Synthesis of Electron-Rich Thiamacrocycles

Petr Holý,*[a] Michal Buchta,[a,b] Jiří Rybáček,[a] Jana Hodačová,[a,b] Ivana Císařová[c]

[a] Institute of Organic Chemistry and Biochemistry, v.v.i., Academy of Sciences of the Czech Republic, Flemingovo n. 2., 166 10 Prague 6, Czech Republic
Fax +420(2)20183560; E-mail: petrholy@uochb.cas.cz

[b] Department of Organic Chemistry, Institute of Chemical Technology Prague, Technická 5, 166 28 Prague 6, Czech Republic

[c] Department of Inorganic Chemistry, Faculty of Natural Sciences, Charles University, Prague, Hlavova 2030, 128 40 Prague 2, Czech Republic

Received 13 August 2010; revised 17 September 2010

Abstract: The stepwise syntheses of large [4+4] electron-rich thiamacrocycles, which aim at fullerene complexation, were performed using two types of building blocks, viz. 1,4-bis(bromomethyl)benzene or its dibutoxylated analogue and 4,5-bis(2-cyanoethylsulfanyl)-1,3-dithiole-2-thione. Alternatively, a multicomponent mixture of thiamacrocycles, ranging in size from [2+2] to [6+6] units, was generated by the direct reaction of bis(tetraethylammonium) bis(thioxo-1,3-dithiole-4,5-dithiol)zincate with 1,4-bis(bromomethyl)-2,5-dibutoxybenzene, and the individual macrocycles were successfully separated.

Key words: alkylation, arenes, atropoisomerism, macrocycles, thiols

The chemistry of cyclic ligands attracts continued attention due to their preformed cavities, which facilitate interactions with selected guests. 1,3-Dithiole-2-thione units and especially the related tetrathiafulvalene derivatives (TTFs), well-known electron-rich redox-active components, have been widely used in macrocyclic and supramolecular chemistry.[1] 4,5-Disulfanyl-1,3-dithiole-2-thione units have been employed as link elements in the formation of heteroaromatic macro-rings[2] or in the structure of crown-ether-like macrocycles of different ring size.[3] Macro-rings composed of electron-rich TTF units are known to be good ligands for various electron-poor compounds, particularly for cyclic bipyridinium acceptors.[4] Also, a strong monocation–π interaction has been observed, e.g. for different ammonium ions and electron-rich cyclophane receptors.[5]

Fullerenes represent another kind of weak electron-acceptor that are the center of attention for their unique properties. Many ligands, both cyclic and noncyclic, were synthesized and the formation of their inclusion complexes with fullerenes was studied,[6] but only a few of them feature the dithiolethione or TTF units.[7]

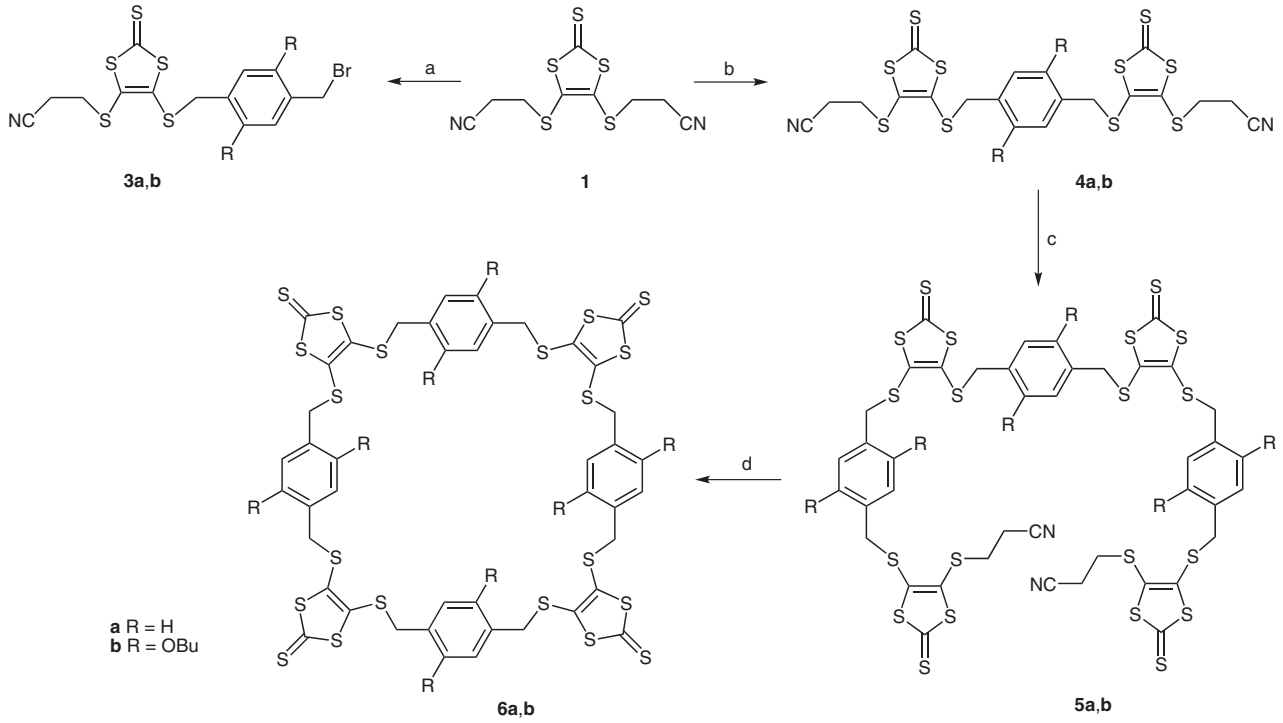
An obvious obstacle in any preparation of macrocycles is the inevitable formation of linear oligomers as byproducts. In this regard, 4,5-bis(2-cyanoethylsulfanyl)-1,3-dithiole-2-thione (**1**) is a very profitable building block because either one or both of its cyanoethyl protective groups can be selectively removed by a stoichiometric amount of base.[8] Such controlled liberation of thiolate species facilitates the preparation of proper acyclic precursors in the overall synthesis of macrocycles. Here we present a new series of electron-rich thiamacrocycles possessing scalable internal cavities, which should be considered as prospective ligands for size-matched acceptors starting with small guests, optionally even chiral, up to spacious molecules like fullerenes.

Considering the protected dithiole **1** and 1,4-bis(bromomethyl)benzene (**2a**) as two complementary building blocks, we have shown by simple molecular modeling that a [4+4] cyclic arrangement of these units forms a cavity large enough for a conceivable inclusion of fullerene C_{60}. Therefore we designed and performed[9] the synthesis of the large [4+4] thiamacrocycle **6a** based on several successive deprotection/alkylation steps illustrated in Scheme 1. This trial procedure provided reasonable yields in all steps, but the limited solubility of the final compound **6a** rendered any solution-phase complexation experiments impossible. Nevertheless, a cation complexation study was performed in the gas phase.[9] After this we decided to repeat this synthetic scheme with a more suited aromatic building block, namely 1,4-bis(bromomethyl)-2,5-dibutoxybenzene (**2b**). Apart from the desired effect on solubility, the alkoxy groups also promote the electron-donating character of the target macrocyclic ligand **6b**.

The macro-ring construction in **6a**,**b** proceeded in four steps (Scheme 1). While the monothiolate derived from **1** reacted with only one bromomethyl group of **2a**,**b** (used in large excess) to give the two-membered acyclic precursors **3a**,**b**, its reaction with both functional groups of **2a**,**b** afforded the three-sectional compounds **4a**,**b** in very good yields. The double attachment of the two-membered parts **3a**,**b** onto the three-sectional block of **4a**,**b** gave smoothly the seven-membered precursors **5a**,**b**. The final cyclizations of acyclic components **5a**,**b** with bis(bromomethyl) derivatives **2a**,**b** were performed under high-dilution conditions leading to the [4+4] thiamacrocycles **6a**,**b** in satisfactory yields.

The ^{1}H and ^{13}C NMR spectra confirmed the symmetry of the final [4+4] macrocycles and their elemental compositions were unambiguously confirmed by HRMS measurements.

SYNTHESIS 2010, No. 24, pp 4169–4176
Advanced online publication: 14.10.2010
DOI: 10.1055/s-0030-1258297; Art ID: T15910SS



Scheme 1 Four-step synthesis of [4+4] macrocycles. *Reaction conditions*: (a) (i) CsOH (1 equiv), MeOH, r.t., 45 min; (ii) **2a** or **2b** (12 equiv), DMF, r.t., 5 h, 42% (**3a**), 67% (**3b**); (b) (i) CsOH (1 equiv), MeOH, r.t., 45 min; (ii) **2a** or **2b** (0.5 equiv), DMF, r.t., 5 h, 69% (**4a**), 91% (**4b**); (c) (i) CsOH (2 equiv), MeOH, r.t., 45 min; (ii) **3a** or **3b** (2 equiv), DMF, r.t., 4 h, 79% (**5a**), 72% (**5b**); (d) (i) CsOH (2 equiv), MeOH, r.t., 30 min; (ii) **2a** or **2b** (1 equiv), DMF, 8 h, dual-syringe pump, then 20 h, r.t., 26% (**6a**), 48% (**6b**).

The crystal structure of the [4+4] macrocycle **6b** (Figure 1) served as independent proof of the constitution of the target compound. Strong π-π interactions between the aromatic segments were found to play an important role in the conformation of the macrocycle [Figure 1 (a)] as well as in the crystal packing [Figure 1 (b)].

The solubility of the macrocycle **6b** in toluene or chloroform is quite sufficient for a complexation study with fullerene C_{60}, but a preliminary measurement by UV-vis spectroscopy did not provide distinct proof of an interaction of the ligand **6b** with C_{60}.

We also attempted the reaction of dithiolates derived from **4a** or **4b** with two equivalents of bis(bromomethyl) derivatives **2a** or **2b**. However, regardless of the structure of the bis(bromomethyl) unit, the small [2+2] macrocycles **8a**,**b** were formed as the dominant products instead of the desired five-sectional precursors **7a**,**b** (Scheme 2). Higher isolated yields of **8a**,**b** were obtained using an equimolar ratio of the components (**4a** + **2a**) or (**4b** + **2b**). In the latter case we have also proved by thorough chromatography of the crude product the formation of the even-numbered

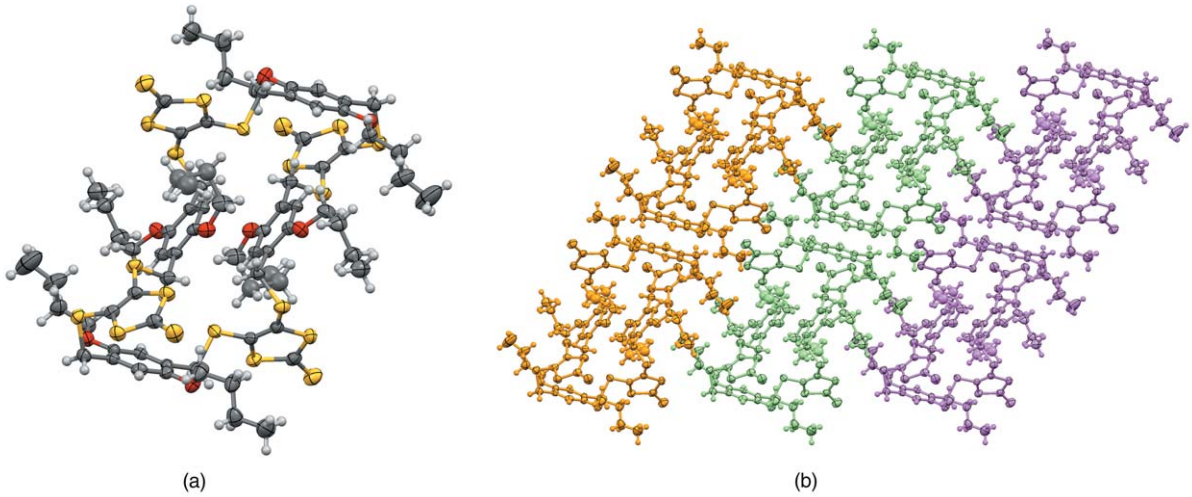
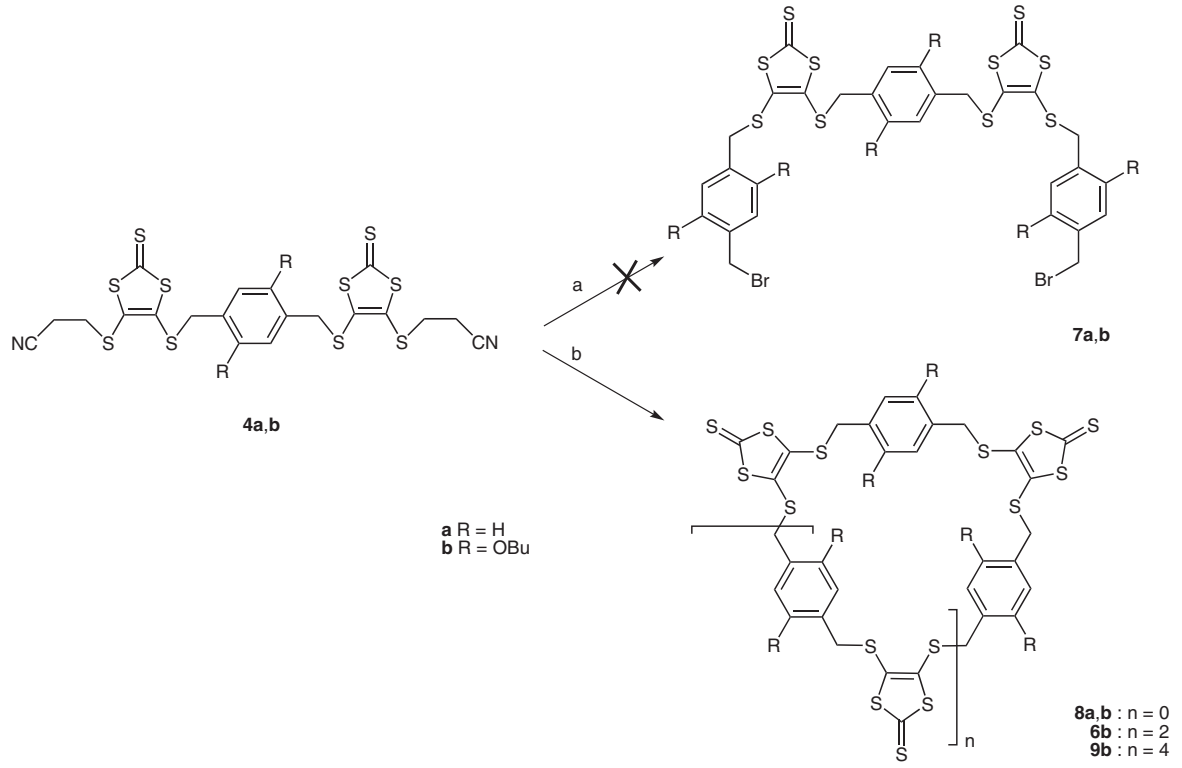


Figure 1 The crystal structure of the [4+4] macrocycle **6b**: (a) This shows the conformation of the macro-ring directed by intramolecular π-π interactions. Only one position of disordered butyl moiety was drawn for clarity. (b) This shows molecular stacks (outlined in different colors) are governed by intermolecular π-π stacking.



Scheme 2 Formation of the [2+2] macrocycles. *Reaction conditions*: (a) (i) CsOH (2 equiv), MeOH, r.t., 15 min; (ii) **2a** or **2b** (2.2 equiv), DMF, r.t., 5 h; (b) (i) CsOH (2 equiv), MeOH, r.t., 15 min; (ii) **2a** or **2b** (1.0 equiv), DMF, r.t., 5 h, 54% (**8a**), 39% (**8b**), 16% (**6b**), 5% (**9b**).

[4+4] macrocycle **6b** and [6+6] macrocycle **9** as minor components.

Notably, the [2+2] macrocycle **8b** was in some respect different from its **8a** analogue. ^{1}H and ^{13}C NMR spectra of the isolated product revealed two cognate sets of signals. By subsequent chromatography we were able to separate the mass of [2+2] macrocycle **8b** into two distinct components, **8b**-*syn* and **8b**-*anti* (Figure 2). The bulky butoxy groups attached to the aromatic units prevent their free rotation and thus give rise to atropoisomerism. The structure of the isomer **8b**-*syn* corresponds to the *meso* form, whereas the **8b**-*anti* isomer represents the racemic mixture of two enantiomers.

The assignment of the appropriate structures to the particular isomers **8b**-*anti*/**8b**-*syn* was based primarily on two independent single crystal X-ray analyses. The structure of the first-eluted isomer **8b**-*anti* confirmed its chiral nature [Figure 3 (b)]; the *meso* configuration belongs to the second isomer **8b**-*syn* [Figure 3 (a)].

Additional proof of this assignment came from the successful analytical resolution of the isomer **8b**-*anti* by HPLC using a chiral stationary phase.

After thermal equilibration, the ratio of **8b**-*anti*/**8b**-*syn* reached 55:45. Thus it can be concluded that the energy difference between the two isomers is rather small. On the other hand, the energy barrier for the *syn*-to-*anti* interconversion is sufficiently high for customary separation of the two rotamers at room temperature. A preliminary kinetic measurement at 50 °C in deuterochloroform showed the Gibbs activation energy for the thermal interconversion to be higher than 100 kJ mol^{-1}.

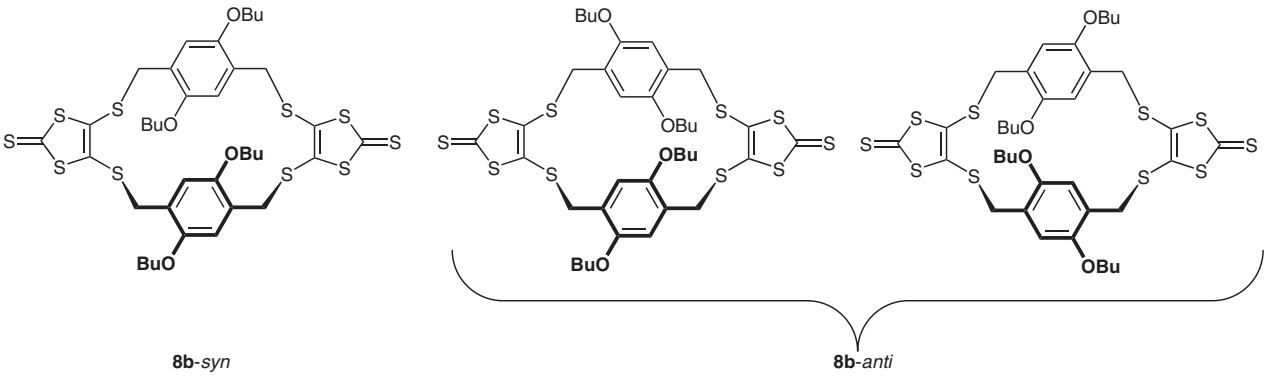


Figure 2 Representation of the **8b**-*syn* and **8b**-*anti* isomers

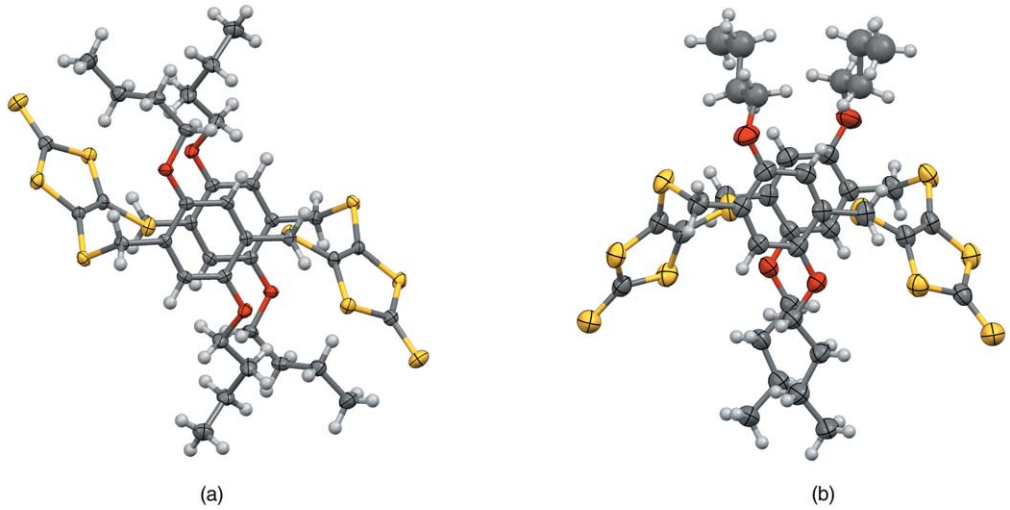


Figure 3 Crystal structures of the both isomers of [2+2] macrocycle **8b**: (a) **8b**-*syn* isomer; (b) **8b**-*anti* isomer (only one enantiomer was shown). Also only one position of disordered butyl moiety was drawn for clarity. Ellipsoids on 50% probability level.

Though we have proved that the multistep preparation of the [4+4] macrocycles outlined in Scheme 1 is in principle applicable to various bis(bromomethyl) blocks, the requisite large excess of the reagent in an early step makes this approach less favorable for more advanced bis(bromomethyl) derivatives. Therefore, we decided to study the direct alkylation of the stable dithiole–zincate[10] **10**. Of course, a complex mixture was anticipated in the reaction with a bifunctional alkylation reagent. Indeed, as concluded from the GPC analysis (Figure 4), the reaction of the

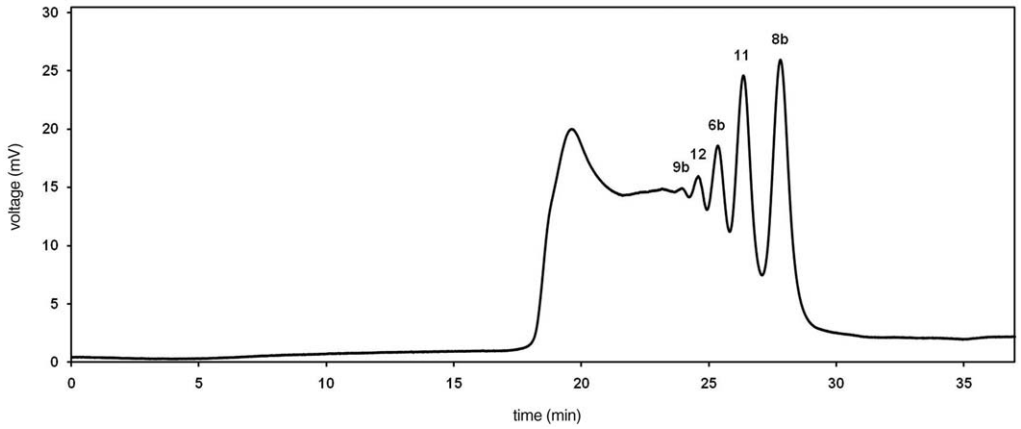
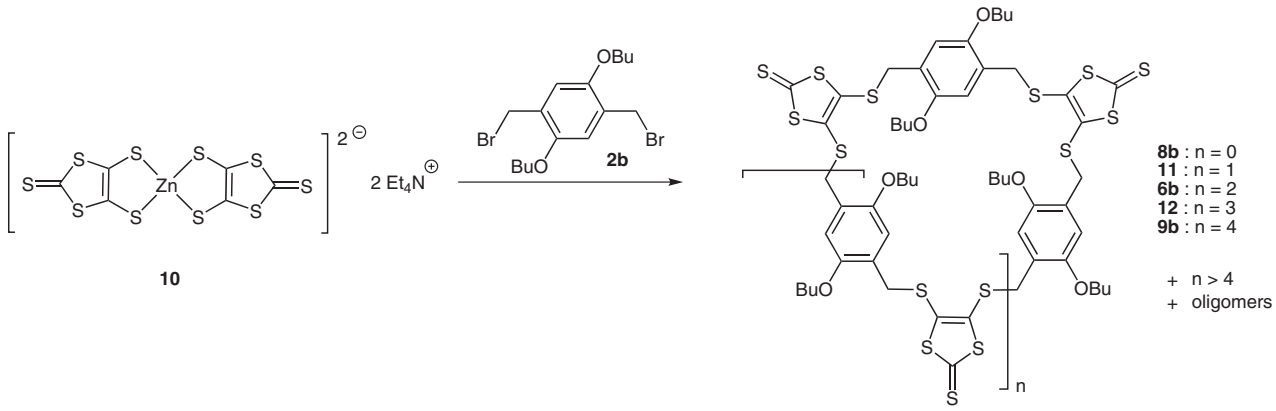


Figure 4 Gel-permeation chromatogram of the crude reaction mixture of the reaction in Scheme 3. The peaks of ascending elution times correspond to the cyclic compounds with descending numbers of involved building blocks (for detailed chromatographic conditions see the experimental part).



Scheme 3 Direct reaction of the zincate salt **10** with 1,4-bis(bromomethyl)-2,5-dibutoxybenzene (**2b**). *Reaction conditions*: **10**/**2b** (1:2), DMF, r.t., 24 h.

salt **10** with 1,4-bis(bromomethyl)-2,5-dibutoxybenzene (**2b**) gave a mixture composed of lower-mass cyclic and higher-mass linear oligomeric compounds (Scheme 3).

The peaks in the GPC chromatogram corresponding to [2+2] macrocycle **8b**, [4+4] macrocycle **6b**, and [6+6] macrocycle **9b** were identified by comparison with authentic samples obtained by the stepwise procedures (*vide supra*). We were able to separate the crude mixture by preparative column chromatography on silica gel to the individual cyclic products (Table 1).

Table 1 Individual Cyclic Compounds Formed in the Direct Reaction of the Zincate Salt **10** with Bis(bromomethyl) Derivative **2b**

Compound	Elution time (min)	Isolated yield (%)
8b[a]	27.8	18.0
11	26.3	10.1
6b	25.3	7.2
12	24.6	3.6
9b	23.9	1.4

[a] The sum of *syn*- and *anti*-isomers.

Although the total yield of the isolated cyclic compounds reached only about 40%, the straightforward approach, apart from its simplicity, seems to be effective for the preparation of a wider family of multi-sized macrocycles. For example, the [4+4] macrocycle **6b** was obtained in this manner as a pure compound in 7.2% yield, which is comparable to the overall yield of the multistep synthesis.

Melting points were determined on a Mikro-Heiztisch Polytherm A apparatus (Hund Wetzlar, Germany) and are uncorrected. NMR spectra were measured on Bruker Avance 400 (^{1}H at 400 MHz and ^{13}C at 101 MHz) and Bruker Avance 600 (^{1}H at 600 MHz and ^{13}C at 151 MHz) spectrometers referenced to TMS or solvent peaks as internal standards. Mass spectra were recorded on a ZAB-EQ (VG-Analytical/Waters, EI, 70 eV) spectrometer, and LCQ Classic (Thermo Finnigan) and Q-Tof micro (Waters) spectrometers with ES or APC ionization. IR spectra were measured on a Bruker Equinox 55 FT-IR spectrophotometer in $CHCl_3$ solns. Gel permeation chromatography (GPC) was performed on a Knauer chromatograph with UV detection at 254 nm equipped with a tandem array of columns Eurogel SEG100 (8 × 300 mm) and TSK gel G2000 (8 × 300 mm), eluent THF, flow rate 0.5 mL min^{-1}. The reaction progress was monitored by TLC on aluminum sheets pre-coated with silica gel 60 F_{254} (Merck) and column chromatography was carried out using silica gel 60 (Merck). Commercially available reagent grade chemicals and anhyd solvents were used as received. Hexanes = a mixture of aliphatic hydrocarbons bp 60–80 °C.

Bis(bromomethyl) derivative **2b** was prepared as described in the literature.[11] Syntheses of compounds **3a**, **5a**, **6a** are described elsewhere[9] and the synthesis of compound **4a** is described in the literature.[12] Zincate salt **10** was prepared according the published, improved, large-scale procedure.[10]

Notably, the character of the new compounds in this study hampered the determination of elemental composition with satisfactory precision. We found that the substances in general bind solvent molecules very tightly in non-stoichiometric ratios and their thermal stability prevents long-term vacuum drying at elevated temperatures.

X-ray Crystallography[13]

Single-crystal diffraction data for compounds **6b**, **8b**-*syn*, and **8b**-*anti* were collected on a Nonius KappaCCD diffractometer using MoKα radiation (λ = 0.71073 Å, graphite monochromator) via φ and ω scans. The structures were solved by direct methods (SIR-92[14]) and refined by full-matrix least squares based on F^2 (SHELXL-97[15]). The hydrogen atoms were found on difference Fourier maps and recalculated into idealized positions, all hydrogens were fixed into their positions (riding model) with assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$ (pivot atom) or $H_{iso}(H) = 1.2\ U_{eq}$ (pivot atom) for the methyl moiety.

3-[(5-{[4-(Bromomethyl)-2,5-dibutoxybenzyl]sulfanyl}-2-thioxo-1,3-dithiol-4-yl)sulfanyl]propanenitrile (3b)

$CsOH·H_2O$ (72.1 mg, 0.493 mmol) was dissolved in MeOH (3 mL) and added dropwise under argon to the soln of **1** (150 mg, 0.493 mmol) in degassed anhyd DMF (6 mL) at r.t. over 30 min. After stirring for an additional 45 min, 1,4-bis(bromomethyl) derivative **2b** (2.32 g, 5.68 mmol) in degassed anhyd DMF (36 mL) was added over 30 min and the mixture was stirred at r.t. for 5 h. Then, the mixture was diluted with H_2O (250 mL). The precipitate was filtered off, washed with H_2O, and dried. Column chromatography (silica gel, 50 × 400 mm, hexanes–Et_2O–acetone, 60:25:15) initially eluted excess of **2b**, followed by **3b**; yield: 191 mg (67%); mp 91–92 °C.

IR ($CHCl_3$): 2958, 2929, 2856, 2255, 1602, 1512, 1464, 1422, 1067, 1035, 618, 515 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 1.48–1.54 (m, 4 H), 1.74–1.84 (m, 4 H), 2.49 (t, *J* = 7.2 Hz, 2 H), 2.83 (t, *J* = 7.2 Hz, 2 H), 3.95 (t, *J* = 6.2 Hz, 2 H), 3.97 (t, *J* = 6.2 Hz, 2 H), 4.06 (s, 2 H), 4.54 (s, 2 H), 6.71 (s, 1 H), 6.86 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.9, 13.9, 18.4, 19.3, 19.4, 28.9, 31.3, 31.4, 31.9, 36.3, 68.6, 68.9, 114.2, 114.4, 117.1, 125.8, 127.0, 134.6, 140.6, 150.4, 150.5, 210.4.

MS (EI$^+$): *m*/*z* (%) = 577 (0.2, [M]$^+$), 327 (75), 271 (30), 215 (20), 57 (70), 41 (100).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{22}H_{28}NO_2S_5Br$: 576.9916; found: 576.9907.

3,3′-{(2,5-Dibutoxybenzene-1,4-diyl)bis[methanediylsulfanediyl(2-thioxo-1,3-dithiole-5,4-diyl)sulfanediyl]}dipropanenitrile (4b)

$CsOH·H_2O$ (352 mg, 2.01 mmol) was dissolved in MeOH (7 mL) and added dropwise under argon to the soln of **1** (609 mg, 2.00 mmol) in degassed anhyd DMF (30 mL) at r.t. over 30 min. After stirring for an additional 45 min, the bis(bromomethyl) derivative **2b** (408 mg, 1.00 mmol) in degassed anhyd DMF (20 mL) was added over 30 min and the mixture was stirred at r.t. for 4 h, then H_2O (250 mL) was added. The precipitate was collected by filtration, washed with H_2O, dried, and crystallized (acetone); yield: 685 mg (91%); mp 148–150 °C.

IR ($CHCl_3$): 2961, 2935, 2874, 2255, 1612, 1507, 1467, 1420, 1234, 1069, 1028, 869, 515 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.2 Hz, 6 H), 1.47–1.54 (m, 4 H), 1.76–1.84 (m, 4 H), 2.57 (t, *J* = 6.8 Hz, 4 H), 2.94 (t, *J* = 6.8 Hz, 4 H), 3.93 (t, *J* = 6.8 Hz, 4 H), 4.09 (s, 4 H), 6.84 (s, 2 H).

^{13}C NMR (101 MHz, CDCl3): δ = 13.9, 18.6, 19.4, 31.5, 32.0, 36.2, 68.9, 114.2, 117.1, 125.2, 133.8, 141.1, 150.6, 210.4.

MS (ESI$^+$): *m*/*z* = 771 ([M + Na]$^+$), 748 ([M]$^+$).

HRMS (ESI$^+$): *m/z* [M + H]$^+$ calcd for $C_{28}H_{33}N_2O_2S_{10}$: 748.9744; found: 748.9748; *m/z* [M + Na]$^+$ calcd for $C_{28}H_{32}N_2O_2S_{10}Na$: 770.9563; found: 770.9567.

3,3′-{(2,5-Dibutoxybenzene-1,4-diyl)bis[methanediylsulfanediyl(2,5-dibutoxybenzene-4,1-diyl)methanediylsulfanediyl(2-thioxo-1,3-dithiole-5,4-diyl)sulfanediyl]}dipropanenitrile (5b)

CsOH·H_2O (53.7 mg, 0.319 mmol) was dissolved in MeOH (3 mL) and added dropwise under argon to the soln of compound **4b** (120 mg, 0.160 mmol) in degassed anhyd DMF (15 mL) at r.t. over 30 min. After stirring for an additional 45 min, the dark red soln was added dropwise into the stirred soln of compound **3b** (185 mg, 0.319 mmol) in degassed anhyd DMF (20 mL) over 30 min. The mixture was stirred for 4 h, then H_2O (400 mL) was added. The mixture was extracted with $CHCl_3$ (3 × 100 mL), and the combined organic phases were washed with H_2O (3 × 100 mL) and dried (Na_2SO_4). Solvents were removed in vacuo and a yellow deposit crystallized (acetone–*n*-hexane) to give a yellow powder; yield: 190 mg (72%); mp 80–82 °C.

IR ($CHCl_3$): 3000, 2930, 2855, 2256, 1602, 1462, 1421, 1067, 1035, 515 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96–1.00 (m, 18 H), 1.46–1.52 (m, 12 H), 1.72–1.78 (m, 12 H), 2.54 (t, *J* = 6.8 Hz, 4 H), 2.92 (t, *J* = 6.8 Hz, 4 H), 3.87–3.93 (m, 12 H), 3.97 (s, 4 H), 3.98 (s, 4 H), 4.06 (s, 4 H), 6.64 (s, 2 H), 6.69 (s, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.9, 13.9, 18.6, 19.4, 31.4, 31.5, 32.1, 36.1, 36.2, 36.3, 68.9, 114.2, 114.3, 117.0, 124.9, 125.2, 125.6, 138.5, 141.2, 150.5, 150.6, 210.4, 211.5.

MS (APCI$^+$): *m/z* = 1659 [M + Na]$^+$, 1637 [M + H]$^+$, 1636 [M]$^+$.

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{66}H_{81}N_2O_6S_{20}$: 1637.0477; found: 1637.0503.

[4+4] Macrocycle 6b

CsOH·H_2O (40.8 mg, 0.243 mmol) was dissolved in MeOH (1 mL) and added dropwise under argon to the soln of compound **5b** (188 mg, 0.114 mmol) in degassed anhyd DMF (29 mL) over 10 min and the resulting soln was stirred for 30 min. Bis(bromomethyl) derivative **2b** (51.2 mg, 0.125 mmol) was dissolved in degassed anhyd DMF (30 mL). The two solns were simultaneously added (using the dual syringe pump) to the flask containing anhyd DMF (40 mL) with stirring over 8 h. After stirring for an additional 20 h, the soln was diluted with H_2O (400 mL). The mixture was extracted with $CHCl_3$ (3 × 100 mL), and the combined organic phases were washed with H_2O (3 × 100 mL) and dried (Na_2SO_4). Solvents were removed in vacuo and the yellow deposit was subjected to column chromatography (silica gel, 30 × 300 mm, hexanes–CH_2Cl_2, 1:1). Evaporation of collected fractions and crystallization (CH_2Cl_2–*n*-hexane) gave the macrocycle **6b**; yield: 97.0 mg (48%); mp 134–137 °C.

IR ($CHCl_3$): 2961, 2934, 2874, 1604, 1507, 1466, 1429, 1405, 1390, 1314, 1235, 1066, 1030, 868, 516 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.6 Hz, 24 H), 1.46–1.51 (m, 16 H), 1.71–1.76 (m, 16 H), 3.84 (s, 16 H), 3.86 (t, *J* = 6.4 Hz, 16 H), 6.58 (s, 8 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.0, 19.4, 31.6, 36.3, 69.0, 114.3, 125.3, 138.6, 150.5, 211.4.

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{76}H_{97}O_8S_{20}$: 1777.1592; found: 1777.1546.

X-ray Crystal Data

6b: $C_{76}H_{96}O_8S_{20}$, M_r = 1778.73, triclinic, $P\bar{1}$ (No. 2), *a* = 11.1065(5) Å, *b* = 14.1727(6) Å, *c* = 15.1553(7) Å, *α* = 67.256(2)°, *β* = 84.538(2)°, *γ* = 81.493(2)°, Z = 1, D_x = 1.359 g cm^{-3}, orange crystal of dimensions 0.30 × 0.17 × 0.17 mm, *T* = 150(2) K, absorption was neglected (μ = 0.544 mm^{-1}); 32458 diffractions collected (θ_{max} = 25°), 7720 independent (R_{int} = 0.040) and 5680 observed [$I > 2\sigma(I)$]. One of the three symmetrically independent butyl moieties is disordered into 2 positions with equal occupancy, disordered atoms were refined isotropically; 468 refined parameters, GOF 1.022, final *R* indices $R[F^2 > 2\sigma(F^2)]$ = 0.0499, $wR(F^2)$ = 0.1422, maximal/minimal residual electron density $\Delta\rho_{max}$ = 0.72 e Å^{-3}, $\Delta\rho_{min}$ –0.71 e Å^{-3}.

[2+2] Macrocycle 8a

CsOH·H_2O (144 mg, 0.986 mmol) was dissolved in MeOH (3 mL) and added dropwise under argon to the soln of **4a** (298 mg, 0.493 mmol) in degassed anhyd DMF (20 mL) at r.t. over 15 min. After stirring for an additional 15 min, 1,4-bis(bromomethyl)benzene (**2a**, 131 mg, 0.496 mmol) in degassed anhyd DMF (15 mL) was added over 2 h and the mixture was stirred at r.t. for 5 h. Then, the mixture was diluted with H_2O (250 mL), and the precipitate was filtered off, washed with H_2O, and dried. Column chromatography (silica gel, column 30 × 250 mm, hexanes–CH_2Cl_2, 40:60) eluted the [2+2] macrocycle **8a**; yield: 160 mg (54%); mp 240–244 °C (*n*-hexane–$CHCl_3$).

IR ($CHCl_3$): 3055, 3020, 3000, 2929, 2855, 1603, 1512, 1462, 1422, 1066, 1035, 1021, 829, 515 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.92 (s, 8 H), 7.04 (s, 8 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 40.2, 129.4, 136.0, 136.2, 210.8.

MS (EI$^+$): *m/z* (%) = 600 (23, [M]$^+$), 300 (22), 166 (47), 104 (100), 76 (75), 64 (35).

HRMS (EI$^+$): *m/z* [M]$^+$ calcd for $C_{22}H_{16}S_{10}$: 599.8459; found: 599.8449.

[4+4] Macrocycle 6b [2+2] Macrocycle 8b, and [6+6] Macrocycle 9b

CsOH·H_2O (177 mg, 1.05 mmol) was dissolved in MeOH (3 mL) and added dropwise under argon to the soln of **4b** (376 mg, 0.501 mmol) in degassed anhyd DMF (20 mL) at r.t. over 15 min. After stirring for an additional 15 min, 1,4-bis(bromomethyl) derivative **2b** (225 mg, 0.551 mmol) in degassed anhyd DMF (15 mL) was added over 2 h and the mixture was stirred at r.t. for 8 h. Then, the mixture was diluted with H_2O (250 mL), and the precipitate was filtered off, washed with H_2O, and dried. Column chromatography (silica gel, column 30 × 350 mm, hexanes–CH_2Cl_2, 60:40) initially eluted the [2+2] macrocycle **8b** [ratio **8b**-*anti*/**8b**-*syn*, 55:45 (^{1}H NMR signal integration)]; yield: 175 mg (39%). Further elution (hexanes–CH_2Cl_2, 50:50) afforded [4+4] macrocycle **6b** [yield: 58 mg (13%)] and the [6+6] macrocycle **9b** [yield: 22 mg (5%)].

[2+2] Macrocycle 8b-*anti* and 8b-*syn*

MS (EI$^+$): *m/z* (%) = 888 (20, [M]$^+$), 691 (25), 248 (100), 215 (20), 76 (80).

HRMS (ESI$^-$): *m/z* [M – H]$^-$ calcd for $C_{38}H_{47}O_4S_{10}$: 887.0687; found: 887.0672.

[4+4] Macrocycle 6b

The analytical data of [4+4] macrocycle **6b** prepared in this manner were consistent with those of the product obtained by the stepwise procedures (*vide supra*).

[6+6] Macrocycle 9b

Mp 87–89 °C.

IR ($CHCl_3$): 2960, 2933, 2873, 1613, 1507, 1466, 1429, 1405, 1390, 1314, 1235, 1065, 1030, 867, 516 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.4 Hz, 36 H), 1.43–1.52 (m, 24 H), 1.70–1.77 (m, 24 H), 3.87 (t, *J* = 6.4 Hz, 24 H), 3.92 (s, 24 H), 6.63 (s, 12 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.0, 19.4, 31.5, 36.2, 68.9, 114.3, 125.3, 138.5, 150.6, 211.4.

HRMS (APCI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{114}H_{145}O_{12}S_{30}$: 2665.2352; found: 2665.2379.

By subsequent chromatography of the mixture of **8b**-*anti* and **8b**-*syn* (160 mg) (silica gel, column 30 × 300 mm, hexanes–acetone–Et_2O, 80:10:10) the pure **8b**-*anti* isomer was eluted first [yield: 72 mg after crystallization (*n*-hexane–$CHCl_3$); mp 150–152 °C], followed by mixed fractions and finally by the pure **8b**-*syn* isomer [yield: 48 mg after crystallization (*n*-hexane–$CHCl_3$); mp 192–194 °C].

8b-*anti*

IR ($CHCl_3$): 2961, 2935, 2874, 1614, 1508, 1466, 1432, 1421, 1390, 1234, 1066, 1036, 867, 518 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.4 Hz, 12 H), 1.45–1.59 (m, 8 H), 1.71–1.84 (m, 8 H), 3.52 (d, *J* = 11.8 Hz, 4 H), 3.86–3.91 (m, 8 H), 4.19 (d, *J* = 11.8 Hz, 4 H), 6.42 (s, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.9, 19.4, 31.6, 36.5, 69.0, 114.1, 125.8, 138.8, 150.7, 212.3.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{38}H_{48}O_4S_{10}$: 888.0760; found: 888.0754.

A sample of the **8b**-*anti* isomer was subjected to HPLC analysis on a chiral stationary phase (column Knauer Eurocel 01, 5 μm, 250 × 4.6 mm, *n*-heptane–*i*-PrOH, 99.5:0.5, 1 mL min^{-1}, Knauer isocratic instrument with UV and polarimetric detectors). Two peaks with the same integral intensity were recorded at 16.6 min for the (+)-**8b**-*anti* enantiomer and at 34.0 min for the (–)-**8b**-*anti* enantiomer.

8b-*syn*

IR ($CHCl_3$): 2961, 2934, 2874, 1613, 1508, 1467, 1432, 1422, 1406, 1390, 1233, 1066, 1036, 867, 518 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.4 Hz, 12 H), 1.46–1.55 (m, 8 H), 1.73–1.79 (m, 8 H), 3.50 (d, *J* = 12.1 Hz, 4 H), 3.83–3.89 (m, 8 H), 4.24 (d, *J* = 12.1 Hz, 4 H), 6.52 (s, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.0, 19.5, 31.6, 36.6, 68.9, 114.3, 126.1, 138.2, 150.7, 212.0.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{38}H_{48}O_4S_{10}$: 888.0760; found: 888.0754.

X-ray quality single crystals of the both isomers (**8b**-*anti* and **8b**-*syn*) were grown by a slow evaporation of their solns (*n*-hexane–$CHCl_3$ mixtures).

X-ray Crystal Data

8b-*anti*: $C_{38}H_{48}O_4S_{10}$, M_r = 889.36, monoclinic, *C2/c* (No. 15), *a* = 13.9823(3) Å, *b* = 21.2394(6) Å, *c* = 15.3770(4) Å, *β* = 107.1324(12)°, *Z* = 4, D_x = 1.354 g cm^{-3}, yellow crystal of dimensions 0.25 × 0.20 × 0.12mm, *T* = 230(2) K (the crystal splits below this temperature), absorption was neglected (μ = 0.54 mm^{-1}); 30959 diffractions collected (θ_{max} = 26°), 4455 independent (R_{int} = 0.043) and 3397 observed [$I > 2\sigma(I)$]. One of the two symmetrically independent butyl moieties is disordered into three positions with 0.5:0.3:0.2 occupancies, disordered atoms were refined isotropically; 248 refined parameters, goodness of fit 1.02, final *R* indices $R[F^2 > 2\sigma(F^2)]$ = 0.038, $wR(F^2)$ = 0.107, maximal/minimal residual electron density $\Delta\rho_{max}$ = 0.52 e Å^{-3}, $\Delta\rho_{min}$ –0.42 e Å^{-3}.

8b-*syn*: $C_{38}H_{48}O_4S_{10}$, M_r = 889.36, monoclinic, $P2_1/c$ (No. 14), *a* = 16.4958(10) Å, *b* = 8.4573(11) Å, *c* = 16.7316(17) Å, β = 117.082(6)°, Z = 2, D_x = 1.421 g cm^{-3}, yellow crystal of dimensions 0.35 × 0.35 × 0.08 mm, absorption was neglected (μ = 0.57 mm^{-1}), 36931 diffractions collected (θ_{max} = 27.5°), 4504 independent (R_{int} = 0.058) and 3608 observed [$I > 2\sigma(I)$], 237 parameters, goodness of fit 1.04, final *R* indices $R[F^2 > 2\sigma(F^2)]$ = 0.034, $wR(F^2)$ = 0.081, maximal/minimal residual electron density $\Delta\rho_{max}$ = 0.61 e Å^{-3}, $\Delta\rho_{min}$ –0.26 e Å^{-3}.

Direct Reaction of Bis(tetraethylammonium) Bis(2-thioxo-1,3-dithiole-4,5-dithiol)zincate (10) with 1,4-Bis(bromomethyl)-2,5-dibutoxybenzene (2b)

The mixture of bis(bromomethyl) derivative **2b** (408 mg, 1.00 mmol) and zincate salt **10** (360 mg, 0.500 mmol) in degassed anhyd DMF (20 mL) was stirred at r.t. for 24 h. The mixture was diluted with H_2O (150 mL), the resulting precipitate was filtered off, washed with H_2O, dried and subjected to column chromatography (silica gel, 50 × 450 mm, hexanes–CH_2Cl_2, 2:1 to 1:1). Five individual macrocycles were successively eluted in order of their increasing size and identified by comparison with authentic samples prepared previously and by their NMR and HRMS spectral data. Yields of the pure macrocycles were as follows: [2+2] macrocycle **8b** (mixture of *syn*- and *anti*-isomers): 140 mg (18%); [3+3] macrocycle **11**: 84 mg (10%); [4+4] macrocycle **6b**: 32 mg (7%); [5+5] macrocycle **12**: 18 mg (3%), [6+6] macrocycle **9b**: 18 mg (1.4%).

[3+3] Macrocycle 11

Mp 59–62 °C.

IR ($CHCl_3$): 2961, 2934, 2874, 1611, 1507, 1466, 1430, 1405, 1390, 1314, 1235, 1066, 1030, 868, 516 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 18 H), 1.46–1.55 (m, 12 H), 1.73–1.80 (m, 12 H), 3.78 (s, 12 H), 3.88 (t, *J* = 6.5 Hz, 12 H), 6.56 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.0, 19.5, 31.6, 36.5, 69.0, 114.2, 125.5, 138.6, 150.5, 211.5.

HRMS (APCI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{57}H_{73}O_6S_{15}$: 1333.1212; found: 1333.1188.

[5+5] Macrocycle 12

Mp 66–68 °C.

IR ($CHCl_3$): 2961, 2933, 2873, 1613, 1507, 1466, 1429, 1405, 1390, 1314, 1235, 1066, 1030, 867, 516 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 30 H), 1.43–1.52 (m, 20 H), 1.70–1.77 (m, 20 H), 3.86 (t, *J* = 6.5 Hz, 20 H), 3.90 (s, 20 H), 6.62 (s, 10 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.0, 19.4, 31.5, 36.2, 68.9, 114.3, 125.3, 138.6, 150.6, 211.4.

HRMS (APCI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{95}H_{121}O_{10}S_{25}$: 2221.1972; found: 2221.2010.

Acknowledgment

This work was carried out under the research project Z4 055 0506. The financial support provided by the Grant Agency of the Academy of Sciences of the Czech Republic (grant No. IAA400550704) is gratefully acknowledged. I.C. thanks to MSM0021620857.

References

(1) (a) Nielsen, M. B.; Li, Z.-T.; Becher, J. *J. Mater. Chem.* **1997**, *7*, 1175. (b) Becher, J.; Li, Z.-T.; Blanchard, P.; Svenstrup, N.; Lau, J.; Nielsen, M. B.; Leriche, P. *Pure Appl. Chem.* **1997**, *69*, 4655. (c) Nielsen, M. B.; Lomholt, C.; Becher, J. *Chem. Soc. Rev.* **2000**, *29*, 153.

(2) Girmay, B.; Kilburn, J. D.; Underhill, A. E.; Varma, K. S.; Hursthouse, M. B.; Harman, M. E.; Becher, J.; Bojesen, G. *J. Chem. Soc., Chem. Commun.* **1989**, 1406.

(3) (a) Hansen, T. K.; Jørgensen, T.; Stein, P. C.; Becher, J. *J. Org. Chem.* **1992**, *57*, 6403. (b) Simonsen, K. B.; Thorup, N.; Becher, J. *Synthesis* **1997**, 1399.
(4) Nielsen, M. B.; Hansen, J. G.; Becher, J. *Eur. J. Org. Chem.* **1999**, 2807.
(5) Sarri, P.; Venturi, F.; Cuda, F.; Roelens, S. *J. Org. Chem.* **2004**, *69*, 3654.
(6) (a) Diederich, F.; Gómez-López, M. *Chem. Soc. Rev.* **1999**, *28*, 263. (b) Kawase, T.; Kurata, H. *Chem. Rev.* **2006**, *106*, 5250.
(7) (a) Izuoka, A.; Tachikawa, T.; Sugawara, T.; Suzuki, Y.; Konno, M.; Saito, Y.; Shinohara, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1472. (b) Izuoka, A.; Tachikawa, T.; Sugawara, T.; Saito, Y.; Shinohara, H. *Chem. Lett.* **1992**, 1049. (c) Konarev, D. V.; Kovalevsky, A. Yu.; Coppens, P.; Lyubovskaya, R. N. *Chem. Commun.* **2000**, 2357. (d) Pérez, E. M.; Sierra, M.; Sánchez, L.; Torres, M. R.; Viruela, R.; Viruela, P. M.; Ortí, E.; Martín, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 1847.
(8) (a) Becher, J.; Lau, J.; Leriche, P.; Mørk, P.; Svenstrup, N. *J. Chem. Soc., Chem. Commun.* **1994**, 2715. (b) Simonsen, K. B.; Svenstrup, N.; Lau, J.; Simonsen, O.; Mørk, P.; Kristensen, G. J. *Synthesis* **1996**, 407.
(9) Tsierkezos, N. G.; Buchta, M.; Holý, P.; Schröder, D. *Rapid Commun. Mass Spectrom.* **2009**, *23*, 1550.
(10) Wang, C.; Batsanov, A. S.; Bryce, M. R.; Howard, J. A. K. *Synthesis* **1998**, 1615.
(11) Eldo, J.; Arunkumar, E.; Ajayaghosh, A. *Tetrahedron Lett.* **2000**, *41*, 6241.
(12) Allen, D. W.; Berridge, R.; Bricklebank, N.; Cerrada, E.; Light, M. E.; Hursthouse, M. B.; Laguna, M.; Moreno, A.; Skabara, P. J. *J. Chem. Soc., Dalton Trans.* **2002**, 2654.
(13) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre 12, Union Road, Cambridge, CB2 1EZ, UK under deposition numbers: **6b**: CCDC 786385; **8b**-*anti*: CCDC 786386; **8b**-*syn*: CCDC 786387 [fax: +44(1223)336033, e-mail: deposit@ccdc.cam.ac.uk].
(14) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
(15) Sheldrick, G. M. *SHELXL-97: A Program for Crystal Structure Refinement*; University of Göttingen: Germany, **1997**.