DOI: 10.1002/ejoc.200700118

Shape-Persistent Macrocycles: A Synthetic Strategy that Combines Easy and Site-Specific Decorations with Improved Cyclization Efficiency

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Keywords: Repetitive synthesis / Molecular scaffolds / Coumarin / Cross-coupling / Molecular devices / Synthesis design

A flexible route to shape-persistent macrocycles based on a collection of building blocks has been devised that allows the easy introduction of several different functional units at predetermined positions and the obtainment of cycles as analytically pure materials in high isolated yields of 22–45 % in the final cyclization process. Each step of the assembly process is based on high-yielding and robust Suzuki- and Sonogashira-type cross-coupling reactions. In the latter, the best results were obtained in the absence of Cu^{I} iodide and with relatively large amounts of a palladium catalyst precursor. This holds true specifically for the cyclization reaction itself with these factors considered the key to the rather successful synthesis of the shape-persistent macrocycles described herein. Each growth step is followed by a rather simple work up based on preparative gel-permeation chromatography that allows the separation of 1 g and 300 mg of crude material at a time depending on whether an open column set up or a recycling GPC apparatus, respectively, is used.

Introduction

Reduced conformational flexibility is the main reason for the considerable ongoing research into shape-persistent macrocycles.[1] It not only makes these compounds form ordered structures like tubular channels or two-dimensional nanopatterns on surfaces, but also allows their use as scaffolds for placing functional units at predetermined spatial positions to one another. This latter aspect offers intriguing possibilities for targeting, sensing, and catalysis, but also allows energy- and electron-transfer processes to be studied on the basis of defined distance relationships.[2] All that is still needed for these scaffold applications are macrocycles site-specifically decorated with several different functionalities.

In light of the considerable potential importance of shape-persistent macrocycles, numerous synthetic routes have been developed[1] that can mainly be sorted into two categories: I) the cyclic oligomerization of small building blocks, whereby the two terminal connecting sites of each building block are unprotected and ready to undergo successive bond formation and II) the stepwise assembly of building blocks with the help of protecting group chemistry until only a few precursors for cyclization are obtained (ultimately only one) which are then cyclized. In this study, shape-persistent macrocycles **1**–**3** (Figure 1) were designed and synthesized according to method II. They all have the same hexagonal backbone composed of unsaturated carbon and nitrogen atoms with two bipyridinyl (bpy) units embedded on opposite sides. Their exocyclic peripheries are decorated with three different combinations of the chromophores

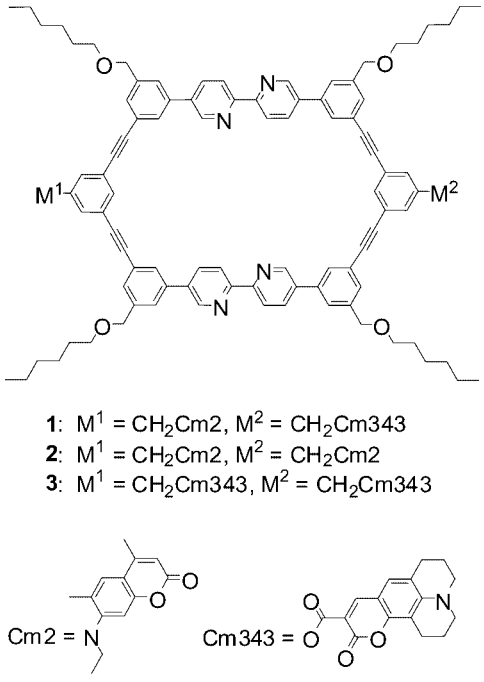

Figure 1. Chemical structures of the target macrocycles **1**–**3** with different combinations of the coumarin dyes Cm2 and Cm343 at opposing corners of the hexagonal framework.

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coumarin 2 (Cm2) and coumarin 343 (Cm343) (2/2, 2/343, 343/343) at the two corners that are farthest apart and have the bpy units between them. Finally, all cycles carry four hexyloxymethyl chains at the remaining four corners for solubilization. With this structural set up, these macrocycles may act as molecular triad systems and are interesting candidates for molecular switch applications.[2,3]

Results and Discussion

Comments on Strategy

Both strategies I and II have intrinsic advantages and disadvantages. The former has mainly been used because of the ease of synthesis, but usually suffers from low yields as a result of numerous cyclic and noncyclic side-products.[4,5] Recently, some elegant developments of this strategy were reported[6–10] which constitute a significant advance as far as suppression of side-reactions during cyclization is concerned. The building blocks required, however, have a higher structural complexity which unfortunately directly translates into greater effort in their synthesis. It also negatively impacts on the flexibility of any application-oriented macrocycle design. Furthermore, strategy I intrinsically provides access only to those macrocycles that consist of a sequence of identical repeating units. This clearly allows it to be used only for cycles that either have random or uniform decorations on each repeat unit. Cycles for scaffold applications can practically not be obtained. Strategy II, in which large cyclization precursors are constructed, involves numerous sequential steps and is therefore necessarily quite demanding. However, it has the key advantage that fully tailor-made macrocycles can be made. Sites at which the cycle should carry a certain functionality (for example, dyes for energy transfer) can be placed exactly where they are needed. This strategy was therefore chosen in this study. Because of the intrinsic synthetic complexity involved, high-yielding steps were included whenever possible and the sequence was streamlined to a maximum. Another aspect that had to be considered was the stage of the sequence at which the dyes should be introduced. Should this be done before or after cyclization? Although the introduction of functionality after cyclization would in principle be possible, it was nevertheless considered disadvantageous. Not only would it require the use of orthogonal protecting groups, but it was also expected to pose serious solubility and purification problems at the stage of cycle modification. It was therefore decided to introduce this functionality before cyclization.

The above considerations led to the simple retrosynthetic analysis of the target macrocycles **1**–**3** shown in Figure 2, leading to the key building blocks **4**–**7**. Compounds **4**–**7** were considered ideal because they combine the application of reliable Suzuki and Sonogashira cross-coupling protocols with a minimum of easy protecting-group manipulations. Separation and purification of all the intermediates en route to the cycles was to be done by simple preparative gel-permeation chromatography (GPC), exploiting the considerable molecular weight differences of the compounds before and after each coupling step. Macrocycle **1** is the only one of the three target structures that carries two different chromophores. Its synthesis therefore required a desymmetri-

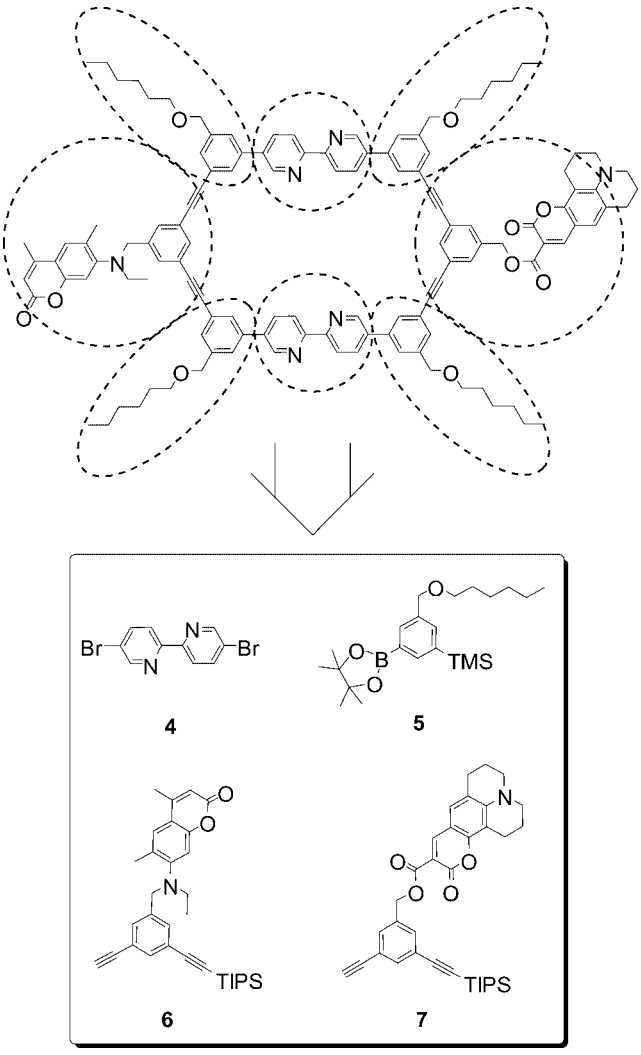


Figure 2. Exemplary assembly of macrocycle **1** from the four building blocks **4**–**7** according to strategic considerations described in the text.

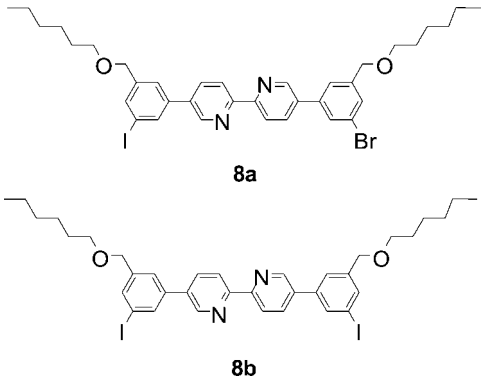


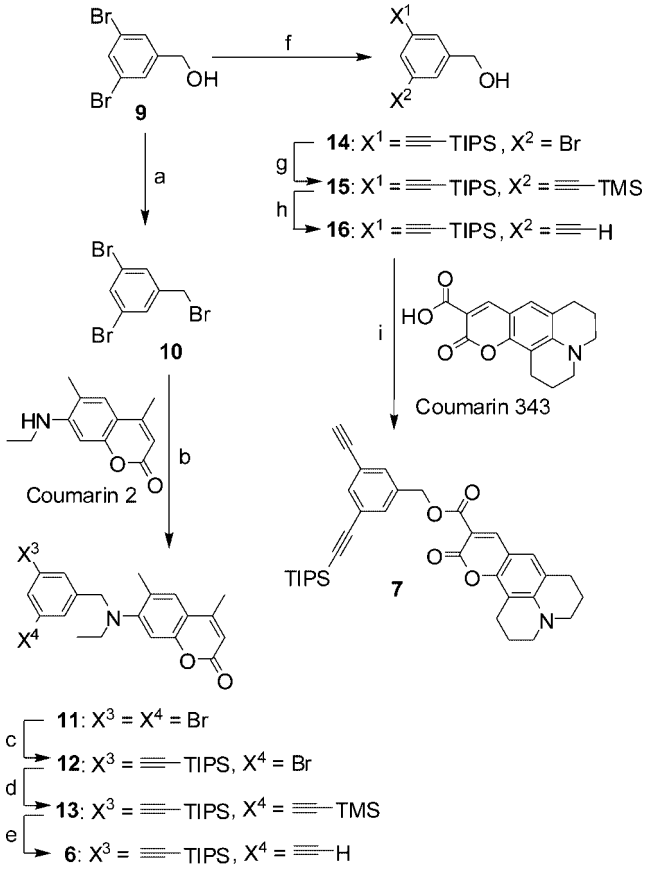
Figure 3. Chemical structures of an unsymmetrical (**8a**) and symmetrical (**8b**) building block for potential use in the macrocycle synthesis.

zation step. In a previous report,[11] the bpy derivative **8a** (Figure 3) with its iodinated and brominated termini was described. Being already unsymmetrical it looked ideal for the present purpose. However, its accessibility was considered too limited to be integrated at an early stage of a sequence that was supposed to be as simple and straight forward as possible. Its symmetric diiodo analogue **8b**, whose synthesis has been reported on the 10 g scale,[11] was chosen instead (Figure 3). Although its desymmetrization required a statistical reaction step, it was nevertheless attractive because both products of a statistical reaction a) would be useful for subsequent steps and b) should be easily separable because of their molecular weight difference.

Synthesis of the Building Blocks and Stepwise Assembly

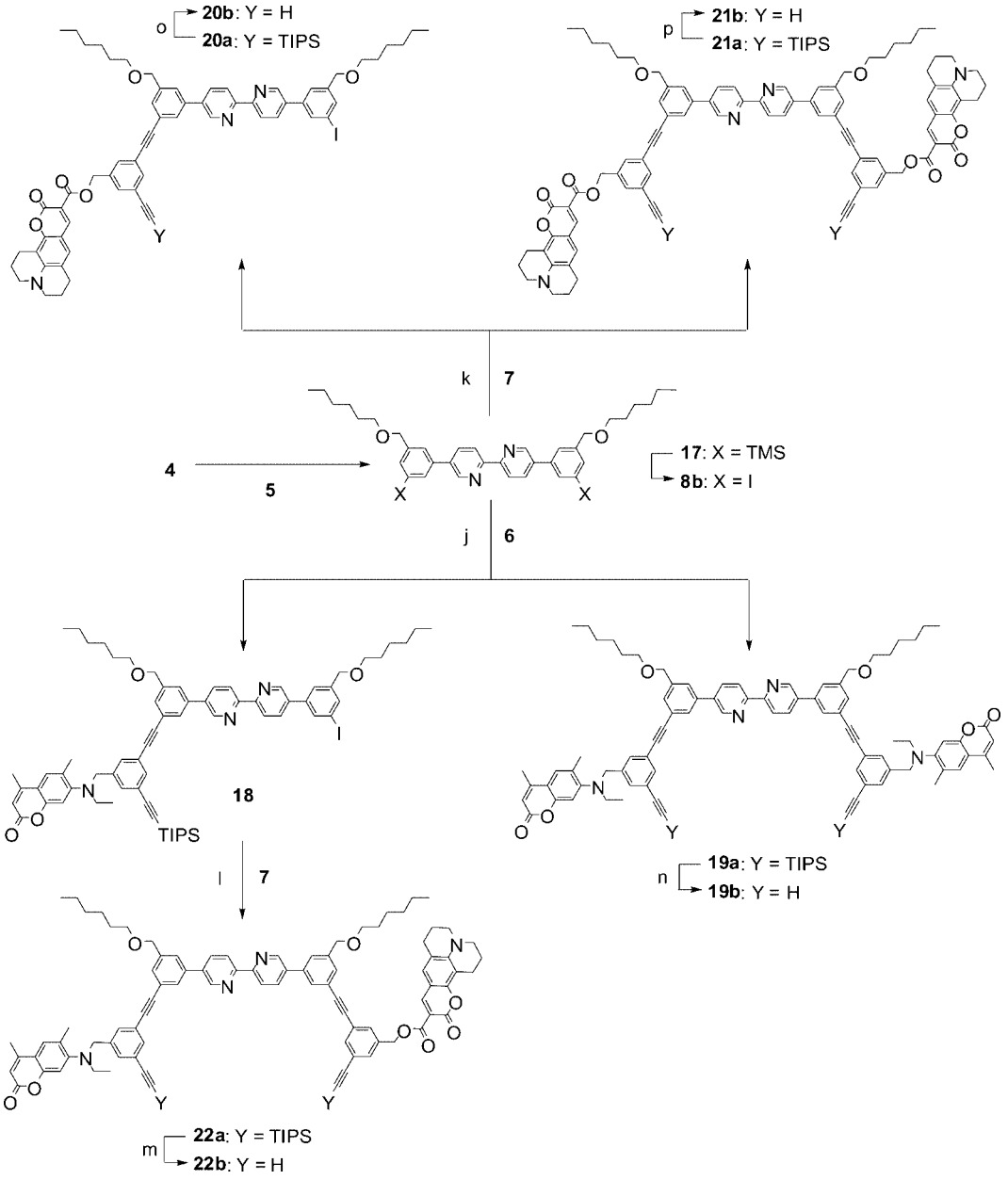
The building blocks **4** and **5** were prepared in accordance with reported procedures.[12,13] The sequences leading to the other two building blocks **6** and **7** are shown in Scheme 1. The benzylic alcohol **9**[14] was first converted into bromide **10** whose reaction with Cm2 gave **11**.[15] This compound was then subjected to successive Sonogashira coupling reactions to finally furnish building block **6** via the intermediates **12** and **13**. Purification of each product was performed mainly by silica gel chromatography. The Cm2 moiety was stable under the reaction conditions. Building block **7** was obtained by first performing a few cross-coupling reactions to give **16** via **14** and **15** followed by the esterification of **16** with Cm343 under Mitsunobu conditions. The benzylic alcohol **14** was used in the subsequent steps without protection. Note the ease with which both coumarins are introduced into the respective building blocks. This opens up numerous future options for cycle decoration.

The stepwise assembly of the four building blocks **4**–**7** is shown in Scheme 2. Building block **4** was first subjected to a two-fold Suzuki cross-coupling reaction with 2 equivalents of **5** to afford **17**,[11] whose TMS groups served as "place holders" for the iodides of **8b**. The conversion of **17** into **8b** proceeded virtually quantitatively.[16] Diiodide **8b** was then used in statistical Sonogashira-type cross-coupling reactions with 1 equivalent of either building block **6** or **7**. This led to mixtures of the mono- and dicoupled products in one pot (**18** plus **19a** and **20a** plus **21a**, respectively) which could be easily separated by GPC. The isolated yields were 45% **18** and 25% **19a** as well as 39% **20a** and 11% **21a**. Of the two monocoupled products **18** and **20a**, the former was selected to generate **22a**, the building block which carries both coumarins 2 and 343 in one molecule. For this purpose, **18** was treated with building block **7** which readily gave **22a** in a yield of 94%. In order to convert compounds **19a**, **21a**, and **22a** into precursors for bimolecular cyclization with **8b**, their triisopropylsilyl (TIPS) protecting groups were removed with tetrabutylammonium fluoride (TBAF). In contrast to **19b** and **22b**, the solubility of **21b** turned out to be too low, not only for its purification and characterization, but, more importantly, for use in the cyclization experiments. Thus, the plan was changed and the readily soluble compound **20b**, which is an AB-type building block, was employed instead as a precursor for macrocycle **3**. The other cycles **1** and **2** were synthesized as intended (see below). All the products were purified mainly by preparative GPC [BioRAD, Biogel SX1 with dichloromethane/hexane (2:1) as eluent]. Compounds **19b**, **20b**, and **22b** were prepared on the 0.1–1 g scale.



Scheme 1. Synthesis of building blocks **6** and **7**. Reagents and conditions: a) PPh_3, CBr_4, THF, room temp., 96%; b) K_2CO_3, MeCN, reflux, 62%; c) TIPS-acetylene, $[Pd(PPh_3)_4]$, NEt_3, 80 °C, 56%; d) TMS-acetylene, $[Pd(PPh_3)_4]$, CuI, NEt_3, 80 °C, 85%; e) Amberlyst A26, CH_2Cl_2/MeOH (1:1), room temp., 79%; f) TIPS-acetylene, $[Pd(PPh_3)_4]$, NEt_3, 80 °C, 56%; g) TMS-acetylene, $[Pd(PPh_3)_4]$, CuI, NEt_3, 80 °C, 99%; h) NaOH (aq), CH_2Cl_2/MeOH (1:1), room temp., 86%; i) PPh_3, DEAD, THF, room temp., 39%.

Note that tetrakis(triphenylphosphane)palladium(0) was employed here as the sole catalyst in the "Sonogashira" reactions.[17] No copper(I) iodide was added.[18] Nevertheless, the coupling reactions proceeded very well to afford the products in competitive yields over prolonged reaction times. This measure was adopted for several reasons. First, it facilitated the work up. When CuI was present, some of it bonded to the bpy units and had to be removed by treating the crude mixtures with potassium cyanide. Secondly, undesired side-reactions such as homocoupling between terminal ethynyl groups were reduced to the degree that they were not observed (by TLC and NMR).[19] Thirdly, the overall functional group tolerance was expected to be higher. In order to test the impact of copper salts on the

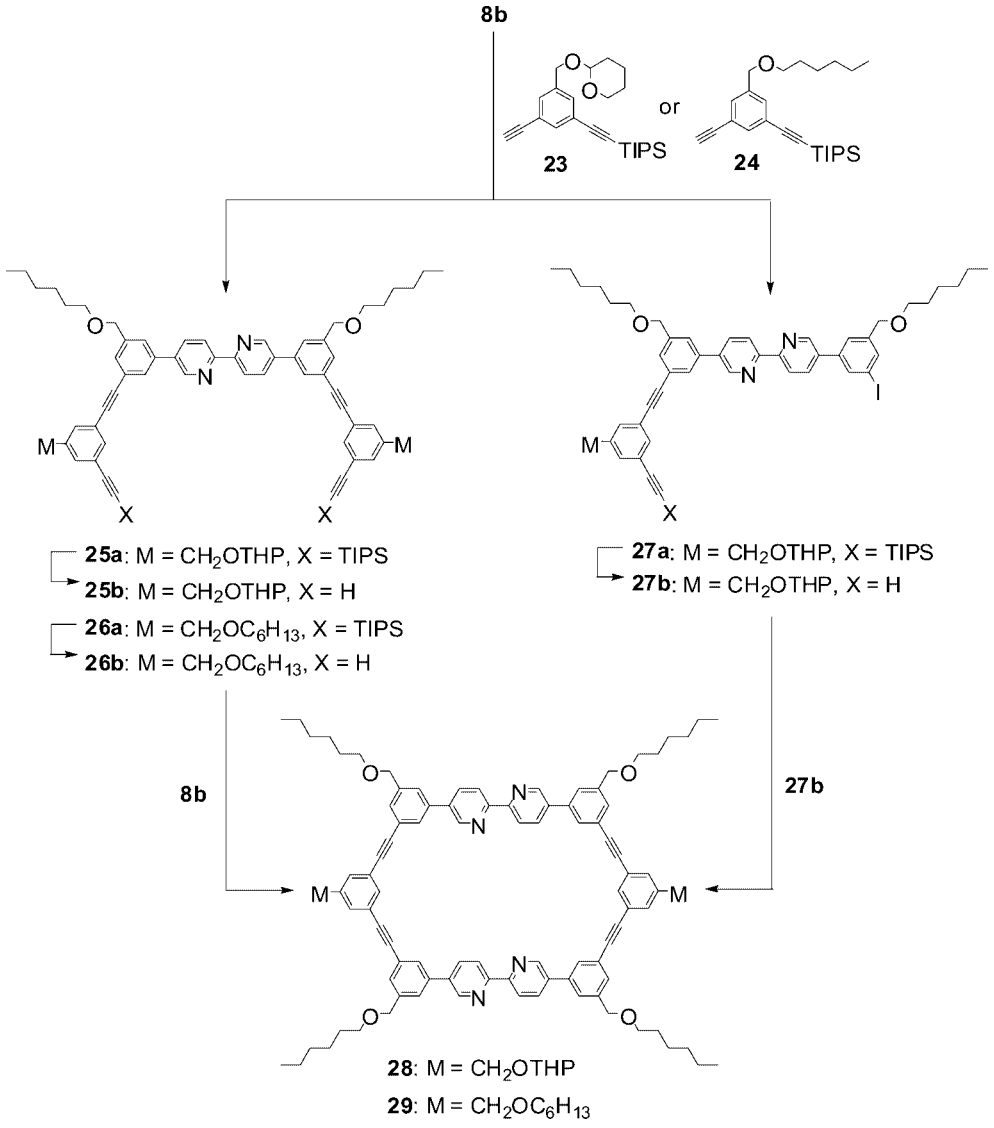


Scheme 2. Stepwise assembly of building blocks **4**–**7** to yield macrocycle precursors **8b**, **22b**, **19b**, and **20b**. Reagents and conditions: j) $[Pd(PPh_3)_4]$, NEt_3/THF (1:1), 60 °C, 45% **18** and 25% **19a**; k) $[Pd(PPh_3)_4]$, NEt_3/THF (2:1), 60 °C, 39% **20a** and 11% **21a**; l) $[Pd(PPh_3)_4]$, NEt_3/THF (1:1), 60 °C, 94%; m) TBAF, AcOH, THF, room temp., 75%; n) TBAF, AcOH, THF, room temp., 76%; o) TBAF, AcOH, THF, room temp., 81%; p) TBAF, AcOH, THF, room temp., **21b** not isolated.

cyclization reaction (see below) the model precursors **25b**, **26b**, and **27b** were synthesized according to the sequence shown in Scheme 3. All the steps involved were similar to those described above.

Macrocyclization

Before the precursors **19b**, **22b**, and **8b** as well as **20b** were cyclized to the target cycles **1**–**3**, model cyclization reactions were performed in order to optimize the conditions. The factors considered were the presence and absence of CuI, the stoichiometric ratio of $[Pd(PPh_3)_4]$ to the cyclic precursors, and the temperature. The model reaction between **25b** and **8b** was studied in quite some detail including by direct monitoring by analytical GPC measurements (see electronic Supporting Information). First the reaction was run in the presence and absence of CuI at 60 °C. As can be seen from the GPC elution curves of the chloroform-soluble part[20] of the crude products in Figure 4, less oligomers were formed if there was no CuI present. The same holds true for the entire reaction course, as was proven by direct monitoring of the reaction. In accordance with this the isolated yields of cycle **28** were 13 and 30%, respectively. As expected, the reaction times differed considerably.[17b] In the presence of CuI approximately 90% consumption (as calculated from the GPC curve) of the two substrates



Scheme 3. Synthesis of model precursors **25b**, **26b**, and **27b** and their cyclization to **28** and **29**.

($[1.4\ mM]_o$) was achieved within 1 d, whereas in its absence nearly 3 d were required. If the same reaction was performed in the absence of CuI at 45 °C instead of at 60 °C, completion of the reaction required more than 7 d and an overall increase of oligomeric side-products was observed although the higher molar mass oligomers decreased. In fact, the isolated yield of **28** after 7 d was lower (22%). Therefore all further reactions were carried out at 60 °C.

Next the impact of the stoichiometry of the palladium catalyst precursor was tested at 60 °C. Upon increasing $[Pd(PPh_3)_4]$ from 2.7 to 10 mol-% per iodo group of **8b**, the reaction without CuI finished within 1 d and, more importantly, furnished cycle **28** in an isolated yield of 42%. In agreement with this rather surprising and positive finding, the GPC elution curve of this latter experiment (Figure 4, c) shows a grossly reduced amount of oligomeric side-products. Note that the cycle and some oligomers eluted simultaneously which rendered an assessment of product composition by visual inspection of GPC curves difficult. Finally, the other building blocks, **26b** and **27b**, were also tested. The cyclization of **26b** with **8b** under the improved conditions [10 mol-% $[Pd(PPh_3)_4]$, absence of CuI, 60 °C] afforded the corresponding macrocycle **29** in 46% isolated yield and the cyclic dimerization of **27b** gave cycle **28** in 42% yield. All the cyclization experiments described so far were reproduced several times and can therefore be considered representative. Given the fact that not only the substrates, but also the modes of cyclization, were different, it seems that a more general solution to the high-yielding cyclization of such precursors has been discovered. The yields reported here are amongst the highest ever for comparable cyclization reactions.[1f,21] Cycles **28** and **29** were prepared on relatively small scales of 67 and 116 mg, respectively.

Having improved the cyclization reactions with the help of model reactions, these conditions were applied to the building blocks **19b**, **22b**, **8b**, as well as **20b**. The first two are AA-type building blocks requiring the BB-type counter-

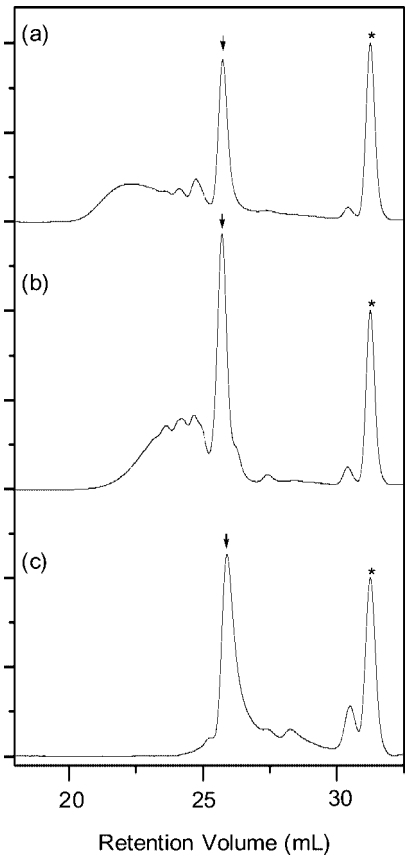
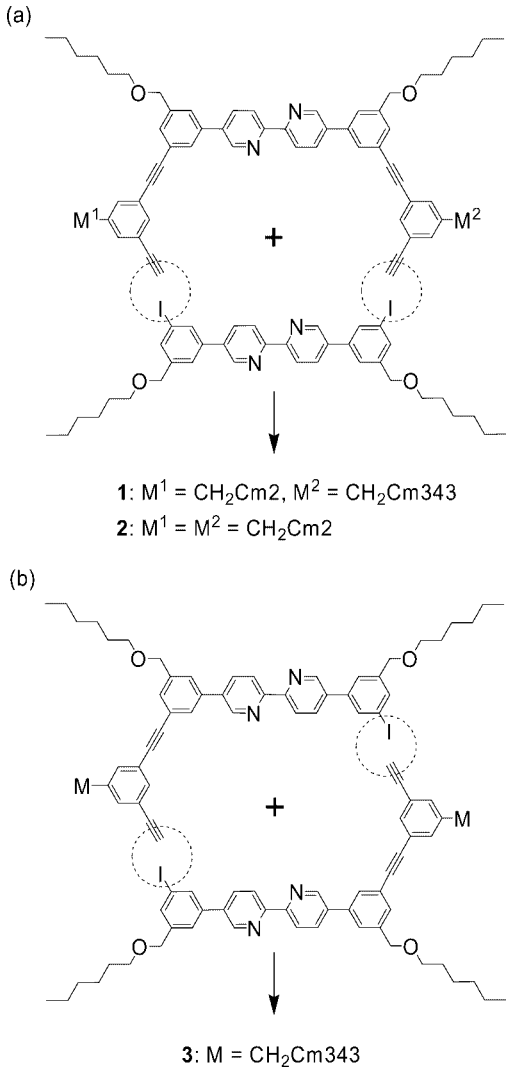


Figure 4. GPC elution curves of the Sonogashira coupling reactions after 3 d between the AA-type building block **25b** and the BB-type counterpart **8b** with 2.7 mol-% $[Pd(PPh_3)_4]$ per iodo group of **8b** in the presence (a) and absence (b) of 2 mol-% of CuI per iodo group of **8b** and with 10 mol-% of $[Pd(PPh_3)_4]$ per iodo group of **8b** and no CuI present (c). The signal of the internal standard toluene is marked (*). The signal due to cycle is marked with an arrow. It superimposes low intensity signals of oligomers. All elution curves were obtained under as identical conditions as possible.



Scheme 4. Two different modes of cyclization using (a) AA- and BB-type precursors (**22b** and **8b** or **19b** and **8b**) and (b) AB-type precursor **20b**.

part **8b** for cyclization, whereas the last precursor is a self-complementing AB-type building block which did not need a complement (Scheme 4). All precursors were used in the same concentrations ([**22b**] = [**19b**] = [**8b**] = 1.4 mM; [**20b**] = 2.8 mM) in a THF/triethylamine (1:1, v/v) mixed solvent. The reactions were carried out at 60 °C under nitrogen for 3 d with 10 mol-% of the $[Pd(PPh_3)_4]$ catalyst precursor per iodide. The cycles **1**–**3** were purified by preparative recycling GPC (see Exptl. Sect.) and obtained in yields of 32, 37, and 22%, respectively, as analytically pure materials on the 100, 80 and 30 mg scale, respectively. The lower yield of cycle **3** may be attributed to its rather low solubility; only a few milligrams of **3** are soluble in 1 mL of chloroform. The structures of the macrocycles **1** and **2** were identified by ^1H and ^{13}C NMR spectroscopy and high-resolution matrix-assisted laser-desorption ionization (MALDI) mass spectrometry. For macrocycle **3**, no reasonable ^{13}C NMR spectrum could be recorded. ^1H NMR spectra of macrocycles **1**–**3** are shown in Figure 5 to prove the structural integrity of the macrocycles and to visualize the degree of purity.

Conclusions and Outlook

A synthetic strategy to the shape-persistent macrocycles **1**–**3** has been presented that puts focus on high-yielding, simple-to-perform, and easy-to-work-up steps. It uses an approach in which the macrocycles are obtained from relatively large precursors that already carry all the required functionalities. The key work-up procedure is preparative gel-permeation chromatography operated either by hand with an open column or in recycling high-pressure equipment. In both cases high loadings of 1 g and 300 mg of crude material, respectively, could be separated. This not only led to extremely efficient work up, but also allowed the required desymmetrization steps to be accomplished by statistical reactions. The strategy is rather flexible. It involves the simple benzylic bromide **10** and the benzylic alcohol **14** which can in principle end up as any of the corner units in a targeted cycle. They are therefore natural sites for anchoring functional units and are desirable as peripheral decorations of the final cycles. In this study they were

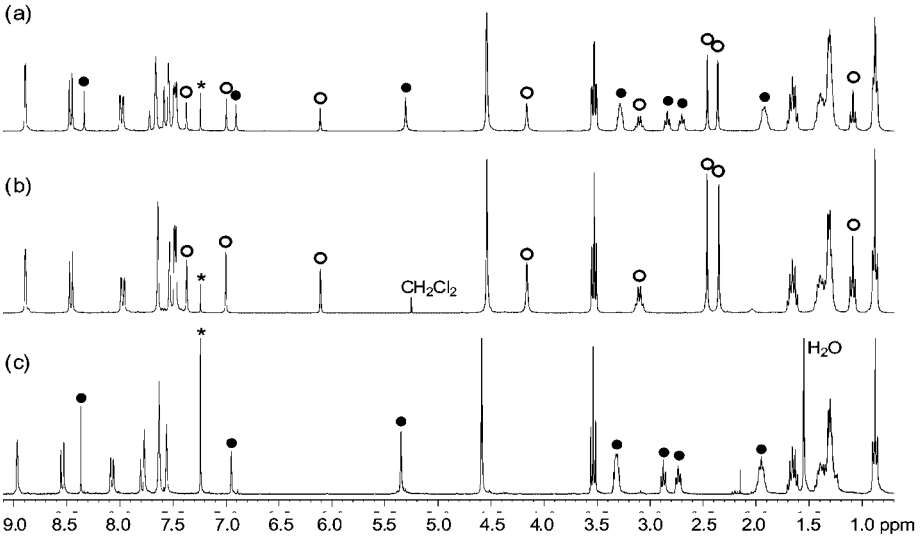


Figure 5. ^{1}H NMR spectra of macrocycles (a) **1**, (b) **2**, and (c) **3**. The chloroform signal at δ = 7.24 is marked (*). The signals due to lateral side-groups including the Cm2 and Cm343 moieties are marked with empty (○) and filled (●) circles, respectively.

introduced into two opposite corners and used for attaching the coumarin dyes Cm2 (bromide **10**) and Cm343 (hydroxide **14**) by simple nucleophilic displacement or Mitsunobu esterification reactions, respectively. Besides realizing this considerable amount of design flexibility, which will have an impact on future applications of such cycles, the cyclization efficiency was investigated in quite some detail in order to find optimum conditions. Given the overall effort associated with the multistep synthesis of shape-persistent macrocycles, the commonly observed cyclization yields of 15–25% were considered unsatisfactory.[1f] If no special effects are operative, most of the tediously prepared cyclization precursors convert either into linear oligomers or unwanted larger cycles, including those with even more complex topologies like catenanes. In this study, the cyclization step is based on Sonogashira cross-coupling reactions. For several precursor combinations the yields per cyclization step could be reproducibly increased from the usual range to 30–45% just by avoiding the use of CuI and by employing 10 mol-% of [$Pd(PPh_3)_4$] per iodinated carbon atom of the cyclization precursors.

Experimental Section

General: All the reactions were carried out under nitrogen by using standard Schlenk techniques and dry solvents. Diethyl ether, toluene, and THF were distilled under nitrogen over sodium/benzophenone, dichloromethane and triethylamine were distilled under nitrogen over CaH_2, and acetonitrile was distilled under nitrogen over P_2O_5. All the reagents were purchased from Acros, Aldrich, or Fluka, and used without further purification. *n*BuLi was used as a 1.6 M solution in *n*-hexane. The palladium catalyst was prepared following the literature procedure[22] and stored under nitrogen at room temperature. Compounds **4**,[12] **5**,[13] **8b**,[11] **9**,[14] **17**[11], 1-ethynyl-3-[(tetrahydropyran-2-yloxy)methyl]-5-[2-(triisopropylsilyl)ethynyl]benzene[23] (**23**), and 1-ethynyl-3-(1-hexyloxymethyl)-5-[2-(triisopropylsilyl)ethynyl]benzene[24] (**24**) were prepared according to literature procedures. Compound **10**[25] is known, but was prepared by another procedure. Purification of the products by column chromatography was performed by using Merck silica gel Si60 (particle size 40–63 μm), BIO-RAD Bio-Beads S-X1 [200–400 mesh, *n*-hexane/dichloromethane (1:2) as eluent, a glass column of 3.5 × 120 cm in which ca. 170 g of Bio-Beads were immersed in the eluent was packed by gravity, flow rate 0.7 mL/min] or preparative recycling GPC (Japan Analytical Industry Co. Ltd., LC 9101) equipped with a pump (Hitachi L-7110, flow rate 3.5 mL/min), a degasser (GASTORR-702), a RI detector (Jai RI-7), a UV detector (Jai UV-3702, λ = 254 nm), and two columns (Jaigel 2H and 2.5 H, 20 × 600 mm for each) using chloroform as eluent at room temperature. NMR spectra were recorded with a Bruker AM spectrometer (^{1}H: 300 MHz; ^{13}C: 75.5 MHz) at room temperature using [D]-chloroform as solvent. The signal from the solvent was used as the internal standard for the chemical shifts (^{1}H: δ = 7.24 ppm; ^{13}C: δ = 77.00 ppm). High-resolution mass spectroscopy (HRMS) analyses were performed by the MS service of the laboratory for organic chemistry at ETH Zürich using an electron-ionization (EI) MS spectrometer (Micromass AutoSpec-Ultima) or a FTMALDI MS spectrometer (IonSpec Ultra Instrument). 3-Hydroxypicolinic acid (3-HPA) or *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) was used as matrix. Analytical GPC measurements were performed with a Viscotek GPC-System equipped with a pump and a degasser (GPC_{max} VE2001, flow rate 1.0 mL/min), RI detector (302 TDA), and three columns (2 × PL-Gel Mix-C and 1 × ViscoGEL GMHHRN 18055, 7.5 × 300 mm for each) using chloroform as eluent at 35 °C.

3,5-Dibromobenzyl Bromide (10): A solution of triphenylphosphane (2.17 g, 8.27 mmol) in dry THF (10 mL) was added dropwise to a solution of **9** (1.76 g, 6.62 mmol) and carbon tetrabromide (2.74 g, 8.27 mmol) in dry THF (16 mL). The mixture was stirred at room temperature for 16 h followed by dropwise addition of methanol (1 mL). The mixture was evaporated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate, 10:1) to afford 2.09 g of **10** (96%).

***N*-(3,5-Dibromobenzyl)coumarin 2 (11):** A mixture of coumarin 2 (2.54 g, 11.7 mmol), **10** (4.90 g, 14.9 mmol), and K_2CO_3 (4.03 g, 29.2 mmol) in dry acetonitrile (300 mL) was stirred under reflux

for 5 d. After cooling to room temperature and filtration, the filtrate was evaporated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate, 8:1) to afford 3.38 g of **11** (62%). ^{1}H NMR: δ = 7.41 (m, 3 H, phenyl-H), 7.35 (s, 1 H, Cm2), 6.89 (s, 1 H, Cm2), 6.06 (d, 1 H, Cm2), 4.13 (s, 2 H, benzyl-H), 3.04 (q, ^3J = 7.0 Hz, 2 H, Cm2), 2.39 (s, 3 H, Cm2), 2.31 (d, 3 H, Cm2), 1.05 (t, ^3J = 7.0 Hz, 3 H, Cm2) ppm. ^{13}C NMR: δ = 160.7, 152.4, 152.0, 151.8, 142.3, 132.1, 129.2, 129.0, 126.3, 122.5, 114.6, 112.2, 108.5, 54.8, 46.5, 18.1, 18.0, 11.3 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 463.9861; found 463.9671.

***N*-{3-Bromo-5-[2-(triisopropylsilyl)ethynyl]benzyl}coumarin 2 (12):** TIPS-Acetylene (1.6 mL, 7.2 mmol) and $[Pd(PPh_3)_4]$ (125 mg, 0.11 mmol) were added to a carefully degassed mixture of **11** (3.37 g, 7.24 mmol) and dry triethylamine (40 mL). The mixture was stirred at 80 °C for 2 d. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 20:1) to afford 2.30 g of **12** (56%). ^{1}H NMR: δ = 7.41, 7.38, 7.30 and 7.27 (4 s, 4 H, phenyl-H and Cm2), 6.86 (s, 1 H, Cm2), 6.05 (s, 1 H, Cm2), 4.08 (s, 2 H, benzyl-H), 3.00 (q, ^3J = 7.0 Hz, 2 H, Cm2), 2.35 (s, 3 H, Cm2), 2.30 (s, 3 H, Cm2), 1.06 (s, 21 H, TIPS), 0.99 (t, ^3J = 7.0 Hz, 3 H, Cm2) ppm. ^{13}C NMR: δ = 161.2, 152.9, 152.4, 152.1, 140.5, 133.2, 130.7, 130.0, 129.4, 126.5, 125.2, 122.0, 114.9, 112.6, 109.1, 105.1, 92.3, 55.5, 46.6, 18.5, 18.4, 18.3, 11.5, 11.1 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 566.2099; found 566.1920.

***N*-{3-[2-(Triisopropylsilyl)ethynyl]-5-[2-(trimethylsilyl)ethynyl]-benzyl}coumarin 2 (13):** CuI (12 mg, 0.061 mmol), $[Pd(PPh_3)_4]$ (70 mg, 0.061 mmol), and TMS-acetylene (0.86 mL, 6.1 mmol) were added to a carefully degassed mixture of **12** (2.29 g, 4.04 mmol) and dry triethylamine (20 mL). The flask was filled with nitrogen gas and sealed. The reaction was performed at 80 °C for 18 h. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 20:1) to afford 2.00 g of **13** (85%). ^{1}H NMR: δ = 7.41 (m, 1 H, phenyl-H), 7.33 (m, 1 H, phenyl-H), 7.31 (m, 2 H, phenyl-H and Cm2), 6.88 (s, 1 H, Cm2), 6.07 (s, 1 H, Cm2), 4.09 (s, 2 H, benzyl-H), 3.01 (q, ^3J = 7.0 Hz, 2 H, Cm2), 2.36 (s, 3 H, Cm2), 2.32 (s, 3 H, Cm2), 1.07 (s, 21 H, TIPS), 1.01 (t, ^3J = 7.0 Hz, 3 H, Cm2), 0.21 (s, 9 H, TMS) ppm. ^{13}C NMR: δ = 161.3, 153.2, 152.5, 152.1, 138.7, 134.0, 131.5, 131.1, 129.4, 126.5, 123.7, 123.3, 114.9, 112.6, 109.1, 105.9, 104.0, 94.9, 91.3, 55.8, 46.5, 18.53, 18.47, 18.38, 11.6, 11.2, –0.2 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 584.3380; found 584.3363.

***N*-{3-Ethynyl-5-[2-(triisopropylsilyl)ethynyl]benzyl}coumarin 2 (6):** Amberlyst A26 (1.70 g) was added, along with methanol (20 mL) dropwise, to a solution of **13** (2.00 g, 3.42 mmol) in dry dichloromethane (20 mL). The mixture was stirred at room temperature for 2 d. After filtration, the filtrate was evaporated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate, 8:1) to afford 1.39 g of **6** (79%). ^{1}H NMR: δ = 7.38 (m, 1 H, phenyl-H), 7.33 (m, 1 H, phenyl-H), 7.30 (m, 1 H, phenyl-H), and 7.26 (s, 1 H, Cm2), 6.83 (s, 1 H, Cm2), 6.00 (d, 1 H, Cm2), 4.06 (s, 2 H, benzyl-H), 3.02 (s, 1 H, ethynyl-H), 2.97 (q, ^3J = 7.0 Hz, 2 H, Cm2), 2.32 (s, 3 H, Cm2), 2.25 (d, 3 H, Cm2), 1.04 (s, 21 H, TIPS), 0.97 (t, ^3J = 7.0 Hz, 3 H, Cm2) ppm. ^{13}C NMR: δ = 161.0, 152.9, 152.3, 152.0, 138.7, 134.0, 131.6, 131.0, 129.3, 126.4, 123.6, 122.3, 114.7, 112.4, 108.9, 105.7, 91.4, 82.5, 77.8, 55.5, 46.5, 18.4, 18.3, 18.2, 11.5, 11.0 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 512.2985; found 512.2970.

3-Bromo-5-[2-(triisopropylsilyl)ethynyl]benzyl Alcohol (14): TIPS-Acetylene (2.0 mL, 8.9 mmol) and $[Pd(PPh_3)_4]$ (140 mg, 0.12 mmol) wee added to a carefully degassed mixture of **9** (2.16 g, 8.11 mmol) and dry triethylamine (50 mL). The mixture was stirred at 80 °C for 2 d. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 8:1) to afford 1.67 g of **14** (56%). ^{1}H NMR: δ = 7.50 (m, 1 H, phenyl-H), 7.40 (m, 1 H, phenyl-H), 7.34 (m, 1 H phenyl-H), 4.57 (s, 2 H, benzyl-H), 2.57 (s, 1 H, OH), 1.11 (s, 21 H, TIPS) ppm. ^{13}C NMR: δ = 142.8, 133.6, 129.6, 128.7, 125.4, 122.1, 105.2, 92.4, 63.8, 18.6, 11.2 ppm. HRMS (EI): *m*/*z* calcd. for $C_{18}H_{27}BrOSi$ $[M]^{+\cdot}$ 366.1015; found 366.1007.

3-[2-(Triisopropylsilyl)ethynyl]-5-[2-(trimethylsilyl)ethynyl]benzyl Alcohol (15): CuI (13 mg, 0.068 mmol), $[Pd(PPh_3)_4]$ (79 mg, 0.068 mmol) and TMS-acetylene (0.96 mL, 6.8 mmol) were added to a carefully degassed mixture of **14** (1.67 g, 4.55 mmol) and dry triethylamine (25 mL). The flask was filled with nitrogen gas and sealed. The reaction was performed at 80 °C for 15 h. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 8:1) to afford 1.74 g of **15** (99%). ^{1}H NMR: δ = 7.47 (m, 1 H, phenyl-H), 7.37 (m, 1 H, phenyl-H), 7.34 (m, 1 H, phenyl-H), 4.55 (s, 2 H, benzyl-H), 3.02 (br., 1 H, OH), 1.11 (s, 21 H, TIPS), 0.23 (s, 9 H, TMS) ppm. ^{13}C NMR: δ = 141.2, 134.2, 130.1, 129.9, 123.8, 123.4, 105.9, 104.0, 94.8, 91.2, 63.9, 18.6, 11.2, –0.2 ppm. HRMS (EI): *m*/*z* calcd. for $C_{23}H_{36}OSi_2$ $[M]^{+\cdot}$ 384.2305; found 384.2296.

3-Ethynyl-5-[2-(triisopropylsilyl)ethynyl]benzyl Alcohol (16): A few drops of 2 N NaOH (aq) were added to a solution of **15** (2.72 g, 7.07 mmol) in dichloromethane/methanol (1:1, 60 mL) . The mixture was stirred at room temperature for 2 d and then passed through silica gel to remove NaOH. After evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 10:1) to afford 1.90 g of **16** (86%). ^{1}H NMR: δ = 7.49 (m, 1 H, phenyl-H), 7.40 (m, 1 H, phenyl-H), 7.35 (m, 1 H, phenyl-H), 4.55 (s, 2 H, benzyl-H), 3.07 (s, 1 H, ethynyl-H), 2.89 (s, 1 H, OH), 1.11 (s, 21 H, TIPS) ppm. ^{13}C NMR: δ = 141.2, 134.5, 130.4, 130.0, 123.9, 122.4, 105.8, 91.6, 82.6, 77.8, 63.9, 18.6, 11.2 ppm. HRMS (EI): *m*/*z* calcd. for $C_{20}H_{28}OSi$ $[M]^{+\cdot}$ 312.1909; found 312.1903.

Coumarin 343 3-Ethynyl-5-[2-(triisopropylsilyl)ethynyl]benzyl Ester (7): A 40% toluene solution of diethyl azodicarboxylate (DEAD) (2.8 mL, 6.1 mmol) was added dropwise to a solution of **16** (1.82 g, 5.82 mmol), triphenylphosphane (1.59 g, 6.08 mmol) and coumarin 343 (1.54 g, 5.40 mmol) in dry THF (50 mL) at room temperature. The mixture was stirred at room temperature for 1 d. The temperature was slowly elevated and kept at 50 °C for another 1 d. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 2:1) to afford 1.21 g of **7** (39%). ^{1}H NMR: δ = 8.25 (s, 1 H, Cm343), 7.53 (m, 1 H, phenyl-H), 7.51 (m, 1 H, phenyl-H), 7.49 (m, 1 H, phenyl-H), 6.85 (s, 1 H, Cm343), 5.23 (s, 2 H, benzyl-H), 3.27 (m, 4 H, Cm343), 3.06 (s, 1 H, ethynyl-H), 2.80 (t, 2 H, Cm343), 2.68 (t, 2 H, Cm343), 1.90 (m, 4 H, Cm343), 1.09 (s, 21 H, TIPS) ppm. ^{13}C NMR: δ = 163.9, 158.4, 153.5, 149.3, 148.7, 136.9, 135.1, 131.8, 131.5, 127.0, 124.0, 122.6, 119.2, 107.4, 106.2, 105.56, 105.51, 91.9, 82.4, 78.0, 65.2, 50.2, 49.8, 27.3, 21.0, 20.0, 19.9, 18.6, 11.2 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 580.2883; found 580.2867.

Compounds 18 and 19a: $[Pd(PPh_3)_4]$ (37 mg, 0.032 mmol) was added to a carefully degassed mixture of **6** (820 mg, 1.60 mmol) and **8b** (1.26 g, 1.60 mmol) in dry THF/triethylamine (1:1, 52 mL).

The mixture was stirred at 60 °C for 1 d. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by GPC (Bio-RAD SX1) to afford 844 mg of **18** (45%) and 625 mg of **19a** (25%). Compound **18**: ^{1}H NMR: δ = 8.93 (d, ^4J = 2.4 Hz, 1 H, pyridinyl-H), 8.86 (d, ^4J = 2.4 Hz, 1 H, pyridinyl-H), 8.52 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.04 (dd, ^4J = 2.4 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.98 (dd, ^4J = 2.4 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.86 (m, 1 H, phenyl-H), 7.71 (m, 2 H, phenyl-H), 7.59 (m, 1 H, phenyl-H), 7.56–7.52 (m, 3 H, phenyl-H), 7.46 (m, 1 H, phenyl-H), 7.36 (m, 1 H, phenyl-H), 7.34 (s, 1 H, Cm2), 6.93 (s, 1 H, Cm2), 6.10 (d, 1 H, Cm2), 4.56 [s, 2 H, benzyl(OC_6H_{13})-H], 4.49 [s, 2 H, benzyl(OC_6H_{13})-H], 4.15 [s, 2 H, benzyl(Cm2)-H], 3.50 (m, 4 H, α-CH_2), 3.06 (q, 2 H, Cm2), 2.40 (s, 3 H, Cm2), 2.35 (d, 3 H, Cm2), 1.63 (m, 4 H, β-CH_2), 1.42–1.23 (m, 12 H, δ-, γ-, ε-CH_2), 1.11 (s, 21 H, TIPS), 1.05 (t, 3 H, Cm2), 0.87 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 161.3, 154.6, 154.3, 153.2, 152.6, 152.1, 147.3, 141.9, 140.2, 139.5, 138.9, 137.7, 136.0, 135.7, 135.4, 135.3, 135.0, 134.9, 133.9, 131.5, 130.8, 130.3, 129.5, 129.2, 126.5, 126.1, 125.3, 123.92, 123.87, 123.3, 121.2, 121.1, 115.0, 112.7, 109.2, 105.9, 95.0, 91.6, 89.4, 89.1, 72.1, 71.6, 71.0, 70.9, 55.9, 46.6, 31.61, 31.60, 29.65, 29.61, 25.82, 25.80, 22.56, 22.55, 18.6, 18.5, 14.0, 11.6, 11.2 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for [M + H]$^+$ 1172.520; found 1172.521. Compound **19a**: ^{1}H NMR: δ = 8.93 (d, ^4J = 2.2 Hz, 2 H, pyridinyl-H), 8.54 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.04 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.71 (m, 2 H, phenyl-H), 7.59 (m, 2 H, phenyl-H), 7.53 (m, 4 H, phenyl-H), 7.46 (m, 2 H, phenyl-H), 7.35 (m, 2 H, phenyl-H), 7.33 (s, 2 H, Cm2), 6.92 (s, 2 H, Cm2), 6.09 (m, 2 H, Cm2), 4.55 [s, 4 H, benzyl(OC_6H_{13})-H], 4.14 [s, 4 H, benzyl(Cm2)-H], 3.51 (t, 4 H, α-CH_2), 3.05 (q, 4 H, Cm2), 2.40 (s, 6 H, Cm2), 2.33 (d, 6 H, Cm2), 1.63 (m, 4 H, β-CH_2), 1.43–1.20 (m, 12 H, δ-, γ-, ε-CH_2), 1.10 (s, 42 H, TIPS), 1.04 (t, 6 H, Cm2), 0.86 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 161.2, 154.5, 153.2, 152.5, 152.1, 147.4, 140.2, 138.9, 137.8, 135.6, 135.3, 133.8, 131.5, 130.7, 130.2, 129.4, 129.1, 126.5, 126.0, 123.9, 123.8, 123.3, 121.1, 114.9, 112.7, 109.2, 105.9, 91.6, 89.4, 89.1, 72.1, 70.9, 55.9, 46.6, 31.6, 29.6, 25.8, 22.5, 18.55, 18.53, 18.4, 14.0, 11.6, 11.2 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for [M + H]$^+$ 1155.898; found 1155.894.

Compound 22a: [$Pd(PPh_3)_4$] (20 mg, 0.017 mmol) was added to a carefully degassed mixture of **18** (364 mg, 0.310 mmol) and **7** (180 mg, 0.310 mmol) in dry THF/triethylamine (1:1, 20 mL). The mixture was stirred at 60 °C for 38 h. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by GPC (Bio-RAD SX1) to afford 472 mg of **22a** (94%). ^{1}H NMR: δ = 8.91 (s, 2 H, pyridinyl-H), 8.52 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.25 (s, 1 H, Cm343), 8.03 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.70 (m, 2 H, phenyl-H), 7.61 (m, 2 H, phenyl-H), 7.58 (m, 2 H, phenyl-H), 7.52 (m, 3 H, phenyl-H), 7.50 (m, 1 H, phenyl-H), 7.45 (m, 1 H, phenyl-H), 7.34 (m, 1 H, phenyl-H), 7.32 (s, 1 H, Cm2), 6.90 (s, 1 H, Cm2), 6.80 (s, 1 H, Cm343), 6.06 (d, 1 H, Cm2), 5.26 [s, 2 H, benzyl(Cm343)-H], 4.54 [s, 4 H, benzyl(OC_6H_{13})-H], 4.13 [s, 2 H, benzyl(Cm2)-H], 3.50 (t, 4 H, α-CH_2), 3.23 (m, 4 H, Cm343), 3.04 (q, 2 H, Cm2), 2.76 (t, 2 H, Cm343), 2.64 (t, 2 H, Cm343), 2.38 (s, 3 H, Cm2), 2.32 (s, 3 H, Cm2), 1.87 (m, 4 H, Cm343), 1.62 (m, 4 H, β-CH_2), 1.42–1.21 (m, 12 H, δ-, γ-, ε-CH_2), 1.10 (s, 21 H, TIPS), 1.09 (s, 21 H, TIPS), 1.03 (t, 3 H, Cm2), 0.85 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 163.8, 161.2, 158.3, 154.3, 153.3, 153.1, 152.5, 152.1, 149.2, 148.6, 147.3, 140.1, 138.9, 137.66, 137.62, 136.9, 135.53, 135.51, 135.3 134.6, 133.8, 131.4, 131.0, 130.7, 130.2, 129.4, 129.0, 126.9, 126.5, 126.0, 124.0, 123.82, 123.75, 123.73, 123.4, 123.2, 121.1, 119.1, 114.8, 112.6, 109.0, 107.3, 106.0, 105.9, 105.6, 105.4, 91.7, 91.5, 89.6, 89.4, 89.0, 88.8, 72.0, 70.82, 70.80, 65.2, 55.7, 50.1, 49.7, 46.6, 31.5, 29.6, 27.2, 25.7, 22.5, 20.9, 19.90, 19.83, 18.53, 18.51, 18.38, 13.9, 11.6, 11.12, 11.11 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for [M + H]$^+$ 1623.888; found 1623.884.

Compound 22b: Acetic acid (45 μL, 0.79 mmol) and, dropwise, a 1.0 M THF solution of TBAF (0.75 mL) were added to a solution of **22a** (600 mg, 0.369 mmol) in dry THF (26 mL). The mixture was stirred at room temperature for 16 h, diluted with chloroform (300 mL), washed successively with sat. aq. $NaHCO_3$/brine (1:1) and with brine, and dried with $MgSO_4$. After evaporation under reduced pressure, the residue was purified by GPC (Bio-RAD SX1) to afford 364 mg of **22b** (75%). ^{1}H NMR: δ = 8.87 (s, 2 H, pyridinyl-H), 8.47 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.22 (s, 1 H, Cm343), 7.98 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.66 (m, 2 H, phenyl-H), 7.60 (m, 1 H, phenyl-H), 7.58–7.47 (m, 9 H, phenyl-H), 7.45 (m, 1 H, phenyl-H), 7.38 (m, 1 H, phenyl-H), 7.29 (s, 1 H, Cm2), 6.87 (s, 1 H, Cm2), 6.78 (s, 1 H, Cm343), 6.04 (d, 1 H, Cm2), 5.24 [s, 2 H, benzyl(Cm343)-H], 4.51 [s, 4 H, benzyl(OC_6H_{13})-H], 4.10 [s, 2 H, benzyl(Cm2)-H], 3.48 (t, 4 H, α-CH_2), 3.21 (m, 4 H, Cm343), 3.09 (s, 1 H, ethynyl-H), 3.08 (s, 1 H, ethynyl-H), 3.01 (q, 2 H, Cm2), 2.74 (t, 2 H, Cm343), 2.62 (t, 2 H, Cm343), 2.35 (s, 3 H, Cm2), 2.29 (s, 3 H, Cm2), 1.84 (m, 4 H, Cm343), 1.60 (m, 4 H, β-CH_2), 1.41–1.19 (m, 12 H, δ-, γ-, ε-CH_2), 1.01 (t, 3 H, Cm2), 0.83 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 163.8, 161.1, 158.2, 154.68, 154.63, 153.3, 153.0, 152.4, 152.1, 149.2, 148.6, 147.4, 140.04, 140.03, 139.0, 137.75, 137.71, 137.0, 135.25, 135.23, 135.0, 134.4, 133.8, 131.3, 131.2, 131.1, 130.12, 130.08, 129.3, 129.0, 126.9, 126.5, 126.0, 123.6, 123.5, 123.3, 122.6, 122.5, 120.8, 119.1, 114.8, 112.5, 108.9, 107.2, 105.9, 105.3, 89.8, 89.6, 88.7, 88.6, 82.5, 82.3, 78.2, 78.0, 72.0, 70.78, 70.77, 65.0, 55.7, 50.0, 49.6, 46.5, 31.5, 29.5, 27.1, 25.7, 22.4, 20.8, 19.84, 19.77, 18.5, 18.3, 13.9, 11.5 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for [M + H]$^+$ 1311.621; found 1311.623.

Compound 19b: Acetic acid (20 μL, 0.35 mmol) and, dropwise, a 1.0 M THF solution of TBAF (0.33 mL) were added to a solution of **19a** (249 mg, 0.160 mmol) in dry THF (12 mL). The mixture was stirred at room temperature for 20 h. After evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 3:2) to afford 150 mg of **19b** (76%). ^{1}H NMR: δ = 8.90 (d, ^4J = 2.3 Hz, 2 H, pyridinyl-H), 8.50 (d, ^3J = 8.4 Hz, 2 H, pyridinyl-H), 8.01 (dd, ^4J = 2.3 Hz, ^3J = 8.4 Hz, 2 H, pyridinyl-H), 7.68 (m, 2 H, phenyl-H), 7.57 (m, 2 H, phenyl-H), 7.51 (m, 4 H, phenyl-H), 7.46 (m, 2 H, phenyl-H), 7.39 (m, 2 H, phenyl-H), 7.31 (s, 2 H, Cm2), 6.90 (s, 2 H, Cm2), 6.07 (m, 2 H, Cm2), 4.53 [s, 4 H, benzyl(OC_6H_{13})-H], 4.11 [s, 4 H, benzyl(Cm2)-H], 3.50 (t, 4 H, α-CH_2), 3.07 (s, 2 H, ethynyl-H), 3.02 (q, 4 H, Cm2), 2.37 (s, 6 H, Cm2), 2.31 (d, 6 H, Cm2), 1.62 (m, 4 H, β-CH_2), 1.42–1.22 (m, 12 H, δ-, γ-, ε-CH_2), 1.02 (t, 6 H, Cm2), 0.84 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 161.3, 154.5, 153.1, 152.5, 152.1, 147.4, 140.1, 139.1, 137.8, 135.4, 135.2, 133.9, 131.4, 131.3, 130.2, 129.4, 129.1, 126.5, 126.1, 123.7, 123.4, 122.5, 121.0, 114.9, 112.6, 109.0, 89.6, 88.8, 82.5, 78.0, 72.0, 70.8, 55.8, 46.5, 31.5, 29.6, 25.7, 22.5, 18.5, 18.4, 13.9, 11.6 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for [M + H]$^+$ 1243.631; found 1243.629.

Compounds 20a and 21a: [$Pd(PPh_3)_4$] (14 mg, 0.012 mmol) was added to a carefully degassed mixture of **7** (346 mg, 0.596 mmol) and **8b** (470 mg, 0.596 mmol) in dry THF/triethylamine (1:2, 30 mL). The mixture was stirred at 60 °C for 43 h. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by GPC (Bio-RAD SX1) to afford 290 mg of **20a** (39%) and 112 mg of **21a** (11%). Compound **20a**: ^{1}H NMR: δ = 8.88 (d, ^4J = 2.3 Hz, 1 H, pyridinyl-H), 8.81 (d, ^4J = 2.3 Hz, 1 H, pyridinyl-H), 8.46 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.24 (s, 1

H, Cm343), 7.99 (dd, ^4J = 2.3 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.91 (dd, ^4J = 2.3 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.82 (m, 1 H, phenyl-H), 7.69 (m, 1 H, phenyl-H), 7.67 (m, 1 H, phenyl-H), 7.61 (m, 1 H, phenyl-H), 7.59 (m, 1 H, phenyl-H), 7.56 (m, 1 H, phenyl-H), 7.53–7.48 (m, 3 H, phenyl-H), 6.80 (s, 1 H, Cm343), 5.25 [s, 2 H, benzyl(Cm343)-H], 4.53 [s, 2 H, benzyl(OC_6H_{13})-H], 4.46 [s, 2 H, benzyl(OC_6H_{13})-H], 3.48 (m, 4 H, α-CH_2), 3.21 (m, 4 H, Cm343), 2.75 (t, 2 H, Cm343), 2.62 (t, 2 H, Cm343), 1.85 (m, 4 H, Cm343), 1.60 (m, 4 H, β-CH_2), 1.41–1.21 (m, 12 H, δ-, γ-, ε-CH_2), 1.10 (s, 21 H, TIPS), 0.84 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 163.8, 158.2, 154.9, 154.6, 153.3, 149.1, 148.5, 147.4, 147.3, 141.8, 140.0, 139.5, 137.7, 136.9, 135.8, 135.4, 135.0, 134.9, 134.67, 134.62, 134.57, 131.4, 131.0, 130.2, 129.0, 126.9, 125.9, 125.1, 124.0, 123.7, 123.4, 120.83, 120.80, 119.1, 107.2, 106.0, 105.6, 105.4, 94.9, 91.7, 89.7, 88.8, 72.0, 71.5, 70.84, 70.79, 65.2, 50.0, 49.6, 31.53, 31.51, 29.57, 29.52, 27.1, 25.74, 25.72, 22.5, 20.9, 19.88, 19.81, 18.5, 13.9, 11.1 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1240.510; found 1240.512. Compound **21a**: ^{1}H NMR: δ = 8.92 (d, ^4J = 2.2 Hz, 2 H, pyridinyl-H), 8.53 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.27 (s, 2 H, Cm343), 8.05 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.71 (m, 2 H, phenyl-H), 7.64–7.57 (m, 6 H, phenyl-H), 7.53 (m, 2 H, phenyl-H), 7.50 (m, 2 H, phenyl-H), 6.84 (s, 2 H, Cm343), 5.27 [s, 4 H, benzyl(Cm343)-H], 4.55 [s, 4 H, benzyl(OC_6H_{13})-H], 3.51 (t, 4 H, α-CH_2), 3.25 (m, 8 H, Cm343), 2.79 (t, 4 H, Cm343), 2.66 (t, 4 H, Cm343), 1.89 (m, 8 H, Cm343), 1.63 (m, 4 H, β-CH_2), 1.43–1.22 (m, 12 H, δ-, γ-, ε-CH_2), 1.10 (s, 42 H, TIPS), 0.85 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 163.9, 158.4, 154.1, 153.4, 149.2, 148.6, 147.3, 140.1, 137.6, 136.9, 135.7, 135.5, 134.6, 131.4, 131.1, 130.4, 129.1, 127.0, 126.1, 124.0, 123.8, 123.4, 121.2, 119.2, 107.3, 106.1, 105.6, 105.5, 91.8, 89.6, 88.9, 72.1, 70.9, 65.3, 50.1, 49.7, 31.6, 29.6, 27.2, 25.8, 22.5, 20.9, 20.0, 19.9, 18.6, 14.0, 11.2 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1691.878; found 1691.873.

Compound 20b: Acetic acid (16 μL, 0.281 mmol) and, dropwise, a 1.0 M THF solution of TBAF (0.28 mL) were added to a solution of **20a** (290 mg, 0.234 mmol) in dry THF (30 mL). The mixture was stirred at room temperature for 5 h. After evaporation under reduced pressure, the residue was purified by GPC (Bio-RAD SX1) to afford 207 mg of **20b** (81%). ^{1}H NMR: δ = 8.87 (d, ^4J = 2.2 Hz, 1 H, pyridinyl-H), 8.80 (d, ^4J = 2.2 Hz, 1 H, pyridinyl-H), 8.44 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.23 (s, 1 H, Cm343), 7.97 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.90 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.81 (m, 1 H, phenyl-H), 7.67–7.64 (m, 2 H, phenyl-H), 7.60 (m, 1 H, phenyl-H), 7.57–7.54 (m, 2 H, phenyl-H), 7.53–7.47 (m, 3 H, phenyl-H), 6.79 (s, 1 H, Cm343), 5.24 [s, 2 H, benzyl(Cm343)-H], 4.51 [s, 2 H, benzyl(OC_6H_{13})-H], 4.45 [s, 2 H, benzyl(OC_6H_{13})-H], 3.47 (m, 4 H, α-CH_2), 3.21 (m, 4 H, Cm343), 3.09 (s, 1 H, ethynyl-H), 2.74 (t, 2 H, Cm343), 2.61 (t, 2 H, Cm343), 1.84 (m, 4 H, Cm343), 1.59 (m, 4 H, β-CH_2), 1.40–1.20 (m, 12 H, δ-, γ-, ε-CH_2), 0.83 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 163.8, 158.2, 154.8, 154.5, 153.3, 149.2, 148.5, 147.4, 147.3, 141.7, 140.0, 139.4, 137.7, 137.0, 135.8, 135.3, 134.96, 134.91, 134.63, 134.57, 134.4, 131.3, 131.1, 130.1, 129.0, 126.9, 125.9, 125.1, 123.6, 123.5, 122.6, 120.81, 120.78, 119.1, 107.2, 105.9, 105.3, 94.9, 89.8, 88.6, 82.3, 78.2, 72.0, 71.5, 70.82, 70.77, 65.0, 50.0, 49.6, 31.50, 31.48, 29.54, 29.49, 27.1, 25.71, 25.68, 22.45, 22.44, 20.8, 19.85, 19.77, 13.9 ppm. HRMS (MALDI, DCTB): *m*/*z* calcd. for $[M + Na]^+$ 1106.358; found 1106.357.

Compounds 27a and 25a: [$Pd(PPh_3)_4$] (60 mg, 0.038 mmol) was added to a carefully degassed mixture of **23** (1.01 g, 2.54 mmol) and **8b** (2.00 g, 2.54 mmol) in dry THF/triethylamine (1:2, 60 mL). The mixture was stirred at 60 °C for 6 h. After cooling to room temperature and evaporation under reduced pressure, the residue was purified by GPC (Bio-RAD SX1) to afford 1.27 g of **27a** (47%) and 743 mg of **25a** (22%). Compound **27a**: ^{1}H NMR: δ = 8.90 (d, ^4J = 2.2 Hz, 1 H, pyridinyl-H), 8.84 (d, ^4J = 2.2 Hz, 1 H, pyridinyl-H), 8.48 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.00 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.93 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.84 (m, 1 H, phenyl-H), 7.72–7.67 (m, 2 H, phenyl-H), 7.59 (m, 1 H, phenyl-H), 7.56 (m, 1 H, phenyl-H), 7.53 (m, 2 H, phenyl-H), 7.50 (m, 1 H, phenyl-H), 7.42 (m, 1 H, phenyl-H), 4.73 [d, ^2J = 13 Hz, 1 H, benzyl(OTHP)-H], 4.70 (t, 1 H, THP), 4.54 [s, 2 H, benzyl(OC_6H_{13})-H], 4.47 [s, 2 H, benzyl(OC_6H_{13})-H], 4.45 [d, ^2J = 13 Hz, 1 H, benzyl(OTHP)-H], 3.89 (ddd, 1 H, THP), 3.54 (ddd, 1 H, THP), 3.51 (t, 2 H, α-CH_2), 3.47 (t, 2 H, α-CH_2), 1.98–1.46 (m, 10 H, β-CH_2 and THP), 1.45–1.20 (m, 12 H, δ-, γ-, ε-CH_2), 1.12 (s, 21 H, TIPS), 0.87 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 154.9, 154.6, 147.5, 147.4, 141.8, 140.1, 139.6, 138.8, 137.8, 135.8, 135.5, 135.06, 135.02, 134.77, 134.72, 134.1, 131.0, 130.5, 130.2, 129.1, 126.0, 125.2, 123.8, 123.2, 120.92, 120.87, 105.9, 97.7, 95.0, 91.4, 89.4, 89.1, 72.1, 71.6, 70.89, 70.84, 67.7, 62.0, 31.59, 31.57, 30.4, 29.63, 29.58, 25.80, 25.78, 25.3, 22.54, 22.53, 19.2, 18.6, 14.0, 11.2 ppm. HRMS (MALDI, DCTB): *m*/*z* calcd. for $[M + H]^+$ 1057.478; found 1057.479. Compound **25a**: ^{1}H NMR: δ = 8.94 (d, ^4J = 2.3 Hz, 2 H, pyridinyl-H), 8.53 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.05 (dd, ^4J = 2.3 Hz, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.73 (m, 2 H, phenyl-H), 7.60 (m, 2 H, phenyl-H), 7.59 (m, 2 H, phenyl-H), 7.55 (m, 2 H, phenyl-H), 7.50 (m, 2 H, phenyl-H), 7.42 (m, 2 H, phenyl-H), 4.74 [d, ^2J = 13 Hz, 2 H, benzyl(OTHP)-H], 4.71 (t, 2 H, THP), 4.58 [s, 4 H, benzyl(OC_6H_{13})-H], 4.47 [d, ^2J = 13 Hz, 2 H, benzyl(OTHP)-H], 3.90 (ddd, 2 H, THP), 3.55 (ddd, 2 H, THP), 3.53 (t, 4 H, α-CH_2), 1.94–1.47 (m, 16 H, β-CH_2 and THP), 1.45–1.23 (m, 12 H, δ-, γ-, ε-CH_2), 1.12 (s, 42 H, TIPS), 0.88 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 154.9, 147.7, 140.2, 138.9, 138.0, 135.6, 135.3, 134.2, 131.1, 130.6, 130.3, 129.3, 126.2, 123.9, 123.3, 121.0, 106.0, 97.8, 91.5, 89.4, 89.1, 72.2, 70.9, 67.9, 62.1, 31.7, 30.5, 29.7, 25.9, 25.4, 22.6, 19.3, 18.6, 14.0, 11.3 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1325.814; found 1325.811.

Compound 25b: Methanol (0.2 mL, 5 mmol) and, dropwise, a 1.0 M THF solution of TBAF (4.2 mL) were added to a solution of **25a** (2.78 g, 2.10 mmol) in dry THF (150 mL). The mixture was stirred at room temperature for 1 d. After evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 3:1) to afford 2.10 g of **25b** (99%). ^{1}H NMR: δ = 8.85 (d, ^4J = 2.2 Hz, 2 H, pyridinyl-H), 8.45 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.92 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.63 (m, 2 H, phenyl-H), 7.54 (m, 2 H, phenyl-H), 7.50 (m, 2 H, phenyl-H), 7.48–7.44 (m, 4 H, phenyl-H), 7.39 (m, 2 H, phenyl-H), 4.68 [d, ^2J = 13 Hz, 2 H, benzyl(OTHP)-H], 4.65 (t, 2 H, THP), 4.47 [s, 4 H, benzyl(OC_6H_{13})-H], 4.39 [d, ^2J = 13 Hz, 2 H, benzyl(OTHP)-H], 3.83 (ddd, 2 H, THP), 3.50 (ddd, 2 H, THP), 3.45 (t, 4 H, α-CH_2), 3.10 (s, 2 H, ethynyl-H), 1.90–1.41 (m, 16 H, β-CH_2 and THP), 1.40–1.17 (m, 12 H, δ-, γ-, ε-CH_2), 0.83 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 154.5, 147.3, 139.9, 139.0, 137.6, 135.1, 134.8, 133.9, 130.8, 130.7, 129.9, 128.8, 125.8, 123.6, 123.2, 122.3, 120.7, 97.6, 89.5, 88.8, 82.5, 77.9, 71.9, 70.7, 67.5, 61.7, 31.5, 30.2, 29.5, 25.70, 25.2, 22.4, 19.0, 13.9 ppm. HRMS (MALDI, DCTB): *m*/*z* calcd. for $[M + H]^+$ 1013.547; found 1013.548.

Compound 27b: Methanol (1 mL) and, dropwise, a 1.0 M THF solution of TBAF (1.77 mL) were added to a solution of **27a** (1.25 g, 1.18 mmol) in dry THF (120 mL). The mixture was stirred at room temperature for 17 h. After evaporation under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 5:1) to afford 1.01 g of **27b** (95%). ^{1}H NMR: δ = 8.93 (d, ^4J = 2.1 Hz, 1 H, pyridinyl-H), 8.87 (d, ^4J = 2.1 Hz, 1 H, pyridinyl-H), 8.51 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 8.04 (dd,

^4J = 2.1 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.98 (dd, ^4J = 2.1 Hz, ^3J = 8.3 Hz, 1 H, pyridinyl-H), 7.88 (m, 1 H, phenyl-H), 7.72 (m, 2 H, phenyl-H), 7.59 (m, 2 H, phenyl-H), 7.58–7.51 (m, 3 H, phenyl-H), 7.46 (m, 1 H, phenyl-H), 4.75 [d, ^2J = 13 Hz, 1 H, benzyl(OTHP)-H], 4.71 (t, 1 H, THP), 4.57 [s, 2 H, benzyl(OC_6H_{13})-H], 4.51 [s, 2 H, benzyl(OC_6H_{13})-H], 4.47 [d, ^2J = 13 Hz, 1 H, benzyl(OTHP)-H], 3.89 (ddd, 1 H, THP), 3.59–3.46 (m, 5 H, THP and α-CH_2), 3.08 (s, 1 H, ethynyl-H), 1.95–1.46 (m, 10 H, β-CH_2 and THP), 1.44–1.20 (m, 12 H, δ-, γ-, ε-CH_2), 0.88 (t, 6 H, CH_3) ppm. ^{13}C NMR: δ = 154.5, 154.2, 147.1, 147.0, 141.5, 139.8, 139.1, 138.9, 137.4, 135.4, 134.8, 134.5, 134.3, 134.1, 133.7, 130.6, 130.5, 129.8, 128.6, 125.5, 124.6, 123.4, 123.0, 122.2, 120.54, 120.49, 97.5, 94.8, 89.5, 88.7, 82.5, 77.9, 71.7, 71.3, 70.58, 70.56, 67.3, 61.5, 31.37, 31.34, 30.1, 29.41, 29.35, 25.60, 25.56, 25.1, 22.33, 22.31, 18.9, 13.8 ppm. HRMS (MALDI, DCTB): *m*/*z* calcd. for $[M + H]^+$ 901.344; found 901.342.

Compound 26a: $[Pd(PPh_3)_4]$ (8.8 mg, 0.0076 mmol) was added to a carefully degassed mixture of **24** (332 mg, 0.837 mmol) and **8b** (300 mg, 0.380 mmol) in dry THF/triethylamine (1:1, 13 mL). The mixture was stirred at 60 °C for 2 d. After cooling to room temperature and evaporation under reduced pressure, the residue was dissolved in chloroform, passed successively through cotton and a membrane filter (PTFE, 0.20 μm pore size), and purified by preparative recycling GPC to afford 356 mg of **26a** (71%). ^{1}H NMR: δ = 8.91 (s, 2 H, pyridinyl-H), 8.51 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.98 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.69 (m, 2 H, phenyl-H), 7.59 (m, 2 H, phenyl-H), 7.55 (m, 2 H, phenyl-H), 7.52 (m, 2 H, phenyl-H), 7.46 (m, 2 H, phenyl-H), 7.40 (m, 2 H, phenyl-H), 4.52 (s, 4 H, benzyl-H), 4.43 (s, 4 H, benzyl-H), 3.50 (t, 4 H, α-CH_2), 3.45 (t, 4 H, α-CH_2), 1.70–1.54 (m, 8 H, β-CH_2), 1.45–1.22 (m, 24 H, δ-, γ-, ε-CH_2), 1.13 (s, 42 H, TIPS), 0.88 (t, 12 H, CH_3) ppm. ^{13}C NMR: δ = 154.7, 147.4, 140.1, 139.3, 137.8, 135.3, 134.9, 134.0, 130.7, 130.2, 130.1, 129.0, 125.8, 123.8, 123.2, 120.8, 106.0, 91.2, 89.4, 89.0, 72.0, 71.7, 70.8, 70.7, 31.59, 31.56, 29.63, 29.56, 25.80, 25.75, 22.53, 22.52, 18.5, 13.95, 13.94, 11.2 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1325.887; found 1325.889.

Compound 26b: Acetic acid (36 μL, 0.64 mmol) and, dropwise, a 1.0 M THF solution of TBAF (644 μL) were added to a solution of **26a** (355 mg, 0.268 mmol) in dry THF (34 mL). The mixture was stirred at room temperature for 38 h. After evaporation under reduced pressure, the residue was dissolved in chloroform, passed successively through cotton and a membrane filter (PTFE, 0.20 μm pore size), and purified by preparative recycling GPC to afford 211 mg of **26b** (78%). ^{1}H NMR: δ = 8.90 (d, ^4J = 2.2 Hz, 2 H, pyridinyl-H), 8.50 (d, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.97 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 2 H, pyridinyl-H), 7.67 (m, 2 H, phenyl-H), 7.57 (m, 2 H, phenyl-H), 7.55 (m, 2 H, phenyl-H), 7.50 (m, 2 H, phenyl-H), 7.48 (m, 2 H, phenyl-H), 7.40 (m, 2 H, phenyl-H), 4.52 (s, 4 H, benzyl-H), 4.42 (s, 4 H, benzyl-H), 3.49 (t, 4 H, α-CH_2), 3.43 (t, 4 H, α-CH_2), 3.09 (s, 2 H, ethynyl-H), 1.69–1.53 (m, 8 H, β-CH_2), 1.44–1.20 (m, 24 H, δ-, γ-, ε-CH_2), 0.86 (t, 12 H, CH_3) ppm. ^{13}C NMR: δ = 154.8, 147.5, 140.1, 139.5, 137.8, 135.3, 135.0, 134.0, 130.8, 130.7, 130.1, 129.0, 126.0, 123.8, 123.3, 122.5, 120.9, 89.5, 88.9, 82.6, 77.8, 72.0, 71.7, 70.8, 70.7, 31.59, 31.57, 29.62, 29.57, 25.80, 25.74, 22.53, 22.52, 14.0 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1013.620; found 1013.621.

Macrocycle 28. Method A: $[Pd(PPh_3)_4]$ (23.7 mg, 0.0205 mmol) was added to a carefully degassed mixture of **25b** (104 mg, 0.102 mmol) and **8b** (80.9 mg, 0.102 mmol) in dry THF/triethylamine (1:1, 74 mL). The mixture was stirred at 60 °C for 3 d. After cooling to room temperature and evaporation under reduced pressure, the residue was dissolved in chloroform, passed successively through cotton and a membrane filter (PTFE, 0.20 μm pore size), and purified by preparative recycling GPC to afford 67 mg of **28** (42%). **Method B:** $[Pd(PPh_3)_4]$ (23.7 mg, 0.0205 mmol) was added to a carefully degassed mixture of **27b** (185 mg, 0.205 mmol) and dry THF/triethylamine (1:1, 74 mL). The mixture was stirred at 60 °C for 3 d. After cooling to room temperature and evaporation under reduced pressure, the residue was dissolved in chloroform, passed successively through cotton and a membrane filter (PTFE, 0.20 μm pore size), and purified by preparative recycling GPC to afford 66 mg of **28** (42%). ^{1}H NMR: δ = 8.86 (d, ^4J = 2.2 Hz, 4 H, pyridinyl-H), 8.44 (d, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 7.94 (dd, ^4J = 2.2 Hz, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 7.64 (m, 2 H, phenyl-H), 7.62 (m, 4 H, phenyl-H), 7.48 (m, 4 H, phenyl-H), 7.46–7.43 (m, 8 H, phenyl-H), 4.78 [d, ^2J = 13 Hz, 2 H, benzyl(OTHP)-H], 4.76 (t, 2 H, THP), 4.52 [s, 8 H, benzyl(OC_6H_{13})-H], 4.49 [d, ^2J = 13 Hz, 2 H, benzyl(OTHP)-H], 3.95 (ddd, 2 H, THP), 3.58 (ddd, 2 H, THP), 3.53 (t, 8 H, α-CH_2), 2.00–1.54 (m, 20 H, THP and β-CH_2), 1.47–1.25 (m, 24 H, δ-, γ-, ε-CH_2), 0.89 (t, 12 H, CH_3) ppm. ^{13}C NMR: δ = 154.7, 147.3, 139.9, 139.0, 137.5, 134.9, 134.8, 134.3, 130.2, 129.8, 129.2, 125.6, 123.8, 123.5, 120.9, 97.9, 89.7, 89.1, 72.2, 70.9, 67.9, 62.1, 31.7, 30.4, 29.7, 25.9, 25.4, 22.6, 19.3, 14.0 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1545.856; found 1545.852.

Macrocycle 29: $[Pd(PPh_3)_4]$ (38 mg, 0.033 mmol) was added to a carefully degassed mixture of **26b** (166 mg, 0.164 mmol) and **8b** (129 mg, 0.164 mmol) in dry THF/triethylamine (1:1, 116 mL). The mixture was stirred at 60 °C for 3 d. After cooling to room temperature and evaporation under reduced pressure, the residue was dissolved in chloroform, passed successively through cotton and a membrane filter (PTFE, 0.20 μm pore size), and purified by preparative recycling GPC to afford 116 mg of **29** (46%). ^{1}H NMR: δ = 8.95 (d, ^4J = 2.3 Hz, 4 H, pyridinyl-H), 8.53 (d, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 8.06 (dd, ^4J = 2.3 Hz, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 7.75 (m, 6 H, phenyl-H), 7.60 (m, 4 H, phenyl-H), 7.53 (m, 4 H, phenyl-H), 7.49 (m, 4 H, phenyl-H), 4.58 (s, 8 H, benzyl-H), 4.51 (s, 4 H, benzyl-H), 3.54 (t, 8 H, α-CH_2), 3.51 (t, 4 H, α-CH_2), 1.72–1.59 (m, 12 H, β-CH_2), 1.47–1.25 (m, 36 H, δ-, γ-, ε-CH_2), 0.94–0.85 (m, 18 H, CH_3) ppm. ^{13}C NMR: δ = 154.7, 147.3, 139.9, 139.4, 137.5, 134.9, 134.7, 134.2, 130.1, 129.8, 129.2, 125.5, 123.8, 123.4, 120.9, 89.6, 89.1, 72.2, 72.0, 70.92, 70.85, 31.7, 29.74, 29.72, 25.91, 25.87, 22.64, 22.63, 14.06, 14.05 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1545.929; found 1545.925.

Macrocycle 1: $[Pd(PPh_3)_4]$ (42 mg, 0.036 mmol) was added to a carefully degassed mixture of **22b** (237 mg, 0.181 mmol) and **8b** (142 mg, 0.181 mmol) in dry THF/triethylamine (1:1, 128 mL). The mixture was stirred at 60 °C for 3 d. After cooling to room temperature and evaporation under reduced pressure, the residue was dissolved in chloroform, passed successively through cotton and a membrane filter (PTFE, 0.20 μm pore size), and purified by preparative recycling GPC to afford 107 mg of **1** (32%). ^{1}H NMR: δ = 8.90 (d, ^4J = 2.1 Hz, 4 H, pyridinyl-H), 8.46 (d, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 8.34 (s, 1 H, Cm343), 7.98 (dd, ^4J = 2.1 Hz, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 7.72 (m, 1 H, phenyl-H), 7.66 (m, 5 H, phenyl-H), 7.58 (m, 2 H, phenyl-H), 7.54 (m, 4 H, phenyl-H), 7.51–7.45 (m, 6 H, phenyl-H), 7.37 (s, 1 H, Cm2), 7.00 (s, 1 H, Cm2), 6.90 (s, 1 H, Cm343), 6.11 (s, 1 H, Cm2), 5.30 [s, 2 H, benzyl(Cm343)-H], 4.54 [s, 8 H, benzyl(OC_6H_{13})-H], 4.16 [s, 2 H, benzyl(Cm2)-H], 3.529 (t, 4 H, α-CH_2), 3.524 (t, 4 H, α-CH_2), 3.28 (m, 4 H, Cm343), 3.10 (q, 2 H, Cm2), 2.84 (t, 2 H, Cm343), 2.70 (t, 2 H, Cm343), 2.46 (s, 3 H, Cm2), 2.36 (s, 3 H, Cm2), 1.92 (m, 4 H, Cm343), 1.66 (m, 8 H, β-CH_2), 1.46–1.24 (m, 24 H, δ-, γ-, ε-CH_2), 1.09 (t, 3 H, Cm2), 0.88 (m, 12 H, CH_3) ppm. ^{13}C NMR: δ = 164.1,

161.4, 158.5, 154.77, 154.73, 153.5, 153.4, 152.6, 152.2, 149.4, 148.7, 147.4, 140.0, 139.2, 137.63, 137.58, 137.1, 135.04, 134.99, 134.9, 130.81, 130.73, 130.0, 129.9, 129.6, 129.3, 127.1, 126.6, 125.7, 123.78, 123.76, 123.71, 123.6, 120.9, 119.2, 115.1, 112.7, 109.2, 107.4, 106.4, 105.6, 89.9, 89.8, 89.1, 88.9, 72.20, 72.18, 70.93, 70.90, 65.5, 56.2, 50.2, 49.8, 46.6, 31.7, 29.7, 27.3, 25.9, 22.6, 21.0, 20.07, 19.99, 18.8, 18.5, 14.0, 11.7 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1843.930; found 1843.926.

Macrocycle 2: $[Pd(PPh_3)_4]$ (29 mg, 0.025 mmol) was added to a carefully degassed mixture of **19b** (158 mg, 0.127 mmol) and **8b** (100 mg, 0.127 mmol) in dry THF/triethylamine (1:1, 90 mL). The mixture was stirred at 60 °C for 3 d. After cooling to room temperature and evaporation under reduced pressure, the residue was dissolved in chloroform, passed successively through cotton and a membrane filter (PTFE, 0.20 μm pore size), and purified by preparative recycling GPC to afford 84 mg of **2** (37%). ^{1}H NMR: δ = 8.89 (d, ^4J = 2.3 Hz, 4 H, pyridinyl-H), 8.46 (d, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 7.97 (dd, ^4J = 2.3 Hz, ^3J = 8.4 Hz, 4 H, pyridinyl-H), 7.64 (m, 6 H, phenyl-H), 7.53 (m, 4 H, phenyl-H), 7.49 (m, 4 H, phenyl-H), 7.47 (m, 4 H, phenyl-H), 7.37 (s, 2 H, Cm2), 7.00 (s, 2 H, Cm2), 6.11 (m, 2 H, Cm2), 4.54 [s, 8 H, benzyl(OC_6H_{13})-H], 4.16 [s, 4 H, benzyl(Cm2)-H], 3.53 (t, 8 H, α-CH_2), 3.10 (q, 4 H, Cm2), 2.46 (s, 6 H, Cm2), 2.35 (d, 6 H, Cm2), 1.66 (m, 8 H, β-CH_2), 1.46–1.25 (m, 24 H, δ-, γ-, ε-CH_2), 1.09 (t, 6 H, Cm2), 0.88 (t, 12 H, CH_3) ppm. ^{13}C NMR: δ = 161.4, 154.7, 153.3, 152.6, 152.2, 147.4, 140.0, 139.2, 137.6, 135.0, 134.8, 134.2, 130.7, 129.8, 129.6, 129.2, 126.6, 125.7, 123.7, 123.5, 120.9, 115.0, 112.7, 109.2, 89.8, 89.1, 72.2, 70.9, 56.2, 46.6, 31.6, 29.7, 25.8, 22.6, 18.7, 18.5, 14.0, 11.7 ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1775.940; found 1775.943.

Macrocycle 3: $[Pd(PPh_3)_4]$ (16 mg, 0.014 mmol) was added to a carefully degassed mixture of **20b** (145 mg, 0.134 mmol) and dry THF/triethylamine (1:1, 48 mL). The mixture was stirred at 60 °C for 3 d. After cooling to room temperature and evaporation under reduced pressure, the residue was dissolved in chloroform, passed successively through cotton and a membrane filter (PTFE, 0.20 μm pore size), and purified by preparative recycling GPC to afford 27 mg of **3** (22%). ^{1}H NMR: δ = 8.97 (d, ^4J = 2.3 Hz, 4 H, pyridinyl-H), 8.54 (d, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 8.37 (s, 2 H, Cm343), 8.07 (dd, ^4J = 2.3 Hz, ^3J = 8.3 Hz, 4 H, pyridinyl-H), 7.80 (m, 2 H, phenyl-H), 7.77 (m, 4 H, phenyl-H), 7.63 (m, 8 H, phenyl-H), 7.56 (m, 4 H, phenyl-H), 6.94 (s, 2 H, Cm343), 5.34 [s, 4 H, benzyl(Cm343)-H], 4.59 [s, 8 H, benzyl(OC_6H_{13})-H], 3.54 (t, 8 H, α-CH_2), 3.32 (m, 8 H, Cm343), 2.88 (t, 4 H, Cm343), 2.74 (t, 4 H, Cm343), 1.95 (m, 8 H, Cm343), 1.66 (m, 8 H, β-CH_2), 1.45–1.20 (m, 24 H, δ-, γ-, ε-CH_2), 0.88 (t, 12 H, CH_3) ppm. HRMS (MALDI, 3-HPA): *m*/*z* calcd. for $[M + H]^+$ 1911.920; found 1911.920.

GPC Analyses: Regarding the five experimental setups shown below (entries 1–5), the course of the reaction was monitored in each case by successive GPC measurements 30 min, 2.5, 5.5, 17 h, 1, 2, 3, 4, 5, 6, and 7 d after the reaction had started. For each GPC analysis, a 1.0 mL aliquot of the reaction mixture was sampled, poured into methanol (2 mL), evaporated under reduced pressure, dissolved in the eluent, and filtered through a membrane (PTFE, 0.20 μm pore size) prior to the GPC measurement.

Entry 1: $[Pd(PPh_3)_4]$ (6.1 mg, 0.0053 mmol) and CuI (0.8 mg, 0.004 mmol) were added to a mixture of **25b** (100 mg, 0.0987 mmol) and **8b** (77.8 mg, 0.0987 mmol) in dry THF/triethylamine (1:1, 70 mL). The mixture was stirred at 60 °C.

Entry 2: $[Pd(PPh_3)_4]$ (6.1 mg, 0.0053 mmol) was added to a mixture of **25b** (100 mg, 0.0987 mmol) and **8b** (77.8 mg, 0.0987 mmol) in dry THF/triethylamine (1:1, 70 mL). The mixture was stirred at 60 °C.

Entry 3: $[Pd(PPh_3)_4]$ (6.1 mg, 0.0053 mmol) was added to a mixture of **25b** (100 mg, 0.0987 mmol) and **8b** (77.8 mg, 0.0987 mmol) in dry THF/triethylamine (1:1, 70 mL). The mixture was stirred at 45 °C.

Entry 4: $[Pd(PPh_3)_4]$ (22.8 mg, 0.020 mmol) was added to a mixture of **25b** (100 mg, 0.0987 mmol) and **8b** (77.8 mg, 0.0987 mmol) in dry THF/triethylamine (1:1, 70 mL). The mixture was stirred at 60 °C.

Entry 5: $[Pd(PPh_3)_4]$ (22.8 mg, 0.020 mmol) was added to a mixture of **27b** (178 mg, 0.198 mmol) and dry THF/triethylamine (1:1, 70 mL). The mixture was stirred at 60 °C.

Supporting Information (see also the footnote on the first page of this article): GPC elution curves for the model cyclization reactions under different Sonogashira conditions (entries 1–5).

Acknowledgments

In its initial phase, this work was supported by the Deutsche Forschungsgemeinschaft (Sfb 448, TP A1). We are very thankful to Dr. D. Opris for helpful discussions and advice and providing us with some samples. We also would like to thank Dr. W. Amrein and his team at ETH Zürich for mass spectrometry measurements, Ms. D. Suter for NMR spectroscopy measurements, and Mr. M. Colussi for all GPC analyses.

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Received: December 18, 2006
Published Online: April 17, 2007

