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Synthesis of a shape-persistent macrocycle with intraannular carboxylic acid groups

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Abstract—The synthesis of a shape-persistent macrocycle based on the phenylene–ethynylene backbone by the intermolecular oxidative Glaser-coupling of appropriate bisacetylenes is described. The ring contains two intraannular methyl carboxylates that were hydrolyzed to give the free diacid. In order to achieve sufficient solubility it was necessary to attach additional intraannular branched alkyl groups to the ring.

1. Introduction

Recently, there has been considerable interest in the design and study of shape-persistent macrocycles with an interior in the nanometer regime. Apart from the their organization in solution, the solid state and at interfaces they offer the possibility to bind large guest molecules.[1–4] The binding of the guest can be non-specific, or specific if the macrocycle contains appropriate intraannular binding sites[5,6] with a polarity and arrangement complementary to the guest molecule.[7–11] Our work has focused on shape-persistent macrocycles based on the phenylene–ethynylene–butadienylene backbone as schematically shown in Figure 1.[12–15]

Depending on the position where the side groups (which can also contain functional groups) are attached to the ring they point either to the inside (intraannular groups I, I′), to the outside (extraannular groups E, E′), or they can switch their orientation and point either to the inside or to the outside (adaptable groups A, A′).[16–19] In terms of our ongoing program towards macrocycles with a highly polar interior we became interested in structures with two convergently arranged carboxylic acid groups (at the positions I).[20,21] They should be able to recognize organic diamines or might be in form of their metal salts the basis for new inorganic/organic hybrid structures. Moreover, attaching oligopeptides through their N-terminal sites could lead to new two-armed peptide receptors.[22,23]

However, the synthesis of macrocycles with two intraannular carboxylic acid groups showed some unexpected difficulties. Shape-persistent macrocycles are compared to non-cyclic or flexible analogues much less soluble. That has its origin in the drastically reduced entropy gain by going from the bulk phase to the solution. On one hand this simplifies the isolation and purification of the compounds which can often be performed by simple recrystallization. On the other hand it is necessary to attach flexible side groups to the rings in order to keep the materials tractable.[24,25]

Here we describe the synthesis of the macrocycle **1** with two intraannular carboxylic acid groups (at the positions I, Fig. 1). **1** contains additionally four intraannular (*S*)-2-methylbutoxy groups (at the positions I′, Fig. 1) providing sufficient solubility of the free diacid. Therefore, **1** might be a good candidate for the above mentioned investigations.[26]

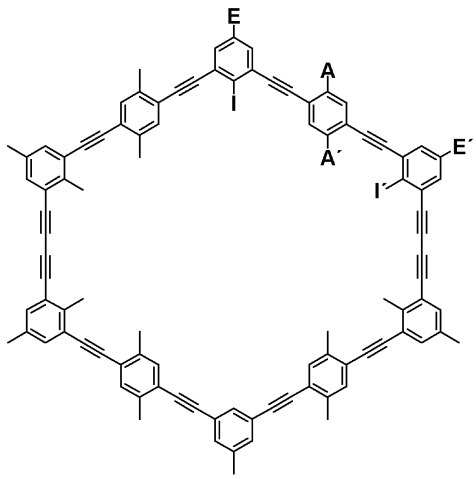

Figure 1.

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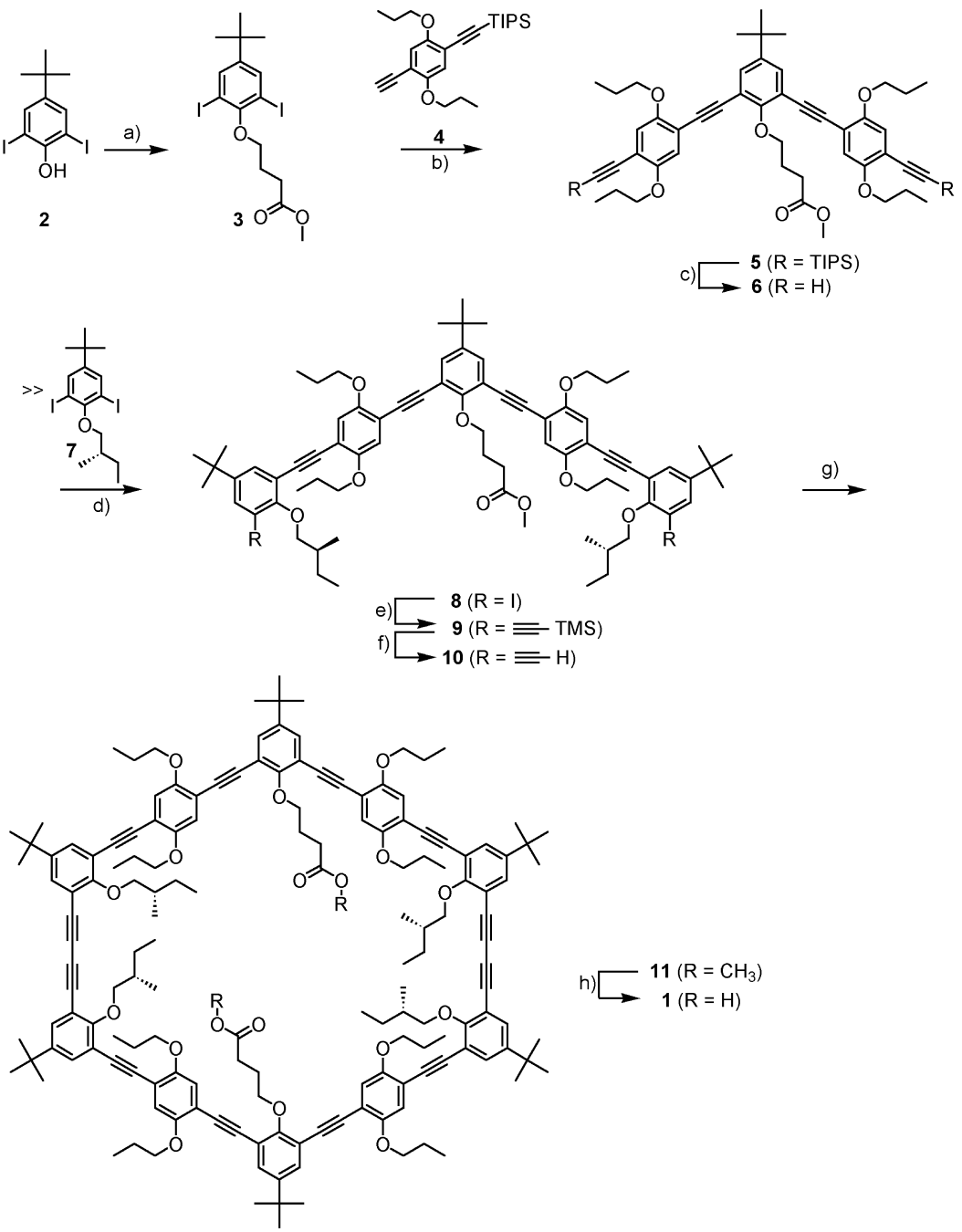
2. Results and discussion

The synthesis of **1** is outlined in Scheme 1.

2,6-Diiodo-4-*tert*-butylphenol (**2**) was alkylated with 4-bromo-trimethylorthobutyrate to give the ester **3** in 57% yield. Palladium-catalyzed Hagihara–Sonogashira coupling of **3** with the mono-protected bisacetylene **4** and subsequent desilylation of **5** (94%) by treating with Bu_4NF gave the bisacetylene **6** (84%). As described previously, the basicity of the fluoride was reduced by adding about 5% of water to the THF.[20] Reaction of **6** with a 4.5-fold excess of the THP-protected diiodophenol **7** gave the diiodo compound **8** in 36% yield.[27] The excess of **7** was nearly quantitatively recovered and could be used for subsequent coupling reactions. Coupling of **8** with trimethylsilyl(TMS)-acetylene yielded **9** (64%), which was desilylated with K_2CO_3 to give **10** (96%). The statistical intermolecular oxidative dimerization of **10** was performed by slow addition of a solution of **10** in pyridine to a suspension of CuCl and $CuCl_2$ in the same solvent at 60°C, a compromise between increased coupling rate and decreased product stability at elevated temperatures.[14] The crude cyclization product was purified by radial chromatography to give pure **11** in 54% isolated yield. Base-catalyzed ester hydrolysis gave the diacid **1** (65%).



Scheme 1. (a) 4-Bromo-trimethylorthobutyrate, K_2CO_3, DMF (57%); (b) $PdCl_2(PPh_3)_2$, CuI, THF/NEt_3 (94%); (c) Bu_4NF, THF/H_2O (84%); (d) $PdCl_2(PPh_3)_2$, CuI, NEt_3/THF (36%); (e) TMS-acetylene, $PdCl_2(PPh_3)_2$, CuI, piperidine (64%); (f) K_2CO_3, MeOH/THF (96%); (g) CuCl, $CuCl_2$, pyridine, (54%); (h) Bu_4NOH, MeOH, THF, 65%.

1 is well soluble in a variety of different organic solvents like CH_2Cl_2, $CHCl_3$ or THF. In this context it is worth to mention that the corresponding diacid with four methoxy groups at the position I′ is nearly insoluble and could not be characterized by solution NMR spectroscopy.[28] Figure 2 displays the ^{1}H NMR spectra of **11** and **1**. It show molecules with a high degree of symmetry, as expected from the molecular structure. The absence of the methyl signal at 3.5 ppm in **1** is a clear indication for the complete ester hydrolysis.

All in all we have described the synthesis of the first nanometer size shape-persistent macrocycle with two intraannular carboxylic acid groups that is soluble enough to be characterized in solution. Simple intraannular methoxy groups did not provide enough solubility and more bulky methylbutoxy groups had to be attached to the ring. However, this chiral groups inside the macrocycle might offer additional features for the recognition of guest molecules of biological origin. In addition, the acid groups can be further functionalized and the macrocycle can act as a new template for two-arm peptide receptors.

3. Experimental

3.1. General

Reactions requiring an inert gas atmosphere were conducted under argon, and the glassware was oven-dried (140°C). THF was distilled from potassium prior to use. Triethylamine and pyridine were distilled over CaH_2 and stored under argon. Commercially available chemicals were used as received. Compounds **2** and **4** are described elsewhere.[20,29] ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 250 or AC 300 spectrometer (250 and 300 MHz for ^{1}H, 62.5 and 75.48 MHz for ^{13}C). Chemical shifts are given in ppm, referenced to residual proton resonances of the solvents. Thin-layer chromatography was performed on aluminum plates precoated with Merck 5735 silica gel 60 F_{254}. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). The gel permeation chromatograms 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, 10^6) and an UV detector operating at λ=254 nm. The molecular weight was obtained from polystyrene calibrated SEC columns. The matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) 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 compounds in THF at a concentration of 10^{-4} mol L^{-1}. In all cases, 1,8,9-trihydroxyanthracene was

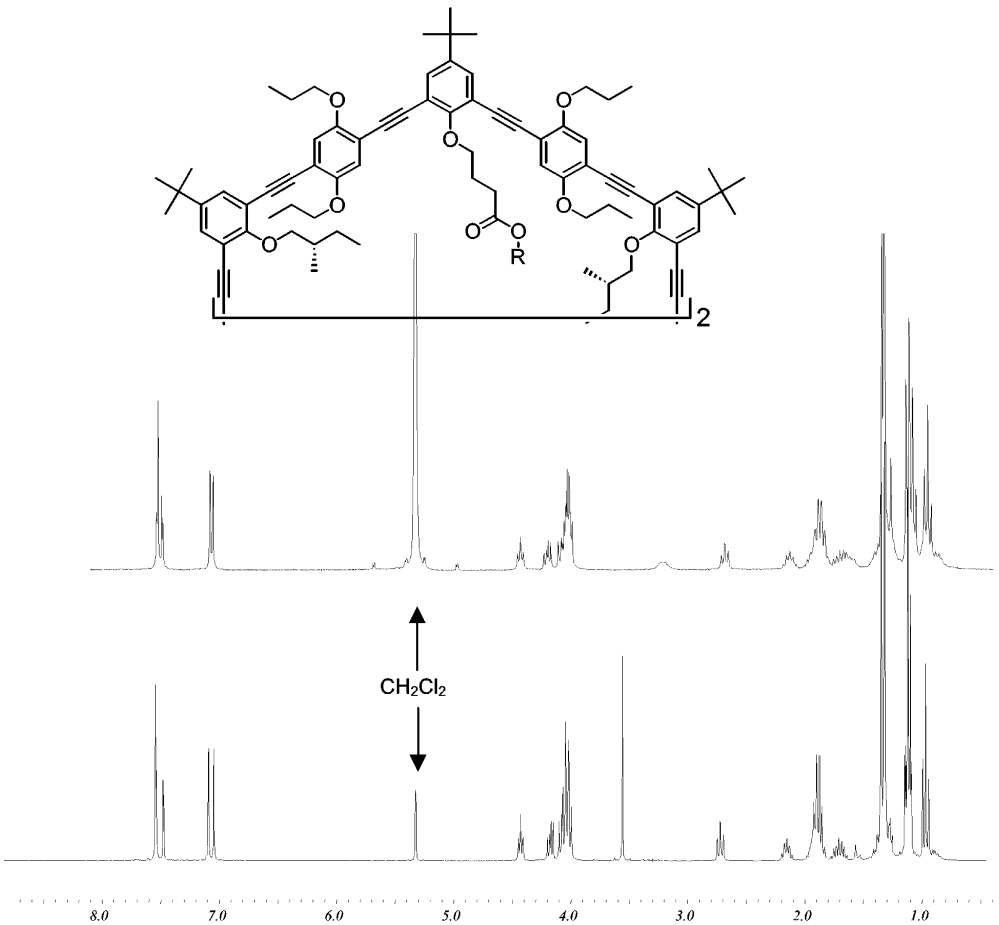


Figure 2. ^{1}H NMR spectra of **11** (bottom) and **12** (top).

used as matrix. Field desorption spectra were recorded on a VG ZAB 2-SE FPD machine. Microanalyses were performed by the University of Mainz. Melting points were measured with a Reichert hot stage apparatus and are uncorrected.

3.1.1. Methyl 4-(*tert*-butyl-2,6-diiodophenoxy)-butyrate 3. 4-*tert*-Butyl-2,6-diiodophenol (**2**) (15.74 g, 39.0 mmol), 4-bromo-trimethylorthobutyrate (8.85 g, 39.0 mmol), K_2CO_3 (5.5 g, 43.0 mmol) and KI (50 mg) were stirred in DMF (70 mL) at 60°C for 20 h and after cooling to room temperature poured into ether and water. The organic phase was separated and extracted with 10% sodium hydroxide solution, water, and brine. After drying over $MgSO_4$ and evaporation of the solvent the crude product was chromatographed over silica gel with CH_2Cl_2/petroleum ether (1:4) as the eluent (R_f=0.83) to give **3** as a slightly beige solid (11.1 g, 57%). The crude product may contain variable minor amounts of the corresponding orthoester product, seeing by an extra NMR signal at 3.19 ppm (s). In that case the crude product was dissolved in CH_2Cl_2 and extracted several times with 10% acetic acid, then water, 10% aqueous sodium hydroxide, water, and brine to complete the transformation of the orthoester to **3**. Mp 153°C; ^{1}H NMR (250 MHz, $C_2D_2Cl_4$): δ=7.63 (s, 2H), 3.90 (t, J=6.0 Hz, 2H), 3.61 (s, 3H), 2.61 (t, J=7.4 Hz, 2H), 2.10–2.25 (m, 2H), 1.17 (s, 9H); elemental analysis for $C_{15}H_{20}I_2O_3$ (502.13): calcd C 35.88, H 4.01; found C 35.94, H 3.93; MS (FD): 502.3 (M^+).

3.1.2. Methyl 4-(2,6-bis-{2-[2,5-dipropyloxy-4-(2-triisopropylsilylethynyl)phenyl]-ethynyl}-4-*tert*-butylphenoxy)-butyrate 5. $Pd(PPh_3)_2Cl_2$ (68 mg) and CuI (35 mg) were added to a solution of **3** (2.11 g, 4.28 mmol) and **4** (3.41 g, 8.55 mmol) in triethylamine/THF (5:1) (120 mL). The solution was stirred for 18 h at room temperature, for 1 h at 50°C and after cooling to room temperature poured into ether and water. The organic phase was separated and extracted with water, 10% acetic acid, water, 10% aqueous sodium hydroxide, water, and brine. After drying over $MgSO_4$ and evaporation of the solvent the crude product was chromatographed over silica gel with CH_2Cl_2/petroleum ether (slow polarity increase from 1:2 to 1:1) as the eluent (R_f (CH_2Cl_2/petroleum ether 1:2)=0.24) to give **5** as a slightly yellow solid (4.16 g, 94%). Mp 122°C; ^{1}H NMR (250 MHz, CD_2Cl_2): δ=7.50 (s, 2H), 6.98 (s, 2H), 6.95 (s, 2H), 4.40 (t, J=6.0 Hz, 2H), 3.86–4.40 (m, 8H), 3.57 (s, 3H), 2.71 (t, J=7.2 Hz, 2H), 2.05–2.20 (m, 2H), 1.75–1.95 (m, 8H), 1.32 (s, 9H), 1.15 (s, 42H), 1.00–1.15 (m, 12H); elemental analysis for $C_{65}H_{94}O_7Si_2$ (1043.64): calcd C 74.81, H 9.08; found C 74.82, H 9.18; MS (FD): 1044.1 (M^+).

3.1.3. Methyl 4-{2,6-bis-[2-(2,5-dipropyloxy-4-ethynylphenyl)-ethynyl]-4-*tert*-butylphenoxy}-butyrate 6. A 1 M solution of Bu_4NF in THF (15.0 mL, 15.0 mmol) was added to a solution of **5** (3.39 g, 3.25 mmol) in THF (30 mL) and water (1.5 mL). The mixture was stirred for 2 h at room temperature and then poured into ether and water. The organic layer was extracted with water and brine and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by chromatography over silica gel with CH_2Cl_2/petroleum ether (slow polarity increase from 1:1 to 3:1) as the eluent to give an oily product (3.2 g) (R_f (CH_2Cl_2/petroleum ether (1:1))=0.70) that was treated with MeOH in order to remove the silanol to give **6** as a slightly yellow solid (2.0 g, 84%). Mp 161–163°C; ^{1}H NMR (250 MHz, CD_2Cl_2): δ=7.50 (s, 2H), 7.04 (s, 2H), 7.00 (s, 2H), 4.37 (t, J=5.9 Hz, 2H), 3.97 (t, J=6.5 Hz, 4H), 3.96 (t, J=6.5 Hz, 4H), 3.52 (s, 3H), 3.39 (s, 2H), 2.66 (t, J=7.2 Hz, 2H), 2.04–2.16 (m, 2H), 1.75–1.90 (m, 8H), 1.32 (s, 9H), 1.00–1.10 (m, 12H); elemental analysis for $C_{47}H_{54}O_7$ (730.45): calcd C 77.23, H 7.45; found C 76.94, H 7.39; MS (FD): 730.6 (M^+).

3.1.4. 4-*tert*-Butyl-2,6-diiodo-1-(2-(*S*)-methylbutoxy)-benzene 7. Diethylazodicarboxylate (2.6 g; 15.0 mmol) were slowly added to a solution of 4-*tert*-butyl-2,6-diiodophenol (**2**) (4.0 g, 10.0 mmol), (*S*)-2-methyl-1-butanol (0.88 g, 10.0 mmol) and PPh_3 (3.9 g, 14.8 mmol) in THF (20 mL) and the mixture was stirred for 12 h at room temperature and then poured into ether and water. The organic phase was separated and extracted with water and brine. After drying over $MgSO_4$ and evaporation of the solvent the crude product was chromatographed over silica gel with petroleum ether as the eluent (R_f=0.30) to give **7** as a colorless oil (4.03 g, 85%). ^{1}H NMR (250 MHz, CD_2Cl_2): δ=7.80 (s, 2H), 3.60–3.90 (m, 2H), 1.95–2.15 (m, 1H), 1.65–1.80 (m, 1H), 1.25–1.45 (m, 1H), 1.32 (s, 9H), 1.09 (d, J=5.9 Hz, 3H); 0.98 (t, J=7.3 Hz, 3H); elemental analysis for $C_{15}H_{20}I_2O$ (472.15): calcd C 38.16, H 4.70; found C 38.32, H 4.65; MS (FD): 472.2 (M^+).

3.1.5. Methyl 4-{2,6-bis-[2-(2,5-dipropyloxy-4-{2-[2-(2-(*S*)-methylbutoxy)-3-iodo-5-*tert*-butylphenyl]ethynyl}-phenyl)ethynyl]-4-*tert*-butylphenoxy}-butyrate 8. $Pd(PPh_3)_2Cl_2$ (30 mg) and CuI (15 mg) were added to a solution of **7** (3.91 g, 8.28 mmol) and **6** (0.92 g, 1.83 mmol) in triethylamine (15 mL), and the mixture was stirred for 18 h at 60°C. Workup was performed as described for compund **5**. The oily crude product was chromatographed over silica gel with CH_2Cl_2/petroleum ether (1:2) as the eluent to recover most of the excess of **7** (2.19 g). Changing the eluent to CH_2Cl_2 yielded **8** (R_f=0.59) as a slightly yellow solid (0.65 g, 36%). Mp 77°C (dec.); ^{1}H NMR (300 MHz, CD_2Cl_2): δ=7.79 (d, J=2.3 Hz, 2H), 7.55 (s, 2H), 7.53 (d, J=2.3 Hz, 2H), 7.10 (s, 2H), 7.04 (s, 2H), 4.43 (t, J=6.1 Hz, 2H), 3.95–4.15 (m, 12H), 3.56 (s, 3H), 2.72 (t, J=7.2 Hz, 2H), 2.11–2.20 (m, 2H), 1.94–2.09 (m, 2H), 1.80–1.93 (m, 8H), 1.64–1.79 (m, 2H), 1.35 (s, 9H), 1.31 (s, 18H), 1.08–1.18 (m, 18H), 0.98 (t, J=7.6 Hz, 6H); elemental analysis for $C_{77}H_{96}I_2O_0$ (1419.43): calcd C 65.16, H 6.82; found C 65.57, H 7.11; MS (FD): 1418.7 (M^+).

3.1.6. Methyl 4-{2,6-bis-[2-(2,5-dipropyloxy-4-{2-[2-(2-(*S*)-methylbutoxy)-3-(2-trimethylsilylethynyl)-5-*tert*-butylphenyl]ethynyl}phenyl)ethynyl]-4-*tert*-butylphenoxy}-butyrate 9. $Pd(PPh_3)_2Cl_2$ (10 mg) and CuI (5 mg) were added to a solution of **8** (0.6 g, 0.42 mmol) and TMS acetylene (0.25 g, 2.54 mmol) in piperidine (10 mL), and the mixture was stirred for 16 h at 60°C. Workup was performed as described for compund **7**. Column chromatography over silica gel with CH_2Cl_2/petroleum ether (2:1) as the eluent (R_f=0.64) and subsequent radial chromatography over silica gel/gypsum with CH_2Cl_2/petroleum ether (8:5) as the eluent gave **9** as a

slightly yellow oil which slowly solidified (0.37 g, 64%). Mp 165°C; ^{1}H NMR (300 MHz, CD_2Cl_2): δ=7.54 (s, 2H), 7.51 (d, J=2.3 Hz, 2H), 7.44 (d, J=2.7 Hz, 2H), 7.09 (s, 2H), 7.04 (s, 2H), 4.43 (t, J=6.1 Hz, 2H), 4.17 (t, J=6.8 Hz, 2H), 3.98–4.10 (m, 10H), 3.56 (s, 3H), 2.72 (t, J=7.2 Hz, 2H), 2.09–2.23 (m, 2H), 1.80–2.00 (m, 10H), 1.63–1.79 (m, 2H), 1.35 (s, 9H), 1.32 (s, 18H), 1.05–1.18 (m, 18H), 0.97 (t, J=7.3 Hz, 6H), 0.27 (s, 18H); elemental analysis for $C_{87}H_{114}O_9Si_9$ (1360.05): calcd C 76.83, H 8.45; found C 77.01, H 8.38; MS (FD): 1361.2 (M^+).

3.1.7. Methyl 4-{2,6-bis-[2-(2,5-dipropyloxy-4-{2-[2-(2-(*S*)-methylbutoxy)-3-ethynyl-5-*tert*-butylphenyl]-ethynyl}phenyl)ethynyl]-4-*tert*-butylphenoxy}-butyrate 10. A 1 M solution of Bu_4NF in THF (1.5 mL, 1.5 mmol) was added to a solution of **9** (305 mg; 0.22 mmol) in THF (20 mL) and water (0.5 mL). The mixture was stirred for 1.25 h at room temperature and then poured into ether and water. The organic layer was extracted with water and brine and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by chromatography over silica gel with CH_2Cl_2/petroleum ether (1:1) as the eluent (R_f=0.86) to give **10** as a slightly yellow solid (261 mg, 96%). Mp 187–190°C; ^{1}H NMR (300 MHz, CD_2Cl_2): δ=7.54 (s, 2H), 7.53 (d, J=2.3 Hz, 2H), 7.48 (d, J=2.3 Hz, 2H), 7.09 (s, 2H), 7.05 (s, 2H), 4.43 (t, J=5.7 Hz, 2H), 4.14–4.20 (m, 2H), 3.98–4.12 (m, 10H), 3.56 (s, 3H), 3.31 (s, 2H), 2.72 (t, J=7.2 Hz, 2H), 2.12–2.22 (m, 2H), 1.81–1.99 (m, 10H), 1.63–1.78 (m, 2H), 1.35 (s, 9H), 1.32 (s, 18H), 1.23–1.40 (m, 2H), 1.08–1.18 (m, 18H), 0.97 (t, J=7.3 Hz, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=173.70, 159.66, 158.26, 153.78, 146.61, 146.27, 131.78, 131.71, 131.31, 117.16, 117.04, 116.81, 115.88, 114.31, 114.10, 91.58, 91.53, 90.07, 89.97, 81.06, 80.42, 79.22, 73.42, 71.26, 71.18, 51.31, 36.06, 34.35, 34.27, 31.03, 30.88, 26.23, 25.88, 22.89, 22.84, 16.56, 11.41, 10.48, 10.43 ppm; elemental analysis for $C_{81}H_{98}O_9$ (1215.68): calcd C 80.03, H 8.13; found C 79.89, H 8.37; MS (FD): 1216.0 (M^+).

3.1.8. Macrocycle 11. A solution of **10** (260 mg, 0.21 mmol) in pyridine (16 mL) was added to a suspension of CuCl (1.16 g, 12.0 mmol) and $CuCl_2$ (0.23 g, 1.0 mmol) in pyridine (30 mL) over 96 h at 60°C. After the completion of the addition, the mixture was allowed to stir for an additional 24 h at room temperature and then was poured into CH_2Cl_2 and water. 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 sodium hydroxide, and brine, and dried over $MgSO_4$. After evaporation of the solvent to a small volume and the coupling products were precipitated by the addition of methanol (50 mL) and collected by filtration. Repeated column chromatography with CH_2Cl_2/methanol (250:1) and THF/petroleum ether (1:4) as eluents gave **11** as a slightly yellow solid (140 mg; 54%) (R_f (THF/petroleum ether (1:4))=0.78). Mp >230°C; ^{1}H NMR (300 MHz, CD_2Cl_2): δ=7.54–7.56 (m, 8H), 7.47–7.49 (m, 4H), 7.09 (s, 4H), 7.06 (s, 4H), 4.41 (t, J=5.7 Hz, 4H), 4.12–4.22 (m, 4H), 3.98–4.10 (m, 20H), 3.51 (s, 6H), 2.64 (t, J=7.6 Hz, 4H), 2.10–2.20 (m, 4H), 1.80–2.00 (m, 20H), 1.61–1.79 (m, 8H), 1.35 (s, 18H), 1.32 (s, 36H), 1.06–1.16 (m, 36H), 0.97 (t, J=7.3 Hz, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=173.99, 161.43, 159.35, 154.10, 154.03, 146.88, 146.69, 132.02, 131.64, 131.04, 117.68, 117.53, 117.42, 115.89, 114.59, 114.54, 91.72, 91.52, 90.68, 90.40, 79.96, 79.38, 78.01, 73.78, 71.68, 71.60, 36.42, 34.67, 31.33, 31.05, 30.11, 26.60, 26.15, 23.15, 23.09, 16.95, 11.73, 10.70, 10.63; elemental analysis for $C_{162}H_{192}O_{18}$ (2427.33): calcd C 80.16, H 7.97; found C 79.78, H 8.16; GPC (PS, THF): single peak with M_w=2450, M_n=2200, PD=1.02. MS (MALDI-TOF): 2535.4 ($M+Ag^+$).

3.1.9. Macrocyclic diacid 1. Tetrabutylamonium hydroxide (0.5 mL, 40% in water) was added to a solution of **11** (30 mg) in THF (10 mL). The mixture was stirred over night at room temperature and 2 mL of hydrochloric acid was added (10%) and the solvent removed in vacuum to a small volume. Methanol (10 mL) and water (2 mL) were added and the precipitate collected by filtration. Purification was performed by column chromatography using CH_2Cl_2 as an eluent to remove less polar impurities and **1** was eluted with THF (20 mg, 65%). Mp >230°C (decomp.). ^{1}H NMR (300 MHz, CD_2Cl_2): δ=7.53 (d, J=2.4 Hz, 4H), 7.52 (s, 4H) 7.48 (m, J=2.4 Hz, 4H), 7.08 (s, 4H), 7.05 (s, 4H), 4.42 (t, J=6.0 Hz, 4H), 4.15–4.24 (m, 4H), 3.97–4.11 (m, 20H), 3.20 (br.s 4H, H_2O), 2.68 (t, J=7.5 Hz, 4H), 2.06–2.18 (m, 4H), 1.78–2.00 (m, 20H), 1.55–1.79 (m, 8H), 1.32–1.40 (m, 4H), 1.35 (s, 18H), 1.32 (s, 36H), 1.06–1.16 (m, 36H), 0.94 (t, J=7.2 Hz, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ=175.09, 161.48, 159.12, 154.05, 146.91, 146.68, 131.96, 131.58, 131.16, 117.65, 117.45, 115.91, 114.65, 114.55, 91.71, 91.56, 90.68, 90.47, 79.96, 79.42, 78.05. 73.63, 71.70, 36.42, 34.67, 31.35, 30.53, 30.11, 26.60, 25.91, 23.14, 23.10, 16.96, 11.75, 10.69, 10.63; elemental analysis for $C_{160}H_{188}O_{18}$ (2399.27): calcd C 80.10, H 7.90; found C 79.81, H 8.02.

Acknowledgements

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