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Towards Multi-generation Assemblies with Tetraphenylmethane Subunits

XUEHE LI and BRUCE C. GIBB*

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

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The synthesis of tetra(4-hydroxymethylphenyl)methane is reported. Possessing four benzyl alcohol groups, this molecule is anticipated to undergo self-assembly processes analogous to previously studied benzyl alcohol derived, deep-cavity cavitands (Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C. *Chem. Commun.* 2000, 363–364). Towards such assembly processes, a bis-protected derivative was synthesized and its ability to undergo a macrocyclization reaction determined. Both the protection strategy employed and the macrocyclization approach are important models for more complex, repetitive self-assembly processes that can be envisaged with these types of molecules.

Keywords: Macrocyclization; Self-assembly

The Future of Supramolecular Chemistry

Supramolecular chemistry is still in its formative years. On the (180-year) organic synthesis scale, we are somewhere in between Kolbe's synthesis of acetic acid (1845), and Fischer's synthesis of glucose (1890). With more researchers and more powerful tools at our disposal, imagine where the supramolecular community can be after 180 years! At some point between now and then, our level of understanding of how to position and orchestrate functionality within molecules will have progressed to the point that synthetic chemists will have more than just natural products to aim for. These include, but are by no means limited to: synthetic and natural polymers with fully controllable secondary, tertiary and quaternary structures that will open the way to artificial viral capsids for gene therapy and drug delivery; the synthetic equivalents of complex biological matrices possessing molecular detectors, triggers, and switchable, multifaceted catalysts that make modern-day reagents look crude and unspecific; crystalline solids that adsorb species for storage, or release selected compounds upon specific stimulus; memory materials, self-repairing materials, molecular machines and molecular computers. The list goes on.

Self-assembly, in a chemical sense the spontaneous creation of supramolecular patterns or order, offers an efficient way to access many of the aforementioned new materials. This ultimate antithesis to entropy has made many advances over the last few years. As a result, nascent frameworks that can be used to identify, characterize, and categorize assembly processes are emerging. Much, however, still remains to be done; both in a conceptual sense and in an empirical sense. Our small contribution presented here pertains to the latter.

Bruce C. Gibb is currently an Associate Professor of Chemistry at the University of New Orleans. His research interests focus on supramolecular chemistry, with a decided tilt towards the organic and bioorganic. He received his undergraduate education at The Robert Gordon's University (Aberdeen, Scotland), and remained there to carry out his PhD studies under the guidance of Philip J. Cox. Shortly thereafter, in 1993, he moved to the University of British Columbia where he carried out postdoctoral research with Professor John C. Sherman. In 1994, he undertook a second period of postdoctoral research, this time with James W. Canary at New York University. Most recently, in 1996, he took up an appointment as an Assistant Professor at the University of New Orleans.

*Corresponding author. E-mail: bgibb@uno.edu

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INTRODUCTION

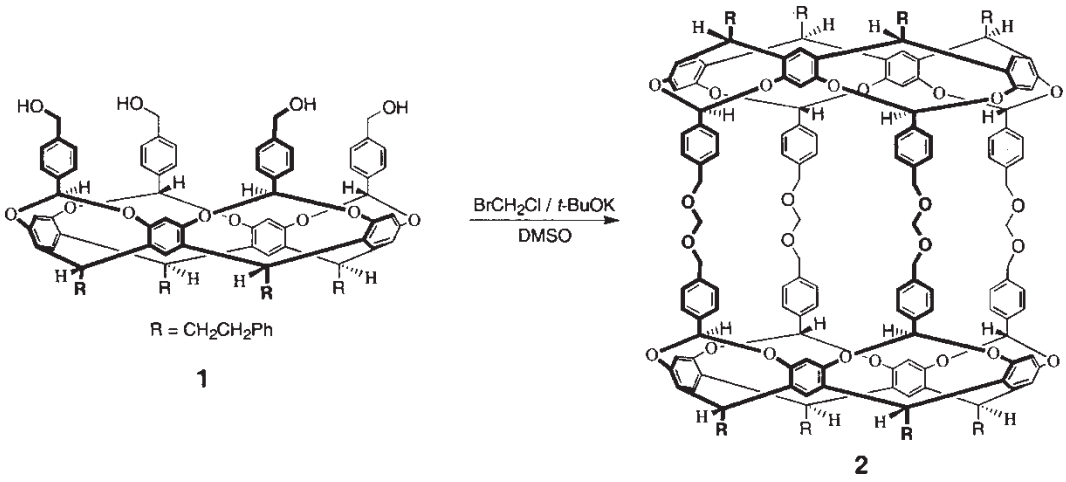
The construction of nano-scale structures via self-assembly is a major facet of supramolecular chemistry [1–6]. To date, most self-assemblies investigated have utilized reversible processes to generate a product corresponding to the thermodynamic minimum for the relevant potential energy surface. As a whole, these investigations point to the power of transition-metal coordination and hydrogen bonding, and their ability to affect assemblies that only 10 years ago were barely conceivable [7]. Concurrently, the breadth of assemblies examined has also engendered considerations of how best to analyze and classify them. Thus, self-assemblies can be viewed in terms of the subunits [8,9], the products [5,10] or the processes that relate the two [11].

Self-assembly with covalent modification is a less explored area of self-assembly. In these processes, an irreversible reaction removes intermediates from the central equilibrium, to form a product comprising only covalent bonds. Their irreversible nature means that each step must be highly efficient as, unlike reversible processes, there is no chance of going back and repairing mistakes. Nevertheless, this is a powerful approach to constructing large, complex molecules such as catenanes, rotaxanes [12,13] and carceplexes [14,15]. Furthermore, as the bond-forming process is irreversible, in theory this approach opens the way to multi-generation assemblies whereby, after the first assembly, functional groups are deprotected to reveal another set of functional groups capable of engendering further assembly. This dendritic-like approach to assembly has the potential to lead to the rapid formation of very large and complex molecules.

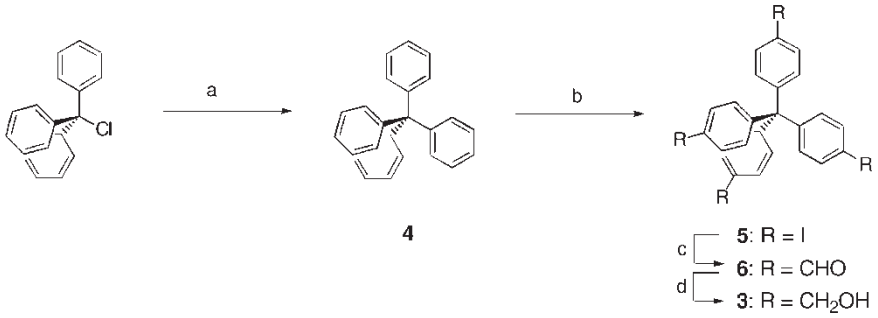
Previous results from this laboratory have identified the benzyl alcohol as a potent functional group for self-assembly (with covalent modification) [16]. Thus, the self-assembly of deep-cavity cavitand [17,18] **1** gave the "dimer" product **2** in 80% yield (Scheme 1) [16]. In view of what is known about the mechanism of carceplex formation [19–21], we envisioned that this highly efficient [11] process was driven by the formation of charged hydrogen bonds between the two deep-cavity cavitands. Regardless of the mechanism, this is an efficient process that occurs in the absence of any single molecular template [22]. Expanding on our investigations into using the benzyl alcohol group in self-assemblies, we report here the synthesis of tetraphenylmethane subunit **3**. Possessing a tetrahedral array of benzyl alcohol groups, **3** and it mono- and bis-protected derivatives can be envisioned to undergo a variety of assembly, and multi-generation assembly, processes. In regard to the latter, an important issue is determining a protection/deprotection protocol that is orthogonal to the assembly conditions. Hence, as a step towards multi-generation assemblies, we identify here a protection/deprotection strategy that is compatible with a simplified model system: the macrocyclization of a bis-protected derivative of **3** under our standard [16] assembly conditions **1** [23].

RESULTS AND DISCUSSION

The synthesis of our central subunit, compound **3**, is outlined in Scheme 2. Tetraphenylmethane **4** was synthesized by coupling trityl chloride with diphenylzinc (generated *in situ* by reacting phenyl lithium with anhydrous zinc chloride in anhydrous diethyl ether) at −42°C [24]. Tetraiodination of **4** was accomplished in 71% yield with a combination of I_2 and bis(trifluoroacetoxy)-iodobenzene in CCl_4 [25].



SCHEME 1 Self-assembly of deep-cavity cavitand **1** to form hemicarcerand **2**.

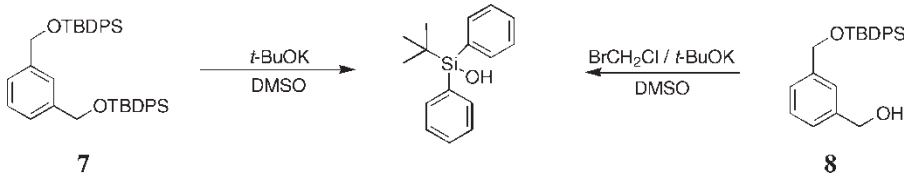


SCHEME 2 Synthesis of tetraphenylmethane subunit **3**. Conditions are: (a) Ph_2Zn, −42°C, CH_2Cl_2; (b) I_2/bis(trifluoroacetoxy)-iodobenzene in CCl_4; (c) *n*-BuLi −78°C, then −30°C, then −78°C, then dimethylformamide; (d) $NaBH_4$.

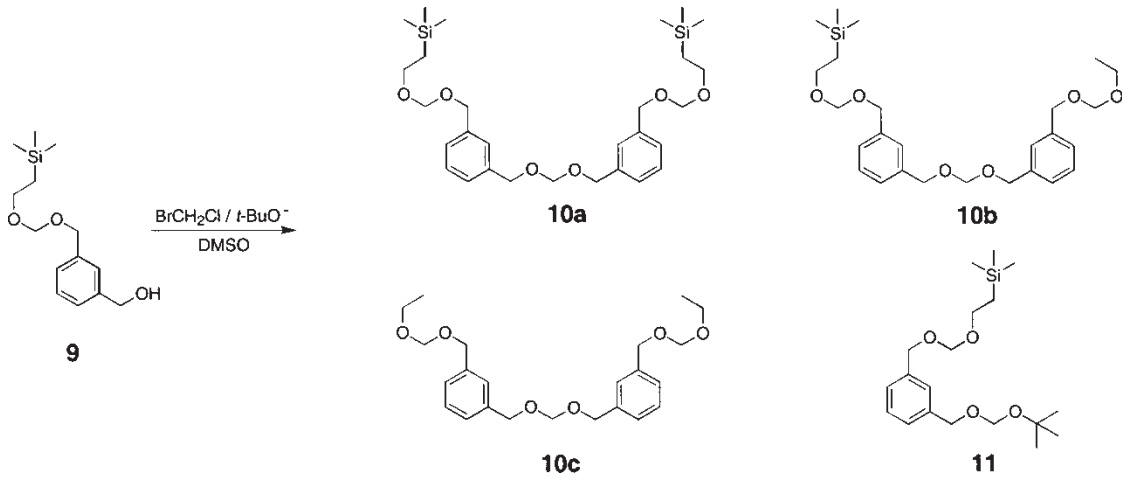
The tetraiodide **5** was then treated with *n*-BuLi and quenched with dimethylformamide (DMF) to give the tetraaldehyde **6**. This reaction was complicated by the poor solubility of both the starting tetraiodide and the corresponding lithiates. Thus, initial attempts at −78°C yielded a mixture of mono-, bis-, and tris- intermediates with unexchanged iodine atoms. The desired **6** was isolated in only ca. 35% yield. However, warming the reaction mixture to ca. −30°C between the addition of *n*-BuLi and DMF (both at −78°C) led to a 70% yield of the desired tetraaldehyde. Finally, tetraaldehyde **6** was converted to tetrol **3** in quantitative yield with $NaBH_4$.

For future multi-generation assemblies, it is necessary to determine protecting groups that can survive both the conditions used for assembly yet be removed using chemistry that is orthogonal to the functionality that hold the subunits together. As the latter are acetal groups, and the former involve strongly basic conditions, we focused on silyl protecting groups [26]. We first examined the *t*-butyldiphenylsilyl (TBDPS) group. To determine the suitability of this group, we synthesized the bis- and mono-protected benzenedimethanol model compounds **7** and **8** (Scheme 3). Treating **7** with *t*-BuOK in DMSO resulted in the generation of *t*-butyldiphenylsilanol in high yield (Scheme 3). This suggested that the TBDPS group was not suitable for our purposes. Furthermore, the fact that the kinetics of this decomposition was faster than the kinetics of coupling was demonstrated by placing the mono-protected **8** under the standard "assembly" conditions; again *t*-butyldiphenylsilanol was formed in good yield, and no trace of the desired "dimer" could be detected. Methylsulfinyl carbanion ($CH_3S(O)CH_2^-$) is generated by mixing *t*-BuOK with DMSO [27], and this species is known to be sufficiently nucleophilic to attack carbonyl centers [28]. We suspect that it may also be sufficiently nucleophilic to attack the benzyl carbon of our model compound and eject $t\text{-BuPh}_2\text{SiO}^-$. However, as we were unable to isolate the corresponding phenethyl methyl sulfoxide, this cannot be unequivocally determined.

The unsuitability of the TBDPS protecting group led us to consider the 2-(trimethylsilyl)ethoxymethyl or SEM group as a suitable means of protection [29]. A model compound, mono-protected benzenedimethanol **9** (Scheme 4) was prepared, but again under our standard reaction conditions, decomposition was noted. This time, the replacement of a TMS group (the bulky proton) [30] by a proton was noted to occur such that the two desilylated compounds **10b** and **10c** were formed along with the expected product **10a** (Scheme 4). A matrix of reactions was generated by changing the variables of temperature, time and base. This revealed that neither time nor temperature could be used to control the reaction, but that changes in the equivalents of base affected the product distribution (Table I). Thus, it was possible to isolate desilylated **10c** by using five equivalents of base. However, it was not possible to balance the reaction conditions such that **9** underwent complete reaction, but that no decomposition occurred. In contrast, and much to our delight, changing the base to sodium *t*-butoxide curtailed



SCHEME 3 Reaction of model compounds **7** and **8**.



SCHEME 4 Products from the reaction of model **9** under the standard "assembly" conditions.

these decomposition pathways with the result that the coupling process went smoothly. The yield of the desired **10a** was 93% with 2.5 equivalents of this base. With a greater excess of base, a small amount of what was tentatively identified as *t*-butyl acetal **11** (Scheme 4) was formed. This presumably arises from the nucleophilic attack of the base on a chloromethyl ether intermediate. Beyond this, no significant side-reactions were noted.

Having established the suitability of the SEM protecting group, we turned our attention to the tetrahedral subunits. Treatment of subunit **3** with four equivalents of SEMCl gave **12** in 41% yield, along with 26% of the mono-protected species **13** (Scheme 5). The remaining mixture was a combination of the tris- and fully protected species. Fortunately, all these by-products could be deprotected to regenerate the starting material. Thus, suitable quantities of **12** were available without difficulty.

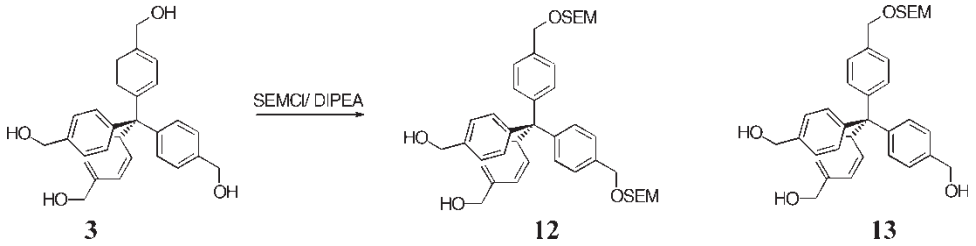
The modified reaction conditions were then applied to subunit **12**. Thus, treating a DMSO solution of **12** with *t*-BuONa, followed by the immediate addition of CH_2BrCl, yielded a mixture of the expected "dimer" **14**, "trimer" **15**, and other cyclic products from "tetramer" through to "hexamer". The major products, **14** and **15**, were readily separated by column chromatography. Unfortunately, we were unable to separate the minor components of the reaction, the "tetramer", "pentamer" and "hexamer". Hence, these compounds were only characterized by mass spectrometry. To optimize the various products, the effects of changing concentration were examined. These experiments demonstrated that the product composition was essentially invariant over the range 2.5–10 mM. Thus, **14** was isolated in 33% yield, the "trimer" **15** in 15% yield, with the combined higher species accounting for 8–10% of the starting material. Previous results focusing on other benzyl alcohol subunits have demonstrated that at greater concentrations, yields of the higher assembly products became significant [31]. Unfortunately, we could not verify if these tetrahedral subunits followed the same trend as, beyond a 15 mM concentration of **12**, the reaction became heterogeneous, and overall yields decreased.

We chose **14** to investigate the orthogonality between the SEM protecting groups and the subunit-linking groups. The protecting groups proved resilient to the most familiar conditions for their removal. Thus, only starting material was recovered when **14** was treated with tetrabutylamonium fluoride (TBAF). In contrast, the more strenuous conditions of CsF in DMF at 130°C were successful in generating the desired tetrol **16** in a very

TABLE I Reaction outcome for the coupling of model compound **9***

Entry	Equivs. of *t*-BuOK	Equivs. of CH_2BrCl	Unreacted 9	Combined yields of **10a–c**	Percentage of TMS groups lost†
1	5.0	4.0	0	58%	70%
2	2.5	2.0	0	71%	26%
3	1.2	1.1	25%	64%	13%

* All reactions carried out at 5 mM in DMSO, rt, 5 h. † Calculated from the ^{1}H NMR spectra obtained from the mixture of **10a**, **10b** and **10c**, by the integration of the signals from the methylene groups α and β to the Si atom.



SCHEME 5 Synthesis of protected subunits **12** and **13**.

satisfying 90% yield (Scheme 6). Hence, by careful choice of assembly conditions and protecting groups, it is possible to make second-generation molecular subunits possessing the same functionality that drove their own synthesis.

CONCLUSION

We have reported here both protection/deprotection protocols and macrocyclizations that demonstrate the feasibility of multi-generation assemblies. The tetraphenylmethane-based subunit **3** can be protected, "dimerized" and then deprotected to form a second-generation subunit. An important component of this process is the determination that SEM protecting group methodologies are compatible with the conditions used to promote coupling/assembly. Subsequently, by repetition of this protocol, it should be possible to prepare higher-generation molecular subunits of considerable scale. We are currently investigating some of the many possibilities that this protocol engenders.

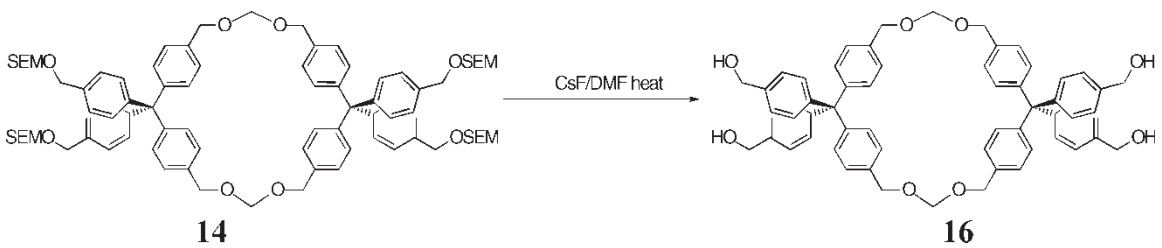
EXPERIMENTAL

General

All reagents were purchased from Aldrich Chemical Company, Mallinckrodt Backer Inc., and E. M. Scientific and, unless otherwise stated, were used as received. Melting points were determined using a hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR were performed at 400 and 100 MHz, respectively. Mass spectra were obtained with CI, ESI or MALDI techniques. Elemental analyses were conducted by Atlantic Microlab. Column chromatography was performed using Natland® International 200–400 mesh silica gel. THF and diethyl ether were distilled over sodium benzophenone ketyl. CH_2Cl_2 was distilled over P_2O_5. Dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMA) were stored over molecular sieves and degassed prior to use. All reactions were carried out under a nitrogen atmosphere.

Synthesis of Tetraphenylmethane (4)

Phenyllithium (26.8 mL, 1.51 M in a cyclohexane/diethyl ether 70/30 solution, 40.5 mmol) was added dropwise to a stirring solution of anhydrous $ZnCl_2$ (2.89 g, 21.2 mmol) in diethyl ether (10 mL). The mixture was stirred at rt for 30 min. The solvent was then removed under reduced pressure, CH_2Cl_2 (114 mL) was added to the remaining solid, and the temperature was lowered to −42°C (acetonitrile/dry ice bath). A solution of triphenylmethyl chloride (5.64 g, 19.6 mmol) in CH_2Cl_2 (20 mL) was then added, and the mixture was kept at −42°C while being stirred for 5 h. After this time, the flask was removed from the cold bath and warmed up to ca. 0°C over 20 min. Aqueous HCl (1 M) was added to quench the reaction until the mixture became acidic. The mixture was then partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The filtrate was concentrated under reduced pressure to give the crude product as a yellow solid. A small amount of diethyl ether was added, and the resulting white precipitate was then filtered off and washed with a further quantity of diethyl ether. The white solid was finally



SCHEME 6 Synthesis of second-generation subunit **16**.

recrystallized from hot $CHCl_3$ to give tetraphenylmethane **4** as colorless needles (2.71 g, 8.46 mmol, 42%). Mp 283°C (literature [32]: 280–282°C) ^{1}H NMR ($CDCl_3$) δ (ppm) 7.15–7.28 (m, 20H). ^{13}C NMR ($CDCl_3$) δ (ppm) 57.3, 126.8, 128.8, 130.0, 144.4. MS (CI) 320 $[M]^+$, 243 $[M - C_6H_5]^+$, 165 $[M - C_{12}H_{11}]^+$.

Synthesis of Tetra(4-iodophenyl)methane (5)

A mixture of tetraphenylmethane, **4**, (1.50 g, 4.69 mmol), bis(trifluoroacetoxy)-iodobenzene (11.80 g, 28.10 mmol) and I_2 (4.70 g, 18.3 mmol) in CCl_4 (50 mL) was stirred at 60°C for 3 days. After this time, the purple color of the reaction had disappeared. The suspended solid was filtered off and washed continuously with acetone and ethanol. The remaining solid was recrystallized from THF to give tetra(4-iodophenyl)methane [24] **5**, as a colorless solid (2.80 g, 3.40 mmol, 71%). Mp >400°C. ^{1}H NMR ($CDCl_3$) δ (ppm) 6.88 (d, J = 8.4 Hz, 8H), 7.58 (d, J = 8.4 Hz, 8H). ^{13}C NMR ($CDCl_3$) δ (ppm) 132.7, 132.8, 137.3, 137.5.

Synthesis of Tetra(4-formylphenyl)methane (6)

A solution of **5** (1.00 g, 1.21 mmol) in THF (150 mL) was cooled to −78°C. *n*-BuLi (4.41 mL, 2.2 M solution in hexanes, 9.68 mmol) was then added dropwise. After this addition, the flask was removed from the cold bath and warmed up slowly (ca. 20 min) to ca. −30°C. The temperature was then reduced to −78°C, and a solution of DMF (3.00 mL, 38.6 mmol) in THF (20 mL) was added. The mixture was stirred at −78°C for 3 h. After this time, the flask was removed from the cold bath and warmed up to ca. 0°C over 30 min. To quench the reaction, aqueous HCl (1 M) was added until the mixture became acidic. The mixture was then partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The filtrate was concentrated under reduced pressure to give the crude product as a yellow solid. Gradient column chromatography with a mobile phase varying from 5 to 25% acetone in hexanes gave tetra(4-formylphenyl)methane 6 (0.38 g, 0.87 mmol, 70%) as a white solid. Mp 215°C. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.43 (d, J = 8.4 Hz, 8H), 7.84 (d, J = 8.4 Hz, 8H), 10.01 (s, 4H, –CHO). MS m/z 433 $[M + H]^+$. Anal. Calcd. For $C_{29}H_{20}O_4$: C: 79.76; H: 4.73. Found: C: 79.64; H: 4.75.

Synthesis of Tetra(4-hydroxymethylphenyl)methane (3)

To a solution of **6** (0.38 g, 0.87 mmol) in THF (10 mL) and methanol (10 mL) was added $NaBH_4$ (0.14 g, 3.49 mmol). The mixture was stirred at rt for 16 h. After this time, the solvent was removed under reduced pressure. The remaining solid was suspended in water and filtered off to give tetra(4-hydroxymethylphenyl)methane **3** (0.39 g, 0.87 mmol, 99%) as a white solid. Mp >400°C. ^{1}H NMR (DMSO-d_6) δ (ppm) 4.45 (d, J = 5.6 Hz, 8H, –CH_2OH), 5.12 (t, J = 5.6 Hz, 4H, –OH), 7.10 (d, J = 8.4 Hz, 8H), 7.22 (d, J = 8.4 Hz, 8H). MS (ESI): 463 $[M + Na]^+$. Anal. Calcd. for $C_{29}H_{28}O_4 \cdot 1.5H_2O$: C, 74.50; H, 6.67. Found: C, 74.38; H, 6.27.

Synthesis of 7

To a solution of 1,3-benzendimethanol (0.50 g, 3.55 mmol) and imidazole (1.21 g, 17.8 mmol) in DMF (10 mL), was added *t*-butyldiphenylsilyl chloride (2.77 mL, 10.7 mmol). The mixture was heated at 60°C for 16 h. The solvent was then removed under reduced pressure, and the mixture partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4, and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Column chromatography with a mobile phase of 10% acetone in hexanes gave 7 (1.75 g, 2.84 mmol, 80%) as a white solid. Mp 45–47°C. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.09 (s, 18H, –CMe_3), 4.76 (s, 4H, ArCH_2O–), 7.30–7.45 (m, 16H), 7.69–7.71 (m, 8H). MS (ESI): 637 $[M + Na]^+$. Anal. Calcd. for $C_{40}H_{46}O_2Si_2$: C, 78.12; H, 7.54. Found: C, 78.32; H, 7.47.

Synthesis of 8

To a solution of benzenedimethanol (0.40 g, 2.89 mmol) and imidazole (0.48 g, 7.23 mmol) in DMF (10 mL) was added *t*-butyldiphenylsilyl chloride (0.75 mL, 2.89 mmol). The mixture was heated at 60°C for 16 h. The solvent was then removed under reduced pressure and the mixture partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Column chromatography with a mobile phase of 10% acetone in hexanes gave 8 (0.54 g, 1.44 mmol, 50%) as a colorless oil [33]. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.10 (s, 9H, –CMe_3), 4.68 (s, 2H), 4.78 (s, 2H), 7.30–7.45 (m, 10H), 7.68–7.72 (m, 4H).

Model Reaction on 7 (Generation of *tert*-Butyldiphenylsilanol)

To a stirred solution of **7** (0.10 g, 1.6×10^{-4} mol) in DMSO (32 mL) was added *t*-BuOK (0.96 g, 8.1×10^{-4} mol). The mixture was stirred at rt for 5 h. After this time, the solvent was removed under reduced pressure and the mixture partitioned between water and $CHCl_3$ three times. The organic

phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Column chromatography with a mobile phase of 10% acetone in hexanes gave *t*-butyldiphenylsilanol (0.68 g, 2.7×10^{-4} mol, 82%) as a colorless oil, which solidified upon standing. Mp 61–63°C (Lit. [34] 62–64°C). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.09 (s, 9H, $-CMe_3$), 7.35–7.45 (m, 6H), 7.72–7.75 (m, 4H). MS (ESI): 279 $[M + Na]^+$, 535 $[2M + Na]^+$.

Model Reaction on 8

To a stirred solution of **8** (50 mg, 1.3×10^{-4} mol) in DMSO (26 mL) was added *t*-BuOK (37 mg, 3.3×10^{-4} mol), followed by the immediate addition of CH_2BrCl (0.17 μL, 2.7×10^{-4} mol). The mixture was stirred at rt for 5 h. After this time, the solvent was removed under reduced pressure and the mixture partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Column chromatography with a mobile phase of 10% acetone in hexanes gave *t*-butyldiphenylsilanol [34] (25 mg, 0.96×10^{-4} mol, 72%) as a colorless oil, which solidified upon standing.

Synthesis of 9

To a solution of 1,3-benzenedimethanol (1.00 g, 7.64 mmol) in THF (16 mL) and CH_2Cl_2 (4 mL) was added *N*,*N*-diisopropylethyl amine (4.00 mL, 23.0 mmol), followed by the 2-(trimethylsilyl)ethoxymethyl chloride (0.66 mL, 3.71 mmol). The mixture was stirred at rt for 24 h. The mixture was then partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Column chromatography with a mobile phase of 30% acetone in hexanes gave 9 (0.98 g, 3.7 mmol, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 0.03 (s, 9H, $-SiMe_3$), 0.93–0.98 (m, 2H, $-OCH_2CH_2SiMe_3$), 3.64–3.69 (m, 2H, $-OCH_2CH_2SiMe_3$), 4.61 (s, 2H), 4.70 (s, 2H), 4.76 (s, 2H, $-OCH_2O-$), 7.26–7.37 (m, 4H). MS (ESI): 291 $[M + Na]^+$. Anal. Calcd. for $C_{14}H_{24}O_3Si$: C, 62.64; H, 9.01. Found: C, 62.60; H, 8.99.

Model Reaction on 9 (Synthesis of 10c)

To a stirred solution of **9** (50 mg, 1.9×10^{-4} mol) in DMSO (20 mL) was added *t*-BuOK (0.11 g, 9.3×10^{-4} mol), followed by the immediate addition of CH_2BrCl (48 μL, 7.44×10^{-4} mol). The mixture was stirred at rt for 5 h. After this time, the solvent was removed under reduced pressure and the mixture partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Column chromatography with a mobile phase of 5% acetone in hexanes gave **10** (66 mg, 1.7×10^{-4} mol, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.24 (t, $J = 7.0$ Hz, 6H, $-OCH_2CH_3$), 3.65 (q, $J = 7.0$ Hz, 4H, $-OCH_2CH_3$), 4.61 (s, 4H), 4.66 (s, 4H), 4.77 (s, 4H), 4.85 (s, 2H, $ArCH_2OCH_2OCH_2Ar$), 7.26–7.36 (m, 8H). MS (ESI): 427 $[M + Na]^+$. Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.28; H, 8.13.

Model Reaction on 9 with Modified Condition (Synthesis of 10a)

To a stirred solution of **9** (50 mg, 1.9×10^{-4} mol) in DMSO (20 mL) was added *t*-BuONa (45 mg, 4.7×10^{-4} mol), followed by the immediate addition of CH_2BrCl (0.24 μL, 3.7×10^{-4} mol). The mixture was stirred at rt for 5 h. After this time, the solvent was removed under reduced pressure and the mixture partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Column chromatography with a mobile phase of 10% acetone in hexanes gave the "dimeric" species 10a (95 mg, 1.7×10^{-4} mol, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 0.03 (s, 18H, $-SiMe_3$), 0.94–0.99 (m, 4H, $-OCH_2CH_2SiMe_3$), 3.64–3.70 (m, 4H, $-OCH_2CH_2SiMe_3$), 4.61 (s, 4H), 4.66 (s, 4H), 4.76 (s, 4H), 4.85 (s, 2H, $ArCH_2OCH_2O-CH_2Ar$), 7.29–7.35 (m, 8H). MS (ESI): 571 $[M + Na]^+$. Anal. Calcd. for $C_{29}H_{48}O_6Si_2$: C, 63.46; H, 8.82. Found: C, 63.28; H, 8.81.

Synthesis of 12, 13

To a solution of **3** (0.36 g, 0.82 mmol) in DMF (26 mL) was added diisopropylethylamine (1.43 mL, 8.20 mmol), followed by 2-(trimethylsilyl)ethoxymethyl chloride (0.58 mL, 3.28 mmol). The mixture was stirred at rt for 24 h. After this time, the solvent was removed under reduced pressure, and the residue was partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Gradient column chromatography with a mobile phase varying from 10 to 40% acetone in hexanes gave:

1. Bis-protected species **12** (0.24 g, 3.4×10^{-4} mol, 41%) as a colorless oil, which solidified upon evaporation from a hexanes slurry. Mp 82–84°C.

^{1}H NMR ($CDCl_3$) δ (ppm) 0.02 (s, 18H, $-SiMe_3$), 0.93–0.99 (m, 4H, $-OCH_2CH_2SiMe_3$), 3.64–3.70 (m, 4H, $-OCH_2CH_2SiMe_3$), 4.56 (s, 4H, $ArCH_2OH$), 4.66 (s, 4H, $ArCH_2O$–SEM), 4.76 (s, 4H, $-OCH_2O-$), 7.20–7.24 (m, 16H). MS (ESI): 723 $[M + Na]^+$. Anal. Calcd. for $C_{41}H_{56}O_6Si_2$: C, 70.24; H, 8.05. Found: C, 70.42; H, 7.93.

2. Mono-protected species **13** (0.12 g, 2.1×10^{-4} mol, 26%) as a white solid. ^{1}H NMR ($CDCl_3$) δ (ppm) 0.02 (s, 9H, $-SiMe_3$), 0.94–0.99 (m, 2H, $-OCH_2CH_2SiMe_3$), 3.65–3.69 (m, 2H, $-OCH_2CH_2SiMe_3$), 4.56 (s, 6H, $ArCH_2OH$), 4.76 (s, 2H, $ArCH_2$-OSEM), 7.20–7.24 (m, 16H). Mp 43–46°C MS (ESI) 593 $[M + Na]^+$. Anal. Calcd. for $C_{35}H_{42}O_5Si(0.5H_2O$: C, 72.50; H, 7.48. Found: C, 72.55; H, 7.47.

Synthesis of 14, 15

To a solution of **12** (50 mg, 7.1×10^{-5} mol) in DMSO (71 mL), was added *t*-BuONa (35 mg, 3.6×10^{-4} mol), followed immediately by CH_2BrCl (19 μL, 2.9×10^{-4} mol). The mixture was stirred at rt for 5 h. After this time, the solvent was removed under reduced pressure and the mixture partitioned between water and $CHCl_3$ three times. The organic phases were combined, dried with anhydrous Na_2SO_4 and the salts filtered off. The solvent of the filtrate was then removed under reduced pressure. Gradient column chromatography with a mobile phase varying from 5 to 20% acetone in hexanes gave:

1. "Dimer" **14** (17 mg, 1.2×10^{-5} mol, 33%) as a white solid. Mp 173°C. ^{1}H NMR ($CDCl_3$) δ (ppm) 0.02 (s, 36H, $-SiMe_3$), 0.93–0.99 (m, 8H, $-OCH_2CH_2SiMe_3$), 3.63–3.69 (m, 8H, $-OCH_2CH_2SiMe_3$), 4.48 (s, 8H), 4.53 (s, 8H), 4.75 (s, 8H, $-CH_2OCH_2O-CH_2CH_2SiMe_3$), 4.95 (s, 4H, $ArCH_2OCH_2OCH_2Ar$), 7.06 (d, $J = 8.1Hz$, 8H), 7.14 (d, $J = 8.1$ Hz, 8H), 7.16 (m, 16H). ^{13}C NMR ($CDCl_3$) δ (ppm) -1.2, 18.4, 65.5, 69.3, 71.3, 94.6, 127.4, 127.6, 131.2, 131.3, 135.8, 136.3, 146.4. MS (MALDI): 1533 $[M + Ag]^+$. Anal. Calcd. for $C_{84}H_{112}O_{12}Si_4$: C, 70.74; H, 7.92. Found: C, 70.62; H, 7.89.
2. "Trimer" **15** (7.6 mg, 3.6×10^{-6} mol, 15%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 0.02 (s, 54H, $-SiMe_3$), 0.94 ~ 0.99 (m, 12H, $-OCH_2CH_2SiMe_3$), 3.64–3.70 (m, 12H, $-OCH_2CH_2SiMe_3$), 4.55 (s, 12H), 4.60 (s, 12H), 4.76 (s, 12H, $-CH_2OCH_2OCH_2CH_2-SiMe_3$), 4.83 (s, 6H, $ArCH_2OCH_2OCH_2Ar$), 7.18–7.23 (m, 48H). ^{13}C NMR ($CDCl_3$) δ (ppm) -1.4, 18.2, 65.3, 68.9, 69.1, 94.4, 127.2, 127.3, 131.0, 131.1, 135.2, 135.6, 146.2, 146.3. MS (MALDI): 2246 $[M + Ag]^+$. Anal. Calcd. for $C_{126}H_{168}O_{18}Si_6$: C, 70.74; H, 7.92. Found: C, 70.64; H, 7.79.

Synthesis of 16

A mixture of **14** (36 mg, 2.5×10^{-5} mol) and CsF (46 mg, 3.0×10^{-4} mol) in DMF (4 mL) was heated at 130°C for 48 h. After this time, the solvent was cooled and removed under reduced pressure. The remaining solid was suspended in water and filtered off to give **16** (20 mg, 2.3×10^{-5} mol) as a white solid. Mp >250°C with decomposition. ^{1}H NMR (DMSO-d_6) δ (ppm) 4.43 (m, 16H, $ArCH_2-$), 4.85 (s, 4H, $-OCH_2O-$), 5.10 (t, $J = 6.0$ Hz, 4H, –OH), 7.02–7.05 (m, 24H), 7.15 (d, $J = 8.4$ Hz, 8H). MS (MALDI): 1012 $[M + Ag]^+$. Anal. Calcd. for $C_{60}H_{56}O_8$: C, 79.62; H, 6.24. Found: C, 79.35; H, 6.27.

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[23] The efficiency of self-assemblies can be measured using probability [11]. This approach also engenders a demarcation between assembly and non-assembly processes. Hence, reactions that yield products in greater yield than probability suggests can be considered self-assemblies,

while those that do not are not. However, some processes, such as the macrocyclizations reactions discussed here, lie in a grey area between self-assembly and non-self-assembly processes. Until a precise method of determining the probability of an assembly is agreed upon, we describe the model reactions here as macrocyclizations rather than self-assemblies.

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