m/z: 485.2 $[M+Na]^+$; elemental analysis calcd (%) for $C_{26}H_{22}O_8\cdot 0.5H_2O$: C 66.24, H 4.92; found: C 66.58, H 4.80.

Compound 23: A solution of compound **22** (0.98 g, 2.11 mmol) and lithium hydroxide monohydrate (0.39 g, 9.39 mmol) in THF (40 mL), water (10 mL), and methanol (10 mL) was stirred at RT for 20 h and then concentrated. The resulting residue was added to water (50 mL) and the mixture extracted with dichloromethane (2×20 mL). The aqueous phase was acidified with hydrochloric acid (3 M) to pH 4 and then refrigerated overnight. The precipitate formed was filtered and purified by recrystallization form ethanol to give compound **23** as a white solid (0.79 g, 86%). ^{1}H NMR ($CDCl_3$): δ = 13.05 (s, 2H), 9.92 (s, 2H), 8.20 (d, J = 2.2 Hz, 2H), 8.04 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 2H), 7.54 (s, 4H), 7.43 (d, J = 8.7 Hz, 2H), 5.35 ppm (s, 4H); ^{13}C NMR ($CDCl_3$): δ = 191.2, 166.6, 161.6, 136.0, 134.3, 132.6, 129.0, 127.4, 122.4, 114.2, 69.9 ppm; MS (MALDI-TOF): m/z: 434.9 $[M+H]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{24}H_{18}O_8Na$ $[M+Na]^+$: 457.0908; found: 457.0894.

Compound 19b: A solution of compound **23** (0.46 g, 1.06 mmol) and triethylamine (0.90 mL, 6.51 mmol) in chloroform (15 mL) was cooled in an ice-bath. Isobutyl chloroformate (0.70 mL, 2.13 mmol) was added slowly to this stirred solution. Stirring was continued for 30 min and then a solution of **2c** (0.99 g, 2.13 mmol) in chloroform (15 mL) was added dropwise. After stirring at RT for 24 h, the solution was washed with a saturated sodium bicarbonate solution (15 mL), water (15 mL), and brine (15 mL), and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the resulting residue was purified by column chromatography (CH_2Cl_2/MeOH, 100:1) to give compound **19b** as a pale-yellow solid (0.88 g, 63%). ^{1}H NMR ($CDCl_3$): δ = 9.96 (s, 2H), 9.91 (s, 2H), 9.14 (s, 2H), 8.82 (d, J = 2.2 Hz, 2H), 7.92 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 2H), 7.41 (s, 4H), 7.06 (d, J = 8.7 Hz, 2H), 6.78 (s, 2H), 6.45 (s, 2H), 5.45 (s, 4H), 3.97 (t, J = 6.5 Hz, 4H), 3.81 (t, J = 6.7 Hz, 4H), 1.88–1.75 (m, 4H), 1.64 (s, 4H), 1.54 (s, 18H), 1.30–1.21 (m, 40H), 0.90–0.87 (m, 6H), 0.82–0.79 ppm (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 190.5, 161.2, 160.2, 152.8, 144.5, 144.2, 135.5, 131.7, 130.7, 127.4, 123.9, 121.5, 121.0, 114.0, 113.4, 97.9, 76.7, 70.9, 69.5, 69.3, 31.8, 31.7, 29.4, 29.3, 29.2, 29.1, 28.4, 26.1, 25.9, 22.7, 22.6, 14.1, 14.0 ppm; MS (MALDI-TOF): m/z: 1348.5 $[M+Na]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{78}H_{110}N_4O_{14}Na$ $[M+Na]^+$: 1349.7936; found: 1349.7911.

Compound 20b: TFA (0.70 mL, 9.10 mmol) was added slowly to a stirred solution of compound **19b** (0.30 g, 0.23 mmol) in chloroform (10 mL). After stirring for 12 h, the solution was washed with a saturated sodium bicarbonate solution (5 mL), water (5 mL), and brine (5 mL), and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, compound **20b** was obtained as a yellow solid (0.25 g, 100%). The product was further recrystallized from ethyl acetate to give a sample for analysis (0.24 g, 95%). ^{1}H NMR ($CDCl_3$): δ = 10.01 (s, 6H), 9.97 (s, 6H), 8.75 (d, J = 2.2 Hz, 6H), 8.10 (s, 6H), 7.92 (dd, J_1 = 8.8 Hz, J_2 = 2.2 Hz, 6H), 7.40 (s, 12H), 7.06 (d, J = 8.8 Hz, 6H), 6.45 (s, 6H), 5.46 (s, 12H), 3.95 (t, J = 6.6 Hz, 12H), 3.80 (t, J = 6.9 Hz, 12H), 1.83–1.80 (m, 12H), 1.51–1.13 (m, 132H), 0.89–0.81 ppm (m, 36H); ^{13}C NMR ($CDCl_3$): δ = 190.4, 161.2, 160.1, 143.0, 140.9, 136.4, 135.5, 132.0, 130.6, 130.0, 127.4, 124.1, 121.8, 114.0, 108.7, 99.4, 70.9, 69.9, 69.1, 31.8, 31.7, 29.5, 29.4, 29.3, 29.2, 29.1, 26.2, 25.9, 22.6, 22.5, 14.1, 14.0 ppm; MS (MALDI-TOF): m/z: 3275.1 $[M+H]^+$, 3296.0 $[M+Na]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{204}H_{271}N_{12}O_{24}$ $[M+H]^+$: 3273.0429; found: 3273.0349.

Compound 25: A suspension of compound **24** (12.0 g, 59 mmol), Me-$(OCH_2CH_2)_3OH$ (21.4 g, 0.13 mol), and potassium carbonate (20.7 g, 0.15 mol) in DMF (40 mL) was stirred at room temperature for 11 h and then concentrated with a rotavapor. The resulting residue was extracted with ethyl acetate (200 mL). The solution was washed with dilute hydrochloric acid (1 N, 50 mL), water (2×100 mL), and brine (100 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was purified by chromatography (petroleum ether/AcOEt, 10:1) to give compound **25** as a yellow oil (24.7 g, 85%). ^{1}H NMR ($CDCl_3$): δ = 6.49 (s, 1H), 6.13 (s, 1H), 4.01 (t, 4H), 3.72–3.54 (m, 24H), 3.36 ppm (s, 6H); MS (ESI): m/z: 433.3 $[M+H]^+$, 455.3 $[M+Na]^+$.

Compound 26: A suspension of **25** (0.83 g, 1.73 mmol) and Pd/C (10%, 0.10 g) in THF (40 mL) was stirred in an autoclave under hydrogen pressure (50 atm) for 7 h. The solid was filtered off and the filtrate concentrated under reduced pressure to give **26** as a grey oil (0.80 g, 100%). The diamine was unstable in air and was used for the next step without further purification.

Compound 27: Triethylamine (0.4 mL, 2.99 mmol) was added to a solution of the above product **26** in THF (15 mL). Then a solution of $(Boc)_2O$ (0.38 g, 1.73 mmol) in THF (10 mL) was added dropwise whilst stirring. Stirring was continued for 14 h and then the solvent was removed. The resulting residue was dissolved in chloroform (20 mL) and the solution was washed with water (3×10 mL) and brine (10 mL), and dried over sodium sulfate. The solvent was then removed under reduced pressure and the resulting crude product purified by column chromatography (petroleum ether/AcOEt, 3:1 to 1:2) to give **27** as a brown oil (0.57 g, 63%). ^{1}H NMR ($CDCl_3$): δ = 7.52 (s, 1H), 7.26 (s, 1H), 6.52 (s, 1H), 4.06–4.04 (m, 4H), 3.72–3.62 (m, 18H), 3.55–3.52 (m, 4H), 3.36 (s, 6H), 1.49 ppm (s, 9H); MS (ESI): m/z: 555.4 $[M+Na]^+$; elemental analysis calcd (%) for $C_{25}H_{44}N_2O_{10}$: C 56.38, H 8.33, N 5.26; found: C 55.66, H 8.69, N 4.75.

Compound 29: A suspension of compounds **8** (1.80 g, 9.98 mmol) and **28** (2.17 g, 4.93 mmol), and potassium carbonate (2.78 g, 20.2 mmol) in DMF (100 mL) was stirred at 60 °C for 40 h and then concentrated under reduced pressure. The resulting slurry was triturated with ethyl acetate (50 mL) and the solution washed successively with dilute hydrochloric acid (1 N, 20 mL), water (30 mL), and brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was purified by column chromatography (petroleum ether/AcOEt, 5:1 to 3:1) to give compound **29** as a colorless oil (1.66 g, 74%). ^{1}H NMR ($CDCl_3$): δ = 9.91 (s, 2H), 8.31 (d, J = 2.2 Hz, 2H), 8.01

(dd, J_1=8.7, Hz, J_2=2.2 Hz, 2H), 7.13 (d, J=8.7 Hz, 2H), 4.25 (t, J=6.9 Hz, 4H), 3.87 (s, 6H), 1.95 (t, J=6.9 Hz, 4H), 1.12 ppm (s, 6H); ^{13}C NMR ($CDCl_3$): δ=190.0, 165.5, 163.0, 134.4, 134.3, 129.0, 120.8, 113.0, 66.4, 52.2, 40.3, 31.9, 21.7 ppm; MS (MALDI-TOF): m/z: 480.0 $[M+Na]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{25}H_{28}O_8Na$ $[M+Na]^+$: 479.1673; found: 479.1676.

Compound 30: A solution of compound **29** (0.21 g, 0.48 mmol) and sodium hydroxide (88 mg, 2.20 mmol) in water (10 mL), THF (30 mL), and MeOH (10 mL) was heated at reflux for 4 h and then concentrated to approximately 10 mL under reduced pressure. The resulting suspension was acidified with dilute hydrochloric acid (1 N) to pH 4 and then extracted with dichloromethane (3×10 mL). The organic phase was washed with water (2×15 mL) and brine (15 mL), and dried over sodium sulfate. After the solvent had been removed with a rotavapor, the resulting residue was recrystallized from ethyl acetate to give compound **30** as a white solid (0.16 g, 76%). ^{1}H NMR ($CDCl_3$): δ=12.92 (s, 2H), 9.88 (s, 2H), 8.13 (d, J=2.1 Hz, 2H), 7.99 (dd, J_1=8.7, Hz, J_2=2.1 Hz, 2H), 7.37 (d, J=8.7 Hz, 2H), 4.22 (t, J=6.7 Hz, 4H), 1.78 (t, J=6.70 Hz, 4H), 1.02 ppm (s, 6H); ^{13}C NMR ($CDCl_3$): δ=191.0, 166.5, 161.9, 134.0, 132.3, 128.5, 122.1, 113.7, 66.2, 40.1, 31.4, 27.4 ppm; MS (MALDI-TOF): m/z: 451.9 $[M+Na]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{23}H_{24}O_8Na$ $[M+Na]^+$: 451.1371; found: 451.1363.

Compound 19c: Isobutyl chloroformate (0.34 mL, 2.61 mmol) was added to a stirred solution of compound **30** (0.21 g, 0.49 mmol) and triethylamine (0.44 mL, 3.18 mmol) in chloroform (10 mL) cooled in an ice-bath. The solution was stirred for 30 min and then a solution of compound **27** (0.54 g, 1.02 mmol) in chloroform (10 mL) was added dropwise. Stirring was continued at RT for 24 h and then the solution was washed with dilute hydrochloric acid (0.5 N, 10 mL), water (10 mL), and brine (10 mL), and dried over sodium sulfate. The resulting residue was purified by column chromatography (CH_2Cl_2/MeOH, 100:1 to 60:1) to give **19c** as a brown oil (0.51 g, 71%). ^{1}H NMR ($CDCl_3$): δ=9.96 (s, 2H), 9.75 (s, 2H), 9.16 (s, 2H), 8.74 (d, J=2.2 Hz, 2H), 7.97 (dd, J_1=8.8 Hz, J_2=2.2 Hz, 2H), 7.09 (d, J=8.8 Hz, 4H), 6.61 (s, 2H), 4.37 (t, J=6.8 Hz, 4H), 4.15–4.10 (m, 8H), 3.88–3.78 (m, 4H), 3.76–3.64 (m, 16H), 3.59–3.55 (m, 8H), 3.39–3.35 (m, 18H), 3.29 (s, 6H), 2.00 (t, J=6.8 Hz, 4H), 1.53 (s, 18H), 1.07 ppm (s, 6H); ^{13}C NMR ($CDCl_3$): δ=190.5, 161.7, 160.8, 152.8, 143.9, 143.4, 136.5, 132.3, 130.2, 123.8, 123.7, 123.2, 113.3, 113.1, 102.0, 72.0, 71.8, 70.8, 70.7, 70.6, 70.5, 70.1, 69.9, 69.6, 69.4, 66.8, 59.0, 58.9, 40.2, 32.0, 28.5, 27.6 ppm; MS (MALDI-TOF): m/z: 1478.2 $[M+Na]^+$; elemental analysis calcd (%) for $C_{73}H_{108}N_4O_{26}$: C 60.15, H 7.47, N 3.84; found: C 60.24, H 7.75, N 3.57.

Compound 20c: TFA (0.35 mL, 4.57 mmol) was added dropwise to a stirred solution of compound **19c** (0.18 g, 0.12 mmol) in chloroform (18 mL). The solution was stirred at room temperature for 35 h and then a saturated sodium bicarbonate solution (10 mL) was added. The mixture was stirred for 10 min and then the organic phase was washed with water (10 mL) and brine (10 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was dissolved in methanol and diethyl ether (5 mL, 1:1). The solution was cooled to 0 °C to give an oily solid. Removal of the organic solvent afforded compound **20c** as a brown oil (0.12 g, 82%). ^{1}H NMR ($CDCl_3$): δ=9.66 (s, 6H), 8.59 (s, 6H), 8.54 (s, 6H), 8.25 (s, 6H), 7.68 (d, J=8.6 Hz, 6H), 6.68 (d, J=8.6 Hz, 6H), 6.74 (s, 6H), 4.41–4.25 (m, 36H), 3.90–3.26 (m, 156H), 2.49–2.45 (m, 6H), 1.99–1.95 (m, 6H), 1.19 ppm (s, 18H); MS (MALDI-TOF): m/z: 3664.6 $[M+H]^+$, 3686.8 $[M+Na]^+$. ^{13}C NMR ($CDCl_3$): δ=161.4, 157.9, 157.1, 156.4, 149.7, 145.8, 137.1, 135.1, 130.1, 129.3, 125.1, 121.3, 112.0, 105.7, 72.2, 71.9, 71.7, 71.6, 70.6, 70.4, 70.3, 70.2, 69.5, 69.1, 68.7, 65.7, 58.9, 58.8, 58.7, 37.8, 32.5, 29.5, 29.3, 29.1 ppm; HRMS (MALDI-TOF): m/z: calcd for $C_{189}H_{264}N_{12}O_{60}Na$ $[M+Na]^+$: 3684.7900; found: 3684.7868.

Compound 31c: A solution of compounds **32** (1.66 g, 5.71 mmol) and **33** (0.20 g, 2.72 mmol) in toluene (50 mL) was heated at reflux azeotropically for 4 h and then concentrated with a rotavapor. The resulting solid (diimine) was dissolved in dried methanol (12 mL) and THF (12 mL). Then sodium borohydride (3.02 g, 79.5 mmol) was added to the solution. The mixture stirred at room temperature for 12 h and then was concentrated. The resulting residue was triturated with dichloromethane (30 mL) and the solution successively washed with water (15 mL) and brine (3×15 mL), and dried over sodium sulfate. Upon removal of the solvent, the resulting solid was dissolved in dichloromethane (40 mL). Trifluoromethanesulfonic acid (0.1 mL) was added to this solution, which was then washed with water (20 mL) and brine (20 mL), and dried over sodium sulfate. The solvent was then removed to give compound **31c** as a yellowish solid (0.48 g, 86% for three steps). ^{1}H NMR ($CDCl_3$): δ=7.74 (s, 4H), 7.29 (d, J=8.6 Hz, 4H), 6.84 (d, J=8.6 Hz, 4H), 4.03 (s, 4H), 3.86 (t, J=6.5 Hz, 4H), 3.01 (s, 4H), 2.77 (s, 4H), 2.32–2.16 (m, 2H), 1.81–1.64 (m, 4H), 1.41–1.26 (s, 32H), 0.87 ppm (t, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ=160.6, 131.7, 121.2, 115.4, 68.3, 52.0, 50.9, 44.3, 32.2, 29.9 (d), 29.8, 29.7, 29.6, 29.4, 26.2, 23.2, 22.9, 14.3 ppm; MS (ESI): m/z: 623.6 $[M+H-2Cl]^+$; elemental analysis calcd (%) for $C_{43}H_{72}F_6N_2O_8S_2\cdot H_2O$: C 54.87, H 7.92, N 2.98; found: C 54.59, H 8.29, N 2.71.

Compound 31d: A solution of compounds **33** (0.23 g, 3.10 mmol) and **34** (1.68 g, 6.23 mmol) in toluene (60 mL) was heated at reflux azeotropically for 5 h and then concentrated under reduced pressure. The resulting solid (diimine) was dissolved in dried methanol (35 mL) and THF (8 mL). Sodium borohydride (3.80 g, 0.10 mol) was added to the solution and the mixture stirred for 12 h. The solvent was removed with a rotavapor and the resulting slurry triturated with dichloromethane (50 mL). The solution was washed with water (25 mL) and brine (25 mL), and dried over sodium sulfate. Upon removal of the solvent, the corresponding diamine was obtained as a colorless oil (1.72 g, 95%). ^{1}H NMR ($CDCl_3$): δ=7.19 (d, J=8.6 Hz, 4H), 6.85 (d, J=8.6 Hz, 4H), 4.12 (t, J=6.7 Hz, 4H), 3.87–3.82 (m, 4H), 3.74–3.55 (m, 20H), 3.37 (s, 6H), 2.69–2.65 (m, 4H), 1.81 (s, 2H), 1.71 ppm (t, J=6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=157.9, 130.8, 129.3, 114.7, 71.9, 70.8, 70.7, 70.6, 69.8, 67.5, 59.0, 53.3, 47.9, 29.7 ppm; MS (ESI): m/z: 601.3 $[M+Na]^+$; HRMS (MALDI-TOF): m/z: calcd for $C_{31}H_{51}N_2O_8$ $[M+H]^+$: 579.3646; found: 579.3640.

Concentrated hydrochloric acid (0.5 mL) was slowly added to a solution of the diamine (0.55 g, 0.95 mmol) in methanol (30 mL). The solvent was then removed under reduced pressure to give **31d** as a yellowish solid (0.61 g, 100%). ^{1}H NMR ($CDCl_3$): δ=10.20 (s, 4H), 7.44 (d, J=2.3 Hz, 4H), 6.88 (d, J=2.3 Hz, 4H), 4.08–3.54 (m, 28H), 3.36 (s, 6H), 2.62 ppm (s, 6H); ^{13}C NMR ($CDCl_3$): δ=159.7, 132.0, 121.6, 115.1, 71.9, 70.8, 70.6, 70.5, 69.6, 67.4, 59.0, 50.8, 43.3, 24.1 ppm. MS (ESI): m/z: 601.2 $[M+Na-2Cl]^+$; elemental analysis calcd (%) for $C_{31}H_{52}Cl_2N_2O_8\cdot H_2O$: C 55.60, H 8.13, N 4.18; found: C 56.09, H 8.67, N 3.91.

Compound 36: A solution of compounds **35** (1.37 g, 6.26 mmol) and **33** (0.23 g, 3.10 mmol) in toluene (60 mL) was heated at reflux azeotropically for 6 h and then concentrated under reduced pressure. The resulting solid (diimine) was dissolved in dried MeOH (26 mL) and THF (8 mL). Sodium borohydride (4.02 g, 106 mmol) was added to the solution and the mixture stirred for 9 h and then concentrated. The resulting slurry was triturated with CH_2Cl_2 (100 mL). The solution was washed with water (50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was then removed with a rotavapor to give **35** as a yellowish oil (1.38 g, 94%). ^{1}H NMR ($CDCl_3$): δ=7.32 (s, 2H), 7.15 (s, 4H), 3.80 (s, 4H), 2.78 (s, 4H), 2.03 (s, 2H), 1.80 (s, 2H), 1.31 ppm (s, 36H); ^{13}C NMR ($CDCl_3$): δ=151.8, 128.6, 124.8, 123.5, 52.1, 43.2, 34.9, 31.4, 31.3 ppm; MS (ESI): m/z: 479.4 $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_{33}H_{55}N_2$ $[M+H]^+$: 479.4346; found: 479.4360.

Compound 31e: Concentrated hydrochloric acid (0.2 mL) was added slowly to a solution of compound **36** (0.62 g, 1.30 mmol) in methanol (40 mL). The solvent was then removed under reduced pressure to give a white solid, which was recrystallized from methanol to give compound **31e** as a white solid (0.67 g, 93%). ^{1}H NMR ($CDCl_3$): δ=10.27 (s, 4H), 7.43 (s, 2H), 7.32 (s, 4H), 4.09 (s, 4H), 2.68 (s, 6H), 1.32 ppm (s, 36H); ^{13}C NMR ($CDCl_3$): δ=151.7, 128.5, 124.8, 123.5, 52.1, 43.2, 34.8, 31.3, 24.1 ppm; MS (ESI): m/z: 479.4 $[M-2Cl-H]^+$; HRMS (ESI): m/z: calcd for $C_{33}H_{55}N_2$ $[M-2Cl]^+$: 479.4346; found: 479.4360.

Acknowledgements

We thank the National Science Foundation of China (Nos. 20621062, 20672137, 20732007, and 20872167), the National Basic Research Program (2007CB808001) and the Chinese Academy of Sciences for financial support.

[1] C. I. Branden, *Introduction to Protein Structure*, Routledge, New York, **1999**, p. 410.

[2] a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180; b) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893–4011; c) B. Gong, *Chem. Eur. J.* **2001**, *7*, 4336–4342; d) I. Huc, *Eur. J. Org. Chem.* **2004**, 17–29; e) M. T. Stone, J. M. Heemstra, J. S. Moore, *Acc. Chem. Res.* **2006**, *39*, 11–20; f) C. M. Goodman, S. Choi, S. Shandler, W. F. DeGrado, *Nat. Chem. Biol.* **2007**, *3*, 252–262; g) Z.-T. Li, J.-L. Hou, C. Li, H.-P. Yi, *Chem. Asian J.* **2006**, *1*, 766–778; h) Z.-T. Li, J.-L. Hou, C. Li, *Acc. Chem. Res.* **2008**, *41*, 1343–1353; i) B. Gong, *Acc. Chem. Res.* **2008**, *41*, 1376–1386; j) W. S. Horne, S. H. Gellman, *Acc. Chem. Res.* **2008**, *41*, 1399.

[3] *Foldamers: Structure, Properties and Applications* (Eds.: S. Hecht, I. Huc), Wiley-VCH, Weinheim, **2007**, p. 428.

[4] a) L. Yuan, W. Feng, K. Yamato, A. R. Sanford, D. Xu, H. Guo, B. Gong, *J. Am. Chem. Soc.* **2004**, *126*, 11120–11121; b) H. Jiang, J.-M. Léger, P. Guionneau, I. Huc, *Org. Lett.* **2004**, *6*, 2985–2988; c) A. Zhang, Y. Han, K. Yamato, X.-C. Zeng, B. Gong, *Org. Lett.* **2006**, *8*, 803–806; d) Y.-Y. Zhu, C. Li, G.-Y. Li, X.-K. Jiang, Z.-T. Li, *J. Org. Chem.* **2008**, *73*, 1745–1751; e) B. Qin, X. Chen, X. Fang, Y. Shu, Y. K. Yip, Y. Yan, S. Pan, W. Q. Ong, C. Ren, H. Su, H. Zeng, *Org. Lett.* **2008**, *10*, 5127–5130.

[5] a) L. J. Prins, P. Timmerman, D. N. Reinhoudt, *Pure Appl. Chem.* **1998**, *70*, 1459–1468; b) J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455–2463; c) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. S. Stoddart, *Angew. Chem.* **2002**, *114*, 938–993; *Angew. Chem. Int. Ed.* **2002**, *41*, 898–952; d) U. Lüning, *J. Inclusion Phenom. Macrocyclic Chem.* **2004**, *49*, 81–84; e) Z. R. Laughrey, B. C. Gibb, *Top. Curr. Chem.* **2005**, *249*, 67–125; f) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652–3711; g) B. de Bruin, P. Hauwert, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 2726–2729; *Angew. Chem. Int. Ed.* **2006**, *45*, 2660–2663; h) K. Severin, *Chem. Commun.* **2006**, 3859–3867; i) J. R. Nitschke, *Acc. Chem. Res.* **2007**, *40*, 103–112; j) C. D. Meyer, C. S. Joiner, J. F. Stoddart, *Chem. Soc. Rev.* **2007**, *36*, 1705–1723; k) J.-M. Lehn, *Chem. Soc. Rev.* **2007**, *36*, 151–160; l) S. Otto, K. Severin, *Top. Curr. Chem.* **2007**, *277*, 267–288; m) R. F. Ludlow, S. Otto, *Chem. Soc. Rev.* **2008**, *37*, 101–108.

[6] *Container Molecules and Their Guests* (Eds.: D. J. Cram, J. M. Cram), RSC, Cambridge, **1997**, p. 223.

[7] a) J. C. Sherman, *Tetrahedron* **1995**, *51*, 3395–3422; b) A. Jasat, J. C. Sherman, *Chem. Rev.* **1999**, *99*, 931–967.

[8] a) C. M. Morgan, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1668; b) J. Rebek, Jr., *Angew. Chem.* **2005**, *117*, 2104–2115; *Angew. Chem. Int. Ed.* **2005**, *44*, 2068–2078; c) L. J. Prins D. N. Reinhoudt, P. Timmerman, *Angew. Chem.* **2001**, *113*, 2446–2492; *Angew. Chem. Int. Ed.* **2001**, *40*, 2382–2426; d) M. Crego-Calama, D. N. Reinhoudt, M. G. J. ten Cate, *Top. Curr. Chem.* **2005**, *249*, 285–316; e) A. Bogdan, Y. Rudzevich, M. O. Vysotsky, V. Böhmer, *Chem. Commun.* **2006**, 2941–2952; f) L. R. MacGillivray, J. L. Atwood, *Angew. Chem.* **1999**, *111*, 1080–1096; *Angew. Chem. Int. Ed.* **1999**, *38*, 1018–1033; g) A. Lützen, *Angew. Chem.* **2005**, *117*, 1022–1025; *Angew. Chem. Int. Ed.* **2005**, *44*, 1000–1002; h) D. M. Vriezema, M. C. Aragones, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan, R. J. M. Nolte, *Chem. Rev.* **2005**, *105*, 1445–1489; i) C. Schmuck, *Angew. Chem.* **2007**, *119*, 5932–5935; *Angew. Chem. Int. Ed.* **2007**, *46*, 5830–5833; j) D. P. Weimann, C. A. Schalley, *Supramol. Chem.* **2008**, *20*, 117–128.

[9] a) M. Fujita, M. Tominaga, A. Hori, B. Therrien, *Acc. Chem. Res.* **2005**, *38*, 369–380; b) D. Fiedler, D. H. Leung, R. G. Bergman, K. N. Raymond, *Acc. Chem. Res.* **2005**, *38*, 349–360; c) T. S. Koblenz, J. Wassenaar, J. N. H. Reek, *Chem. Soc. Rev.* **2008**, *37*, 247–262.

[10] S. Liu, B. C. Gibb, *Chem. Commun.* **2008**, 3709–3716.

[11] a) F. Corbellini, L. Di Costanzo, M. Crego-Calama, S. Geremia, D. N. Reinhoudt, *J. Am. Chem. Soc.* **2003**, *125*, 9946–9947; b) F. Corbellini, R. M. A. Knegtel, P. D. J. Grootenhuis, M. Crego-Calama, D. N. Reinhoudt, *Chem. Eur. J.* **2005**, *11*, 298–307; c) G. V. Oshovsky, D. N. Reinhoudt, W. Verboom, *J. Am. Chem. Soc.* **2006**, *128*, 5270–5278.

[12] Preorganized calix[4]arenes and cavitands have been used to prepare capsules by DCC, see: a) X. Liu, Y. Liu, G. Li, R. Warmuth, *Angew. Chem.* **2006**, *118*, 915–918; *Angew. Chem. Int. Ed.* **2006**, *45*, 901–904; b) Y. Liu, X. Liu, R. Warmuth, *Chem. Eur. J.* **2007**, *13*, 8953–8959; c) X. Liu, R. Warmuth, *J. Am. Chem. Soc.* **2006**, *128*, 14120–14127; d) X. Liu, R. Warmuth, *Nat. Protoc.* **2007**, *2*, 1288–1296; e) D. Xu, R. Warmuth, *J. Am. Chem. Soc.* **2008**, *130*, 7520–7521.

[13] The concept of "predisposition" has been used to prepare cinchonidine-based macrocycles by ester exchange, see: S. J. Rowan, D. G. Hamilton, P. A. Brady, J. K. M. Sanders, *J. Am. Chem. Soc.* **1997**, *119*, 2578–2579.

[14] For representative examples, see: a) O. Storm, U. Lüning, *Chem. Eur. J.* **2002**, *8*, 793–798; b) A. J. Gallant, M. J. MacLachlan, *Angew. Chem.* **2003**, *115*, 5465–5468; *Angew. Chem. Int. Ed.* **2003**, *42*, 5307–5310; c) C. T. L. Ma, M. J. MacLachlan, *Angew. Chem.* **2005**, *117*, 4250–4254; *Angew. Chem. Int. Ed.* **2005**, *44*, 4178–4182; d) K. S. Chichak, S. J. Cantrill, A. R. Pease, S.-H. Chiu, G. W. V. Cave, J. L. Atwood, J. F. Stoddart, *Science* **2004**, *304*, 1308–1312; e) A. R. Williams, B. H. Northrop, T. Chang, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2006**, *118*, 6817–6821; *Angew. Chem. Int. Ed.* **2006**, *45*, 6665–6669; f) C. S. Hartley, J. S. Moore, *J. Am. Chem. Soc.* **2007**, *129*, 11682–11683; g) C. S. Hartley, E. L. Elliott, J. S. Moore, *J. Am. Chem. Soc.* **2007**, *129*, 4512–4513; h) N. Christinat, R. Scopelliti, K. Severin, *Angew. Chem.* **2008**, *120*, 1874–1878; *Angew. Chem. Int. Ed.* **2008**, *47*, 1848–1852; i) M. Hutin, G. Bernardinelli, J. R. Nitschke, *Chem. Eur. J.* **2008**, *14*, 4585–4593; j) J. Luo, T. Lei, X. Xu, F.-M. Li, Y. Ma, K. Wu, J. Pei, *Chem. Eur. J.* **2008**, *14*, 3860–3865; k) K. R. West, R. F. Ludlow, P. T. Corbett, P. Besenius, F. M. Mansfeld, P. A. G. Cormack, D. C. Sherrington, J. M. Goodman, M. C. A. Stuart, S. Otto, *J. Am. Chem. Soc.* **2008**, *130*, 10834–10835.

[15] a) Z.-Q. Wu, X.-B. Shao, C. Li, J.-L. Hou, K. Wang, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2005**, *127*, 17460–17468; b) J.-L. Hou, H.-P. Yi, X.-B. Shao, C. Li, Z.-Q. Wu, X.-K. Jiang, L.-Z. Wu, C.-H. Tung, Z.-T. Li, *Angew. Chem.* **2006**, *118*, 810–814; *Angew. Chem. Int. Ed.* **2006**, *45*, 796–800; c) J. Zhu, J.-B. Lin, Y.-X. Xu, X.-B. Shao, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2006**, *128*, 12307–12313; d) C. Li, Y.-Y. Zhu, H.-P. Yi, C.-Z. Li, X.-K. Jiang, Z.-T. Li, *Chem. Eur. J.* **2007**, *13*, 9990–9998; e) W. Cai, G.-T. Wang, Y.-X. Xu, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2008**, *130*, 6936- 6937; f) W. Cai, G.-T. Wang, P. Du, R.-X. Wang, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2008**, *130*, 13450–13459.

[16] a) J.-B. Lin, X.-N. Xu, X.-K. Jiang, Z.-T. Li, *J. Org. Chem.* **2008**, *73*, 9403–9410; b) J.-B. Lin, J. Wu, X.-K. Jiang, Z.-T. Li, *Chin. J. Chem.* **2009**, *27*, 117–122.

[17] a) S. L. Roberts, R. L. E. Furlan, S. Otto, J. K. M. Sanders, *Org. Biomol. Chem.* **2003**, *1*, 1625–1633; b) R. T. S. Lam, A. Belenguer, S. L. Roberts, C. Naumann, T. Jarrosson, S. Otto, J. K. M. Sanders, *Science* **2005**, *308*, 667–669; c) R. F. Ludlow, J. Liu, H. Li, S. L. Roberts, J. K. M. Sanders, O. Sijbren, *Angew. Chem.* **2007**, *119*, 5864–5866; *Angew. Chem. Int. Ed.* **2007**, *46*, 5762–5764.

[18] R. Lartia, C. Allain, G. Bordeau, F. Schmidt, C. Fiorini-Debuischert, F. Charra, M.-P. Teulade-Fichou, *J. Org. Chem.* **2008**, *73*, 1732–1744.

[19] L. Yuan, A. R. Sanford, W. Feng, A. Zhang, J. Zhu, H. Zeng, K. Yamato, M. Li, J. S. Ferguson, B. Gong, *J. Org. Chem.* **2005**, *70*, 10660–10669.

[20] V. I. Siele, M. Warman, *J. Org. Chem.* **1962**, *27*, 1910–1911.

[21] C.-S. Chang, Y.-T. Lin, S.-R. Shih, C.-C. Lee, Y.-C. Lee, C.-L. Tai, S.-N. Tseng, J.-H. Chern, *J. Med. Chem.* **2005**, *48*, 3522–3535.
[22] This result might reflect the fact that another minor isomer or other byproducts existed that wunderwent exchange with the major product in solution.
[23] a) C. Li, S.-F. Ren, J.-L. Hou, H.-P. Yi, S.-Z. Zhu, X.-K. Jiang, Z.-T. Li, *Angew. Chem.* **2005**, *117*, 5871–5875; *Angew. Chem. Int. Ed.* **2005**, *44*, 5725–5729; b) H.-P. Yi, C. Li, J.-L. Hou, X.-K. Jiang, Z.-T. Li, *Tetrahedron* **2005**, *61*, 7974–7980.
[24] A. R. Sanford, L. Yuan, W. Feng, K. Yamato, R. A. Flowers, B. Gong, *Chem. Commun.* **2005**, 4720–4722.
[25] M. C. Lensen, J. A. A. Elemans, S. J. T. van Dingenen, J. W. Gerritsen, S. Speller, A. E. Rowan, R. J. M. Nolte, *Chem. Eur. J.* **2007**, *13*, 7948–7956.
[26] C. Lottner, K.-C. Bart, G. Bernhardt, H. Brunner, *J. Med. Chem.* **2002**, *45*, 2079–2089.
[27] M. J. Plater, S. Aiken, G. Bourhill, *Tetrahedron* **2002**, *58*, 2405–2413.
[28] The hydrochloric acid salt of **31c** has a low solubility in chloroform.
[29] J. Wu, J.-L. Hou, C. Li, Z.-Q. Wu, X.-K. Jiang, Z.-T. Li, Y.-H. Yu, *J. Org. Chem.* **2007**, *72*, 2897–2905.
[30] H. Benesi, J. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
[31] The sample precipitated at an even lower temperature.

Received: February 5, 2009
Published online: May 6, 2009

