Template-Directed Synthesis of Shape-Persistent Macrocyclic Amphiphiles with Convergently Arranged Functionalities

Sigurd Höger* and Anne-Désirée Meckenstock[a]

Abstract: The template-directed synthesis of shape-persistent macrocyclic amphiphiles is described. Two macrocycles with convergently arranged functional groups (hydroxyl and carboxylic acids) are prepared by intramolecular Glaser coupling of the appropriate templated tetraacetylenes. These structures are formed by the quadruple Hagihara coupling of monoprotected bisacetylenes to appropriate tetraiodides and subsequent desilylation, resulting in a rapid increase of complexity of the intermediates as well as easy formation of structures with different convergent functional groups.

Keywords: cyclizations · macrocycles · supramolecular chemistry · template synthesis

Introduction

Well-defined and properly arranged functional groups play a crucial role in supramolecular chemistry: their interaction with groups of complementary functionality and arrangement often forms the energetic basis of the association between the partners of the complex.[1] Most bi- and polyfunctional organic molecules show a divergent arrangement of functionalities, that is, the groups point in different directions.[2] The synthetic pathway to these structures is well established and, depending on the size of the backbone, the distance between these functionalities is adjustable. Since most guest molecules in supramolecular chemistry also show such an arrangement of functionalities, appropriate host molecules capable of recognizing these species must contain a concave arrangement of the complementary functionalities (endoreceptors).[1a] Although these arrangements can be induced during the act of complexation (induced-fit mechanism),[3] preorganization of the binding sites of the host molecule generally enhances the degree of molecular recognition.[4] Nature solves this problem quite elegantly, offering a nearly infinite pool of such compounds, for example enzymes and antibodies.[5]

Artificial systems containing a concave arrangement of functionalities are also well established.[1] One relatively easy route to shape-persistent cyclic host molecules having extended interiors is the intermolecular oxidative oligomerization of rigid bisacetylenes (shotgun synthesis).[6] It has been shown that the resulting cyclic structures can bind relatively large organic guest molecules by nonspecific[7] or specific interactions.[8] However, during most cyclization processes, complex product mixtures are formed which must be separated prior to further investigations.[9]

The formation of cleftlike or macrocyclic compounds containing two (or more) different functionalities is problematic. Either a proper protective group strategy in which one of two or more equal functionalities is selectively protected is required,[10] or repetitive coupling strategies have to be used. The latter approach has been successfully applied in the preparation of macrocyclic structures based on the phenyl,[11] the phenylethynyl[12] or the phenyldiethynyl backbone[13] by intramolecular cyclization of the appropriate precursor. Contrary to statistical cyclization reactions,[14] structures with a defined arrangement of different components within a ring can be prepared in high yields during the cyclization step. Although this final step usually gives only one product, or at least one major product that is easily separated, this methodology suffers from the time-consuming stepwise formation of the rather large precursor molecules. It seems that the formation of macrocycles remains problematic: On the one hand, small and easily available building blocks give only low yields of a specific cyclized product, and on the other, high yields during the cyclization are only obtained after a time-consuming, multistep precursor synthesis. A remarkable breakthrough is the preparation of cyclic porphyrin–acetylene structures by means of the template effect of an appropriate pyridyl derivative.[15] However, this strategy requires a high association constant between the precursors and the template, and is therefore restricted to metal-containing compounds.

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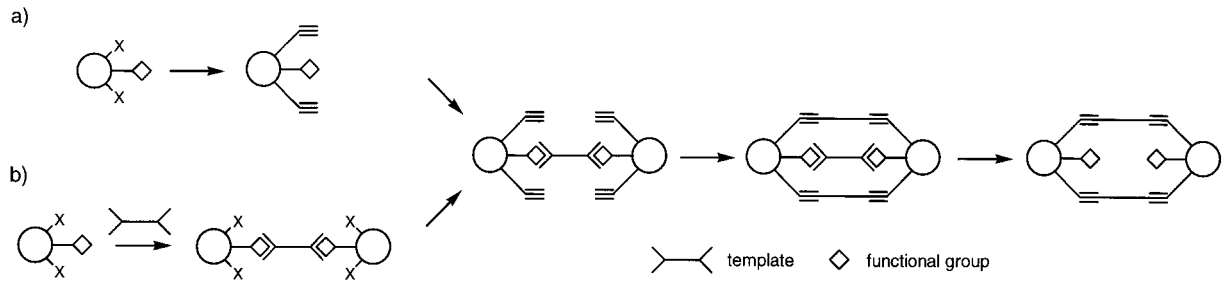


Figure 1. Formation of functionalized aryldiethynyl macrocycles by cyclization of templated precursors. Formation of the templated precursors: a) before attachment of the precursors to the template; b) at the template. The interaction of the template with the precursor may be covalent as well as noncovalent.

Recently, we described an alternative template-based strategy to prepare phenylethynyl macrocycles by the covalent attachment of the bisacetylenic precursors to an appropriate template prior to the cyclization step (Figure 1a).[16–18] This procedure enabled us to obtain macrocycles with switchable amphiphilic units and also with polar side groups pointing to the outside of the ring in very high to nearly quantitative yields.

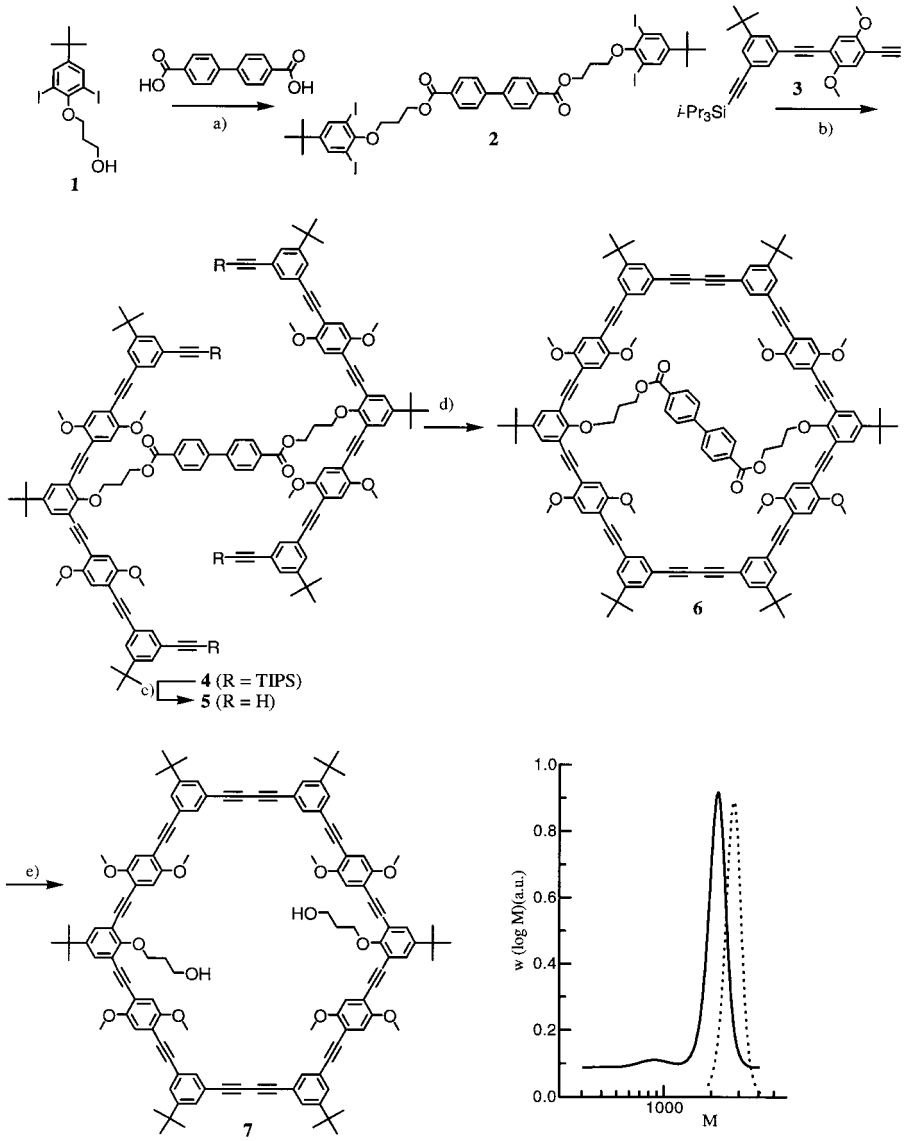
Results and Discussion

Here we describe an alternative way to obtain the templated tetraacetylenes needed for the cyclization. It is based on the finding that it is not necessary to first prepare the bisacetylenes and to attach them in a subsequent step to the template. Rather, it is also possible to prepare the tetraacetylenes *at the template* (see Figure 1b and Scheme 1).

As outlined in Scheme 1, the condensation of the aromatic diiodoalcohol **1** with biphenyl dicarboxylate (the template) using Mitsunobu conditions gave the tetraiodide **2** in good yield. Quadruple palladium-catalysed Hagihara coupling of **2** with the monoprotected bisacetylene **3** provided the templated symmetrical tetraacetylene (TSTA) in its TIPS-protected form (**TSTA-TIPS-4**). Although piperidine is generally a superior solvent for the Hagihara coupling, triethylamine was used in this case to prevent the cleavage of **4** by undesired amide formation.[19] To compensate for the loss of solvent quality, $[PdCl_2(PPh_3)_2]$ and CuI were used as the catalyst system and no further PPh_3 was added. Although under these conditions palladium black begins to precipitate after a few minutes, a high yield of the desired product was obtained. The advantage of the quadruple Hagihara coupling in this step is that the molecular weight and the physical properties of **4** differ strongly from those of the starting materials and of the side-products, allowing for an easy and high-yield purification. Subsequent desilylation of **4** using tetrabutylammonium fluoride gave the templated symmetrical tetraacetylene **5** (**TSTA-5**). In this step, about 5% water was added to the THF in order to prevent ester cleavage. In addition to the reduced basicity of the fluoride, there was an increase in the reaction time and full deprotection of all four TIPS groups was achieved by stirring the reaction mixture overnight. The progress of the reaction and the different stages of deprotection were observed by TLC, where different spots between the starting material and the product began to appear and disappear as the reaction proceeded. Nevertheless, deprotection was very clean and after reaction overnight it was a spot-to-spot conversion on TLC. The cyclization of **5** under pseudo-high-dilution conditions was carried out by slow addition of a solution of **5** in pyridine to a slurry of CuCl/$CuCl_2$ in the same solvent at room temperature.[7b,c] After complete addition the mixture was stirred for an additional two days at room temperature. The GPC data of **5** and of the crude cyclization product indicate that the latter contained more than 95% of **6**, the templated symmetrical macrocycle (**TSM-6**). Chromatographic purification afforded pure **6** in 92% yield. Base-catalysed hydrolysis and subsequent precipitation gave the symmetrical macrocycle **7** (**SM-7**) containing two convergently arranged hydroxy alkyl groups. This result clearly shows that this method allows for the high-yield synthesis of functionalized macrocycles in only a few steps from easily available starting materials. Additionally, the molecular weights and the physical properties of the intermediates change dramatically in every reaction, allowing for an easy and high-yield product purification.

Moreover, as illustrated in Scheme 2, the synthesis of macrocycles containing two different functional groups can be performed by the same reaction sequence as shown before, starting from the asymmetric tetraiodide **12**. Key compound **12** was prepared by the repetitive coupling of the different diiodides **1** and **11** to 4-hydroxymethyl benzoic acid, which acts as the asymmetric template. Not surprisingly, the intramolecular cyclization of the templated asymmetrical tetraacetylene **14** (**TATA-14**) gave the corresponding templated asymmetrical macrocycle **15** (**TAM-15**) in high yield, as

Abstract in German: *Die templatgesteuerte Synthese von formtreuen makrocyclischen Amphiphilen wird beschrieben. Zwei Makrocyclen mit konvergent angeordneten funktionellen Gruppen (Hydroxygruppen und Carbonsäuregruppen) werden durch intramolekulare Glaser-Kupplung der entsprechenden templatgebundenen Tetraacetylene hergestellt. Diese wurden durch vierfache Hagihara-Kupplung einfach geschützter Bisacetylene an die entsprechenden Tetraiodide und anschließende Desilylierung synthetisiert. Diese Vorgehensweise führt zu einem raschen Anstieg der Komplexität der Zwischenstufen und ermöglicht zudem die einfache Herstellung von Verbindungen mit unterschiedlichen, konvergent angeordneten funktionellen Gruppen.*



Scheme 1. a) PPh_3, DEAD, THF (93%); b) $PdCl_2(PPh_3)_2$, CuI, NEt_3 (90%); c) Bu_4NF, THF, H_2O (96%); d) $CuCl/CuCl_2$, pyridine (92%); e) NaOH, LiOH, MeOH, H_2O, THF (91%). GPC of **5** (dotted line) and of the crude cyclization product of **5** (solid line).

determined by GPC analysis. Base-catalysed removal of the template formed the asymmetrical macrocycle **16** (**AM-16**). Compound **16** is a shape-persistent macrocyclic compound with an interior in the nanometer region containing both a hydroxy and a carboxylic acid functionality in a convergent arrangement. The great advantage of the strategy outlined here is that all transformations necessary to obtain the asymmetry in the final product can be performed at the readily available preliminary stages. In addition, the formation of these preliminary stages is based on common and well-documented protective-group methodologies.[20]

In summary, a synthetic route to macrocycles containing a convergent arrangement of functional groups is described. The precursors necessary for the cyclization step are prepared at the template in just a few steps. Owing to the intramolecularity of the cyclization, this procedure not only gives high yields of the corresponding macrocycles, but also allows for the simple purification of the products. In comparison to Still's macrolactamization to peptide receptors[18d] and Moore's Hagihara coupling to molecular turnstiles,[21] transformations which also display template-directed cyclizations using covalently attached precursors, the Glaser coupling described here and by others seems to give superior product yields. In addition, this approach allows for an easy synthesis of macrocycles with different functional groups pointing inside the ring. The synthetic potential of this method and the properties of the new compounds are currently under investigation.

Experimental Section

General methods: Commercially available chemicals were used as received. THF was distilled from potassium prior to use. Triethylamine, piperidine and pyridine were distilled over CaH_2 and stored under argon. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC300 (300 MHz for ^1H, 75.48 MHz for ^{13}C). Thin-layer chromatography was performed on aluminium plates precoated with Merck 5735 silica gel 60 F_{254}. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Radial chromatography was performed with Merck silica gel 60 PF_{254} containing $CaSO_4$. The gel permeation chromatograms (GPCs) were measured in THF (flow rate 1 mL min^{-1}) at room temperature, using a combination of three styragel columns (porosity 10^3, 10^5 and 10^6) and an UV detector operating at $\lambda = 254$ nm. The molecular weight was obtained from polystyrene calibrated SEC columns. The matrix-assisted laser desorption ionization time-of-flight mass spectroscopy measurements were carried out on a Bruker reflex spectrometer (Bruker, Bremen), which incorporates a 337 nm nitrogen laser with a 3 ns pulse duration (10^6–10^7 W cm^{-1}, 100 μm spot diameter). The instrument was operated in a linear mode with an accelerating potential of 33.65 kV. The mass scale was calibrated with polystyrene ($M_p = 2300$), using a number of resolved oligomers. Samples were prepared by dissolving the macrocycle in THF at a concentration of 10^{-4} mol L^{-1}. 10 μL of this solution and 10 μL of a 10^{-3} mol L^{-1} silver trifluoroacetate solution were added to 10 μL of a 0.1 mol l^{-1} matrix solution dissolved in THF. In all cases, 1,8,9-trihydroxyanthracene (Aldrich, Steinheim) was used as matrix. 1 μL of this mixture was applied to the multistage target and air-dried. Microanalyses were performed by the University of Mainz.

Supporting information describing the synthesis and characterization data for all starting materials is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.

Bis[3-(4-*tert*-butyl-2,6-diiodophenoxy)propyl]4,4′-biphenyldicarboxylate (2): Diethyl azodicarboxylate (0.88 g, 5.1 mmol) was slowly added to a suspension of **1** (1.8 g, 3.9 mmol), 4,4′-biphenyldicarboxylic acid (0.43 g, 1.8 mmol) and triphenylphosphine (1.28 g, 4.9 mmol) in THF (20 mL) at

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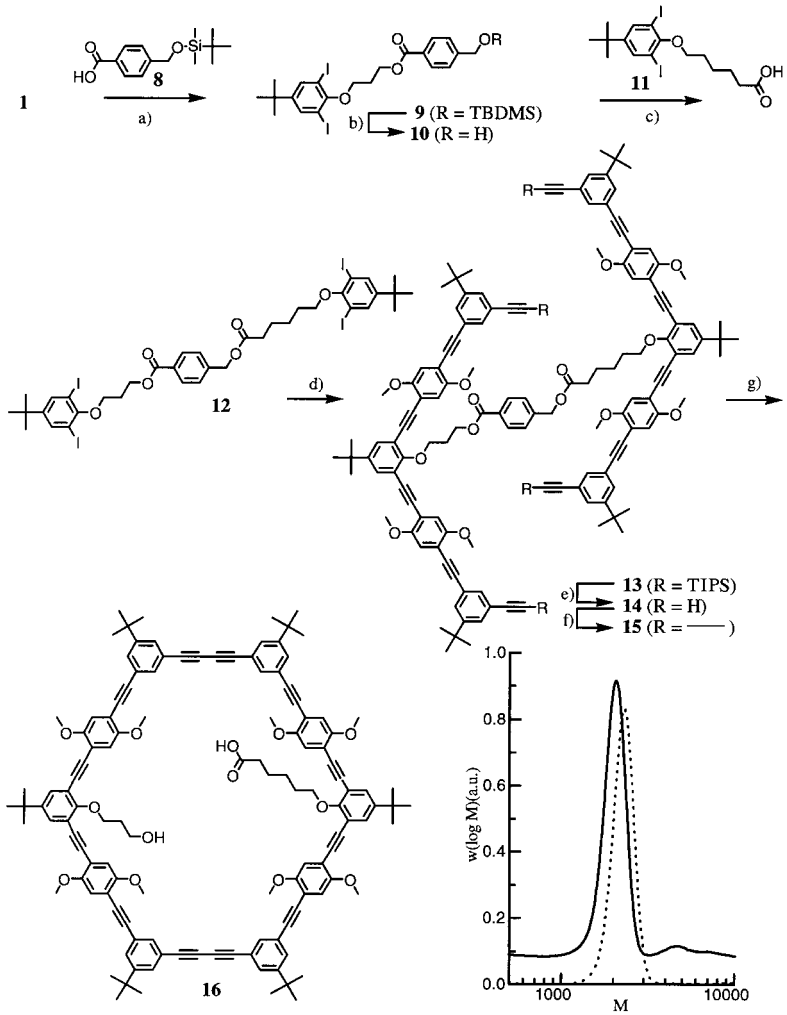

Scheme 2. a) PPh_3, DEAD, THF (93%); b) Bu_4NF, THF, H_2O (87%); c) PPh_3, DEAD, THF (86%); d) $PdCl_2(PPh_3)_2$, CuI, NEt_3 (89%); e) Bu_4NF, THF, H_2O (96%); f) CuCl/$CuCl_2$, pyridine (88%); g) NaOH, LiOH, MeOH, H_2O, THF (90%). GPC of **14** (dotted line) and of the crude cyclization product of **14** (solid line).

room temperature. The starting materials went into solution. After this solution had been stirred for 1 h, ether (150 mL) and water (100 mL) were added, and the organic layer was extracted with water (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed over silica gel using CH_2Cl_2 as the eluent ($R_f = 0.66$) to afford **2** (1.85 g, 93%) as a colourless foamy solid. ^{1}H NMR ($CDCl_3$): $\delta =$ 8.16 and 7.68 (AA′BB′ pattern, 4H each), 7.71 (s, 4H), 4.66 (t, $J = 6.1$ Hz, 4H), 4.13 (t, $J = 5.9$ Hz, 4H), 2.43–2.29 (m, 2H), 1.24 (s, 18H); ^{13}C NMR ($CDCl_3$): $\delta = 166.19$, 155.15, 151.20, 144.31, 137.10, 130.26, 129.91, 127.20, 90.52, 69.35, 61.95, 34.18, 31.16, 29.46; elemental analysis for $C_{40}H_{42}I_4O_6$ (1126.39): calcd C 42.65, H 3.76; found C 42.83, H 3.78.

TSTA-TIPS-4: [$Pd(PPh_3)_2Cl_2$] (20 mg) and CuI (15 mg) were added to a solution of **2** (563 mg, 0.49 mmol) and **3** (1.12 g, 2.25 mmol) in triethylamine (8 mL) at room temperature. The mixture turned dark after a few minutes and was stirred for 6 h at room temperature and then at 40 °C overnight. After cooling to room temperature, ether (100 mL) and water (100 mL) were added. The organic phase was separated and extracted with water (2 × 50 mL), 10% acetic acid (5 × 50 mL), water (2 × 50 mL), 10% aqueous NaOH (3 × 50 mL) and brine (50 mL). Drying over $MgSO_4$ and evaporation of the solvent yielded an amber residue, which was chromatographed over silica gel with hexanes/CH_2Cl_2 (gradient 1:1 to 1:3) as the eluent ($R_f = 0.37$; hexanes/CH_2Cl_2 (1:1)) to afford **4** (1.15 g, 90%) as a slightly brown solid. An analytical sample was prepared by radial chromatography, followed by precipitation from CH_2Cl_2/MeOH. ^{1}H NMR (CD_2Cl_2): $\delta = 7.96$ and 7.61 (AA′BB′ pattern, 4H each); 7.56 (s, 4H); 7.54–7.52 (m, 4H); 7.49–7.44 (m, 8H); 7.06 (s, 4H); 7.02 (s, 4H); 4.67 (t, $J =$ 6.30 Hz, 4H); 4.57 (t, $J = 5.92$ Hz, 4H); 3.88 (s, 12H); 3.87 (s, 12H); 2.41–2.31 (m, 4H); 1.35 (s, 18H); 1.32 (s, 36H); 1.14 (s, 84H); ^{13}C NMR (CD_2Cl_2): $\delta = 166.30$, 158.83, 154.51, 154.45, 152.27, 147.13, 144.51, 132.58, 131.52, 130.38, 130.25, 129.42, 129.21, 127.46, 123.96, 123.47, 117.42, 116.06, 116.00, 113.86, 113.74, 107.08, 94.90, 91.79, 91.16, 90.23, 86.17, 71.27, 62.63, 56.79, 56.74, 35.02, 34.73, 31.40, 31.26, 30.33, 18.88, 11.79; elemental analysis for $C_{172}H_{206}O_{14}Si_4$ (2609.86): calcd C 79.14, H 7.97; found C 78.92, H 8.09.

TSTA-5: Tetrabutylammonium fluoride (1 M solution in THF, 2.5 mL, 2.5 mmol) was added to a solution of **4** (500 mg, 0.19 mmol) in THF/water (20:1; 10 mL). TLC using hexanes/CH_2Cl_2 (1:1.5) as the eluent showed several spots between $R_f = 0.72$ (starting material) and $R_f = 0.42$ (product) after 40 min. After overnight stirring, only the product spot was observed. Ether (100 mL) and water (100 mL) were added and the organic phase was extracted with water (3 × 50 mL) and brine (50 mL). Drying over $MgSO_4$ and evaporation of the solvent yielded an yellow oily residue, which was treated several times with hexanes to give **5** (366 mg, 96%) as a yellow solid. An analytical sample was prepared by radial chromatography, followed by precipitation from CH_2Cl_2/MeOH. ^{1}H NMR (CD_2Cl_2): $\delta = 7.94$ and 7.59 (AA′BB′ pattern, 4H each); 7.57–7.55 (m, 4H); 7.56 (s, 4H); 7.52–7.50 (m, 4H); 7.48–7.46 (m, 4H); 7.06 (s, 4H); 7.01 (s, 4H); 4.67 (t, $J = 6.29$ Hz, 4H); 4.57 (t, $J = 5.92$ Hz, 4H); 3.88 (s, 12H); 3.87 (s, 12H); 3.15 (s, 4H); 2.42–2.31 (m, 4H); 1.36 (s, 18H); 1.32 (s, 36H); ^{13}C NMR (CD_2Cl_2): $\delta = 166.32$, 158.86, 154.48, 152.39, 147.15, 144.46, 132.49, 131.50, 130.38, 130.34, 130.20, 129.82, 129.63, 127.42, 123.63, 122.55, 117.44, 116.03, 113.90, 113.68, 94.73, 91.79, 90.21, 86.31, 83.56, 77.53, 71.26, 62.57, 56.79, 56.74, 35.03, 34.73, 31.39, 31.22, 30.33; elemental analysis for $C_{136}H_{126}O_{14}$ (1984.62): calcd C 82.30, H 6.41; found C 81.95, H 6.40.

TSM-6: A solution of **5** (360 mg, 0.18 mmol) in pyridine (30 mL) was added to a suspension of CuCl (2.56 g) and $CuCl_2$ (0.51 g) in pyridine (100 mL) over 96 h at room temperature. After completion of the addition, the mixture was stirred for an additional 4 d, then poured into CH_2Cl_2 (250 mL) and water (200 mL). The organic phase was extracted with water, 25% NH_3 solution (in order to remove the copper salts), water, 10% acetic acid, water, 10% aqueous NaOH and brine and dried over $MgSO_4$. After evaporation of the solvent to 30–40 mL, the coupling products were precipitated by the addition of 200 mL of methanol and collected by filtration. Column chromatography over silica gel using hexanes/CH_2Cl_2 (1:4) as the eluent ($R_f = 0.59$) gave **6** (331 mg, 92%) as a slightly yellow solid. ^{1}H NMR (CD_2Cl_2): $\delta = 8.18$ and 7.79 (AA′BB′ pattern, 4H each); 7.63–7.61 (m, 4H); 7.58–7.54 (m, 12H); 7.14 (s, 4H); 7.10 (s, 4H); 4.69 (t, $J = 7.25$ Hz, 4H); 4.56 (t, $J = 5.92$ Hz, 4H); 3.93 (s, 12H); 3.92 (s, 12H); 2.41–2.28 (m, 4H); 1.37 (s, 18H); 1.35 (s, 36H); ^{13}C NMR (CD_2Cl_2): $\delta =$ 166.36, 158.94, 154.58, 154.54, 152.60, 147.42, 144.76, 132.93, 130.96, 130.48, 130.20, 130.13, 127.74, 123.88, 122.07, 117.86, 116.16, 116.07, 113.97, 113.66, 94.59, 91.70, 90.37, 86.54, 81.59, 73.95, 70.97, 63.18, 56.89, 56.73, 35.14, 34.80, 31.41, 31.22, 30.00, elemental analysis for $C_{136}H_{122}O_{14}$ (1980.58): calcd C 82.47, H 6.22; found C 82.21, H 6.09.

SM-7: NaOH in MeOH (10%; 1 mL) and LiOH in water (10%; 2 mL) were added to a solution of **6** (0.13 mmol, 250 mg) in THF (20 mL) and the mixture was refluxed for 3 days. After evaporation of the mixture to a small

volume, CH_2Cl_2 (50 mL) and water (50 mL) were added, and the organic phase was extracted with water (3 × 50 mL), 10% aqueous NaOH (3 × 50 mL) and brine (50 mL) and dried over $MgSO_4$. Evaporation of the solvent to a small volume and precipitation with MeOH yielded **7** (204 mg, 91%) as a yellow solid. An analytical sample was obtained by recrystallization from CH_2Cl_2. ^{1}H NMR ($C_2D_2Cl_4$): 7.57–7.51 (m, 8H); 7.48–7.44 (m, 8H); 7.07 (s, 4H); 6.99 (s, 4H); 4.45 (t, J = 5.35 Hz, 4H) 3.90 (t, J = 5.72 Hz, 4H); 3.86 (s, 12H); 3.85 (s, 12H); 2.11–1.99 (m, 4H); 1.27 (s, 54H); ^{13}C NMR ($C_2D_2Cl_4$): δ = 158.68, 154.40, 154.23, 152.28, 147.02, 133.69, 131.20, 129.78, 129.64, 123.64, 121.86, 117.19, 116.28, 116.19, 113.83, 113.63, 94.77, 91.77, 90.17, 86.58, 81.88, 73.06, 61.32, 57.05, 56.93, 35.02, 34.63, 33.13, 31.54, 31.37; elemental analysis for $C_{122}H_{116}O_{12}$ (1774.38): calcd C 82.57, H 6.60; found C 82.15, H 6.61; MS (MALDI-TOF): 1773.3, 1882.3 [M+Ag].

3-(4-*tert*-Butyl-2,6-diiodophenoxy)propyl-4-(*tert*-butyldimethylsilyloxymethyl)benzoate (9): Compound **9** was prepared as for **2**, with diethyl azodicarboxylate (2.70 g, 15.5 mmol), **1** (4.70 g, 10.2 mmol), **8** (2.55 g, 9.6 mmol) and triphenylphosphine (3.90 g, 14.9 mmol) in THF (50 mL) at room temperature. Chromatography over silica gel using hexanes/CH_2Cl_2 as the eluent (R_f = 0.31) afforded **9** (6.30 g, 93%) as a nearly colourless oil. ^{1}H NMR (CD_2Cl_2): δ = 8.04 and 7.60 (AA′BB′ pattern, 2H each), 7.40 (s, 2H), 4.80 (s, 2H), 4.60 (t, J = 6.29 Hz, 2H), 4.13 (t, J = 6.10 Hz, 2H), 2.45–2.29 (m, 2H), 1.26 (s, 9H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (CD_2Cl_2): δ = 166.67, 155.66, 151.71, 147.30, 137.63, 129.89, 129.52, 126.14, 90.76, 69.96, 64.89, 62.04, 34.49, 31.31, 29.87, 26.06, 18.65, −5.23; elemental analysis for $C_{27}H_{38}I_2O_4Si$ (708.49): calcd C 45.77, H 5.41; found C 45.85, H 5.39.

3-(4-*tert*-Butyl-2,6-diiodophenoxy)propyl-4-hydroxymethylbenzoate (10): Tetrabutylammonium fluoride (1M solution in THF, 16 mL, 16 mmol) was added to a solution of **9** (5.2 g, 7.3 mmol) in THF/water (20:1; 50 mL). After stirring for 3 h at room temperature, ether (200 mL) and water (200 mL) were added and the organic phase was extracted with water (3 × 100 mL) and brine (100 mL). Drying over $MgSO_4$ and evaporation of the solvent yielded an oily yellow residue, which was treated several times with hexanes to give **10** (3.8 g, 87%) as a colourless solid. ^{1}H NMR (CD_2Cl_2): δ = 8.05 and 7.44 (AA′BB′ pattern, 2H each), 7.77 (s, 2H), 4.74 (s, 2H), 4.60 (t, J = 6.30 Hz, 2H), 4.13 (t, J = 6.10 Hz, 2H), 2.41–2.29 (m, 2H), 2.20 (br s, 1H), 1.26 (s, 9H); ^{13}C NMR (CD_2Cl_2): δ = 166.63, 155.63, 151.71, 146.81, 137.61, 130.10, 129.90, 126.76, 90.76, 69.94, 64.80, 62.15, 34.48, 31.30, 29.84; elemental analysis for $C_{21}H_{24}I_2O_4$ (594.23): calcd C 42.45, H 4.07; found C 42.49, H 4.02.

4-{Carboxy[3-(4-*tert*-butyl-2,6-diiodophenoxy)propyl]-phenyl}methyl-6-(4-*tert*-butyl-2,6-diiodophenoxy)hexanoate (12): Compound **12** was prepared as for **2**, from diethyl azodicarboxylate (0.45 g, 2.6 mmol), **11** (0.95 g, 1.7 mmol), **10** (0.95 g, 1.6 mmol) and triphenylphosphine (0.65 g, 2.5 mmol) in THF (10 mL). Chromatography over silica gel using CH_2Cl_2 as the eluent (R_f = 0.41) afforded **11** (1.51 g, 86%) as a nearly colourless oil. ^{1}H NMR (CD_2Cl_2): δ = 8.07 and 7.44 (AA′BB′ pattern, 2H each), 7.77 (s, 2H), 7.76 (s, 2H), 5.18 (s, 2H), 4.61 (t, J = 6.30 Hz, 2H), 4.13 (t, J = 5.91 Hz, 2H), 3.94 (t, J = 6.49 Hz, 2H), 2.45 (t, J = 7.25 Hz, 2H), 2.41–2.29 (m, 2H), 1.98–1.85 (m, 2H), 1.85–1.71 (m, 2H), 1.68–1.55 (m, 2H), 1.26 (s, 18H); ^{13}C NMR (CD_2Cl_2): δ = 173.47, 166.36, 155.98, 155.65, 151.72, 151.46, 141.86, 137.62, 137.57, 130.56, 130.16, 127.94, 90.89, 90.79, 73.33, 69.92, 65.61, 62.22, 34.49, 31.33, 30.07, 29.86, 25.93, 25.23; elemental analysis for $C_{37}H_{44}I_4O_6$ (1092.37): calcd C 40.68, H 4.06; found C 40.66, H 4.09.

TATA-TIPS-13: Compound **13** was prepared as for **4**, from $Pd(PPh_3)_2Cl_2$ (20 mg), CuI (15 mg), **12** (810 mg, 0.74 mmol) and **3** (1.70 g, 3.42 mmol) in triethylamine (12 mL) at room temperature. Chromatography over silica gel using hexanes/CH_2Cl_2 (gradient 1:1 to 1:3) as the eluent (R_f = 0.27; hexanes/CH_2Cl_2 (1:1) afforded **13** (1.69 g, 89%) as a yellow solid. An analytical sample was prepared by radial chromatography followed by precipitation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$): δ = 7.88 and 7.30 (AA′BB′ pattern, 2H each); 7.57–7.54 (m, 8H); 7.51–7.49 (m, 4H); 7.49–7.47 (m, 4H); 7.07 (s, 4H); 7.06 (s, 2H); 7.02 (s, 2H); 5.08 (s, 2H); 4.65 (t, J = 6.49 Hz, 2H); 4.56 (t, J = 5.91 Hz, 2H); 4.38 (t, J = 6.49 Hz, 2H); 3.90 (s, 6H); 3.89 (s, 6H); 3.88 (s, 6H); 3.87 (s, 6H); 2.39-2.25 (m, 4H); 1.98–1.85 (m, 2H); 1.72–1.53 (m, 4H); 1.35 (s, 9H); 1.35 (s, 9H); 1.34 (s, 18H); 1.33 (s, 18H); 1.15 (s, 84H); ^{13}C NMR (CD_2Cl_2): δ = 173.33, 166.27, 159.21, 158.81, 154.51, 154.48, 154.44, 152.27, 147.08, 146.79, 141.74, 132.57, 131.6–131.4 several signals (not resolved), 130.35, 129.94, 129.41, 129.23, 127.77, 123.96, 123.49, 123.46, 117.37, 117.33, 116.15, 116.04, 115.99, 114.04, 113.85, 113.70, 107.08, 94.90, 94.87, 92.08, 91.79, 91.15, 90.22, 89.99, 86.16, 74.54, 71.26, 65.59, 62.56, 56.86, 56.79, 56.71, 35.03, 34.72, 34.69, 34.33, 31.40, 31.26, 30.50, 30.29, 26.04, 25.19, 18.88, 11.79; elemental analysis for $C_{169}H_{208}O_{14}Si_4$ (2576.13): calcd C 78.79, H 8.16; found C 78.59, H 8.08.

TATA-14: Compound **14** was prepared as for **5**, from tetrabutylammonium fluoride (1M solution in THF, 3.3 mL, 3.3 mmol) and **13** (660 mg, 0.26 mmol) in THF/water (20:1; 12 mL). Compound **14** (476 mg, 96%) was obtained as a yellow solid. An analytical sample was prepared by radial chromatography with CH_2Cl_2 as eluent (R_f = 0.33, hexanes/CH_2Cl_2 (1:1.5)) followed by precipitation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$): δ = 7.87 and 7.29 (AA′BB′ pattern, 2H each); 7.60–7.57 (m, 4H); 7.56 (s, 2H); 7.54 (s, 2H); 7.53–7.49 (m, 8H); 7.07 (s, 2H); 7.07 (s, 2H); 7.06 (s, 2H); 7.01 (s, 2H); 5.08 (s, 2H); 4.64 (t, J = 6.30 Hz, 2H); 4.55 (t, J = 5.91 Hz, 2H); 4.38 (t, J = 6.49 Hz, 2H); 3.90 (s, 6H); 3.89 (s, 6H); 3.87 (s, 6H); 3.86 (s, 6H); 3.15 (s, 4H); 2.40–2.24 (m, 4H); 1.97–1.86 (m, 2H); 1.74–1.53 (m, 4H); 1.35 (s, 9H); 1.35 (s, 9H); 1.33 (s, 18H); 1.33 (s, 18H); ^{13}C NMR (CD_2Cl_2): δ = 173.32, 166.27, 159.22, 158.82, 154.51, 154.49, 154.47, 152.39, 147.09, 146.80, 141.72, 132.50, 131.6–131.4 several signals (not resolved), 130.31, 129.92, 129.82, 129.65, 127.72, 123.63, 123.60, 122.54, 117.37, 117.33, 116.12, 116.07, 116.01, 114.08, 113.89, 113.63, 94.72, 94.68, 92.08, 91.79, 90.19, 89.97, 86.30, 86.28, 83.56, 77.51, 74.54, 71.24, 65.57, 62.54, 56.86, 56.79, 56.77, 56.70, 35.03, 34.71, 34.68, 34.31, 31.38, 31.22, 30.50, 30.28, 26.04, 25.18; elemental analysis for $C_{133}H_{128}O_{14}$ (1950.61): calcd C 81.88, H 6.63; found C 81.61, H 6.32.

TAM-15: Compound **15** was prepared as for **6**, by addition of a solution of **14** (373 mg, 0.19 mmol) in pyridine (30 mL) to a suspension of CuCl (2.56 g) and $CuCl_2$ (0.51 g) in pyridine (100 mL) over 96 h at room temperature. Column chromatography over silica gel using CH_2Cl_2 as the eluent (R_f = 0.57) gave **15** (226 mg, 88%) as a slightly yellow solid. ^{1}H NMR (CD_2Cl_2): δ = 8.07 and 7.48 (AA′BB′ pattern, 2H each); 7.63–7.54 (m, 16H); 7.12 (s, 2H); 7.10 (s, 2H); 7.09 (s, 2H); 7.08 (s, 2H); 5.20 (s, 2H); 4.71 (t, J = 7.63 Hz, 2H); 4.52 (t, J = 5.92 Hz, 2H); 4.36 (t, J = 6.29 Hz, 2H); 3.94 (s, 6H); 3.93 (s, 6H); 3.92 (s, 12H); 2.45–2.32 (m, 4H); 2.05–1.93 (m, 2H); 1.87–1.63 (m, 4H); 1.37 (s, 9H); 1.36 (s, 27H); 1.35 (s, 18H); ^{13}C NMR ($C_2D_2Cl_4$): δ = 173.47, 166.29, 159.42, 158.61, 154.33, 154.31, 152.29, 152.28, 147.03, 146.65, 141.72, 133.68, 131.3–131.0 several signals (not resolved), 130.31, 130.05, 129.79, 129.62, 128.03, 123.65, 121.85, 121.83, 117.41, 117.21, 116.3–116.0 several signals (not resolved), 114.09, 113.85, 113.60, 113.54, 94.77, 94.73, 92.13, 91.90, 90.20, 89.89, 86.65, 86.60, 81.85, 71.08, 65.61, 63.37, 57.07, 57.03, 56.88, 56.79, 35.02, 34.63, 34.60, 34.16, 31.54, 31.37, 30.73, 30.07, 25.99, 25.24; elemental analysis for $C_{133}H_{124}O_{14}$ (1946.57): calcd C 82.06, H 6.43; found C 81.84, H 6.37.

AM-16: NaOH in MeOH (10%; 1 mL) and LiOH in water (10%; 2 mL) were added to a solution of **15** (0.05 mmol, 100 mg) in THF (10 mL) and the mixture heated under reflux for 3 days. After evaporation to a small volume, the mixture was acidified with 10% HCl and **16** was precipitated by the addition of MeOH. Filtration and careful washing with MeOH yielded **16** (85 mg, 90%) as a yellow solid. An analytical sample was obtained by column chromatography. ^{1}H NMR ($C_2D_2Cl_4$): δ = 7.58–7.55 (m, 4H); 7.54–7.51 (m, 4H); 7.48–7.43 (m, 8H); 7.06 (s, 2H); 6.99 (s, 6H); 4.45 (t, J = 5.34 Hz, 2H); 4.30 (t, J = 6.49 Hz, 2H); 3.91 (t, J = 5.73 Hz, 2H); 3.86 (s, 6H); 3.85 (s, 12H); 3.85 (s, 6H); 2.19 (t, J = 7.06 Hz, 2H); 2.10–2.00 (m, 2H); 1.90–1.78 (m, 2H); 1.65–1.45 (m, 4H); 1.26 (s, 54H); ^{13}C NMR ($C_2D_2Cl_4$): δ = 175.95, 159.19, 158.64, 154.38, 154.31, 154.22, 152.28, 147.01, 146.57, 133.9–133.7 several signals (not resolved), 131.4–131.0 several signals (not resolved), 129.9–129.4 several signals (not resolved), 123.66, 121.86, 117.18, 116.33, 116.27, 116.20, 114.07, 113.83, 113.63, 113.55, 94.78, 94.70, 92.13, 91.78, 90.17, 90.03, 86.61, 81.91, 72.96, 61.26, 57.12, 57.05, 56.92, 56.87, 35.02, 34.63, 34.57, 33.53, 33.13, 31.33, 31.37, 30.32, 25.84, 24.94; elemental analysis for $C_{125}H_{120}O_{13}$ (1830.91): calcd C 82.02, H 6.62; found C 81.75, H 6.46. MS (MALDI-TOF): 1941.8 [M+Ag]; 2045.1 [M+2Ag].

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