‘Click’ [3+2]-Cycloaddition Approach to Novel Cookson’s Birdcage-Derived Thiacrown Ethers

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Abstract: The synthesis of novel Cookson’s birdcage-annulated thiacrowns as well as noncage oligomers with an incorporated 1,2,3-triazole moiety are described. The title compounds were prepared applying a click alkyne–azide cycloaddition reaction in the final macrocyclization step. Using this methodology a series of oligomers containing oxygen, nitrogen, and sulfur were prepared. The effective cycloaddition process was carried out under nonaqueous conditions in the presence of a catalytic amount of copper(I) iodide and *N*,*N*-diisopropylethylamine; the yields of oligomers were moderate to good.

Key words: macrocycles, thiacrown ethers, click chemistry, 1,3-dipolar cycloaddition, cage compounds

Since the first synthesis of a thiacrown ether in 1934,[1] sulfur-containing macrocycles have become one of the most important tools in coordination chemistry, including industrial utility. A series of publications dealing with, for example, polymeric, luminescent, chemosensory, and dye materials illustrate more recent interest in this area.[2] Despite their structural diversity, thiacrown ethers functionalized by simple, highly lipophilic moieties, e.g. terpene-derived building blocks,[3] still represent a rare class of macrocyclic compounds. Several reports exploiting Cookson’s diketone[4] **1** for the preparation of chiral and achiral hydrocarbon-enriched crown ethers such as **2** were published by Marchand and co-workers (Figure 1).[5] As the annular oxygen present in the pentacycloundecane (PCU) derivatives of type **2** can participate in metal ion complexation, the starting polycyclic ketone is an ideal candidate for a rigid subunit in a macrocyclic ether.

In the search for stable and biocompatible[6] silver(I) ion complexing agents,[7] and also for other metals, we turned our attention to 1,2,3-triazole as a readily available linkage. Although the click protocol has already been applied

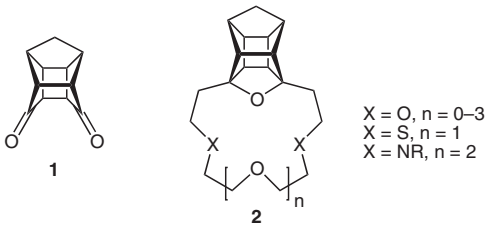
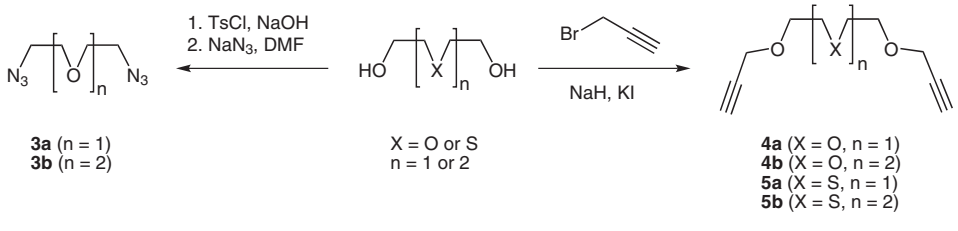


Figure 1 Key building block Cookson’s diketone **1** and selected known birdcage-derived crown ethers **2**

for the construction of crown and lariat ethers,[8] to the best of our knowledge no reports on sulfur-containing analogues have been published to date. Hence, we describe the synthesis of some novel thiacrowns exploiting the Huisgen–Sharpless–Meldal methodology of copper(I)-catalyzed [3+2]-cycloaddition reaction.[9]

The model substrates, two diazido ethers **3a** and **3b**, were selected and prepared following literature protocols (Scheme 1).[10] Thus, commercially available di- and triethylene glycols were converted into the corresponding bistosylated derivatives. Subsequent substitution employing sodium azide in *N*,*N*-dimethylformamide afforded the desired materials in nearly quantitative yield. Taking into account the potentially explosive character of compounds such as **3** (the ‘rule of six’[11]), the syntheses were performed on a small scales (ca. 1–2 mmol), and the freshly prepared crude diazides **3** were used in the next step without storage and further handling.

As shown on Scheme 1, the α,ω-bispropargylated oxa-podands **4a**,**b** were prepared using aforementioned ethylene glycols and propargyl bromide in the presence of a catalytic amount of potassium iodide according to known methodology.[12] An analogous procedure was utilized,



Scheme 1 Synthesis of model podands functionalized with azido and propargyl groups

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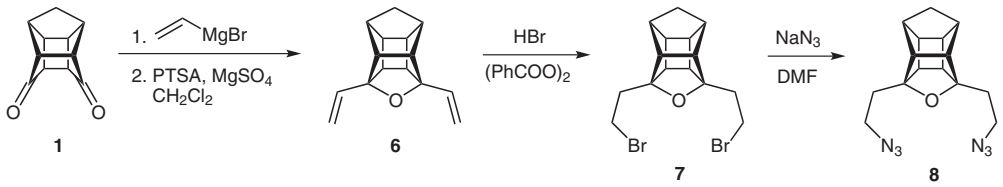


Scheme 2 Synthesis of birdcage-derived diazide **8**

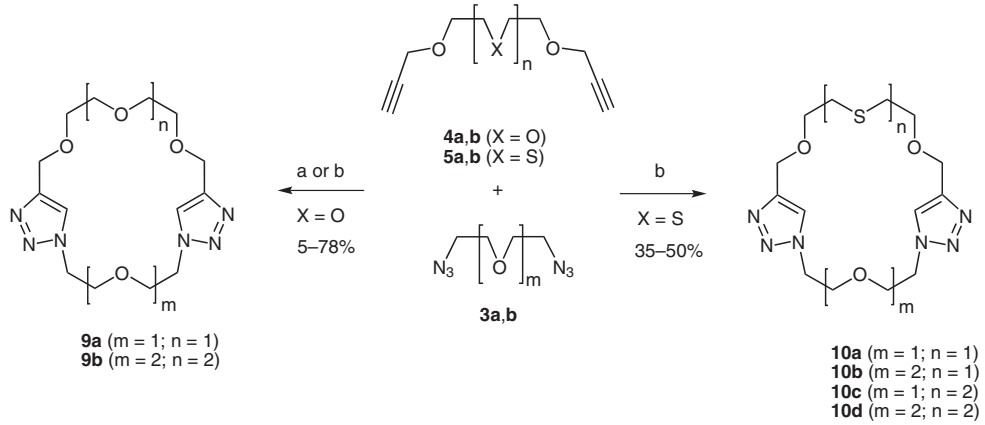
starting with sulfur-containing diols, to provide hitherto unknown compounds **5a** and **5b** in high yield (85% and 77%, respectively).

Similarly, the lipophilic birdcage-derived building block **8** was obtained by halogen–azide exchange under suitable reaction conditions. As depicted in Scheme 2, the desired, fairly stable, material **8** was prepared in four steps, starting with Cookson's diketone **1**, and it was isolated in an acceptable overall yield of 36%. After double addition of the Grignard reagent onto **1**, the crude *endo*-*endo*-diol was dehydrated by a slightly modified literature protocol,[13] and the resulting divinyl derivative **6** was smoothly converted into the respective dibromide **7**.[14] As expected, a strong and broad absorption band, attributed to the azide moieties, was found at 2079 cm^{-1} in the IR spectrum of newly prepared **8**.

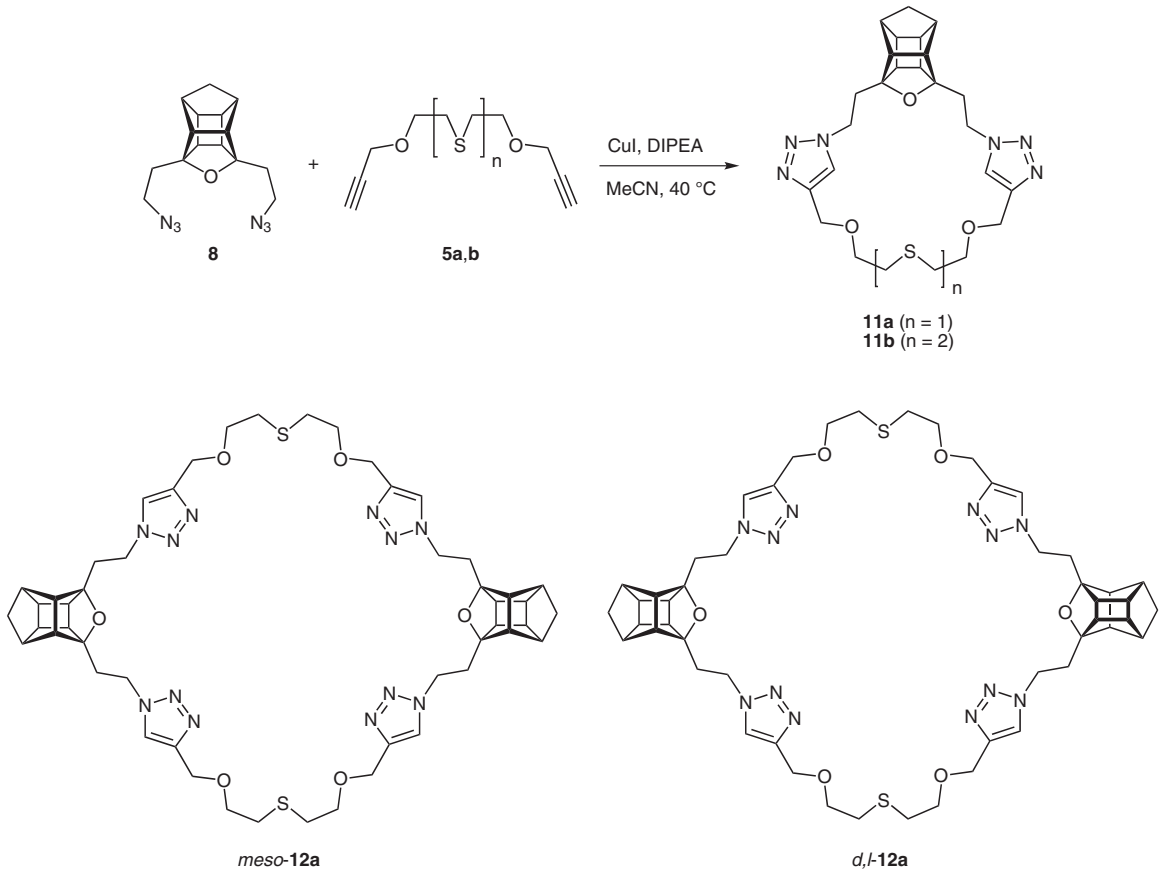
First experiments on the alkyne–azide macrocyclization reactions using model diazide **3a** and bispropargyl ether **4a** were carried out in the presence of copper sulfate and sodium ascorbate as a source of Cu(I), in aqueous methanol. The very slow addition of **3a**/**4a** (1:1) to the reaction mixture under argon was found to be decisive for the formation of the macrocycle **9a**. However, in all attempts the yield of the desired material was only moderate; the best result gave **9a** in 27% yield. As expected, in the ^{1}H NMR spectrum of **9a** the sharp singlet attributed to the C(5)–H of the 1,2,3-triazole ring was found at δ = 7.49. In the quest for a more efficient protocol, the reaction was repeated under nonaqueous conditions (dry acetonitrile) in the presence of catalytic amounts of copper(I) iodide/*N*,*N*-diisopropylethylamine at slightly elevated temperatures (40 °C) as depicted in Scheme 3. After standard workup, the target **9a** was isolated in a satisfactory 78% yield as a pale yellow oil. Analogously, the podands **3b** and **4b** bearing elongated oxo-polyethylene bridges were examined under the same reaction conditions affording the desired macrocycle **9b** in only 36% yield. Apparently, in contrast to **9a**, under aqueous conditions 26-membered crown-like ether **9b** was found only in traces by ^{1}H NMR determination.

Next, with new podands **5a**,**b** in hand, a series of four variably linked sulfur-containing crowns **10a**–**d** were prepared under nonaqueous reaction conditions (Scheme 3). In contrast to the exceptionally high yield of **9a** (78%), the combination of diazide **3a** and **5a** furnished monosulfurated analogue **10a** in an acceptable 35% yield only. It should also be emphasized, that in all cases the isolated products of type **9** and **10** were contaminated with small amounts (below 5%) of double-sized macromolecules. Attempted separations by either standard column or preparative thin-layer chromatography were unsuccessful.

Finally, the birdcage-derived diazide **8** and the bispropargylated podands **5a**,**b** were used as reaction partners in an analogous protocol (Scheme 4). The reaction of **5a** with **8** provided, along with the expected **11a** (48%), significant amounts of double-sized macrocycles of type **12a** (approx. 20%) as a mixture of *meso*- and *d*,*l*-isomers. Unfortunately, none of the major components of the crude mixture could be isolated in a pure state based on standard chromatography techniques. We assume that higher preference for the formation of byproduct **12a** is driven by steric reasons (very likely due to rigidity of the cage-derived substrate). This limitation was overcome by running the reaction under two times higher dilution and prolonging



Scheme 3 Preparation of the 1,2,3-triazole-functionalized macrocycles of type **9** and **10**. *Reagents and conditions*: (a) $CuSO_4$, sodium ascorbate, H_2O–MeOH (2:1), 65 °C, 24 h; (b) CuI, DIPEA, MeCN, 40 °C, 24 h.



Scheme 4 Preparation of birdcage-derived macrocycles **11** and **12**

the reaction time (48 h). Thus the target macrocycle **11a** was isolated in very high yield (76%) and purity (>96%). In the ^{1}H NMR spectrum of **11a** the diagnostic AB-system peaks attributed to the methylene bridge of the PCU cage were found at δ = 1.59 and 1.94 (J = 10.8 Hz, each). Two characteristic singlets of the –CH_2O– group and the C(4)–H of the 1,2,3-triazole ring were found at δ = 4.69 and 7.71, respectively. A similar result was found for bis-thia cage-derived analogue **11b**, but in this case the amount of larger-sized molecules was very low (under general conditions).

The syntheses of coronands are based on either inter- or intramolecular processes.[15] Although the latter approach is more convenient for thermodynamic reasons, it usually requires multistep preparation of properly (bi/poly)functionalized substrates. On the other hand, in the alternative intermolecular condensations the formation of complex mixtures of linear and macrocyclic products are observed. For this reason, the template-directed or high dilution strategies furnishing preferentially the desired oligomeric systems are employed. More recently, the iterative synthetic method based on the intramolecular azide–alkyne [3+2]-cycloaddition protocol leading to a series of crown ethers of C_2-axial symmetry has been described.[8b] The synthesis of topologically isomeric crown-like ethers **9a**,**b** as well as their partially sulfurated analogues **10a**–**d** via the intermolecular route presented in this paper supplements previous reports. Additionally, two exemplary macrocycles **11a**,**b** functionalized with highly lipophilic pentacycloundecane moiety were synthesized in high yields and purities starting with birdcage-derived diazide **8** and two novel propargylic thioether derivatives **5a** and **5b**. The macrocyclic systems presented herein are of current interest to us with respect to their potential complexing properties towards silver(I) and other heavy metal ions.

Ethylene glycols, NaN_3, vinylmagnesium bromide, propargyl bromide, and other common reagents are commercially available. Diketone **1** was prepared according to a known procedure.[4] Diazides **3a**,**b**[10] and bis(propargyl) ethers **4a**,**b**[12] were prepared following literature protocols. NMR spectra were recorded with Bruker (Avance III 600) instruments in $CDCl_3$; chemical shifts reported relative to solvent residual peak (^{1}H: δ = 7.26 [$CDCl_3$]; ^{13}C: δ = 77.0 [$CDCl_3$]). IR spectra were measured with a Nexus FT-IR spectrophotometer. HRMS and elemental analyses were recorded in the analytical laboratories of Polish Academy of Sciences with a Finnigan MAT 95 (EI, FAB) or MaldiSYNAPT G2-S HDMS (ESI) instrument and Vario EL III instrument, respectively.

Bis(propargyl) Sulfides 5; General Procedure

To a soln of the corresponding glycol (0.01 mol) in anhyd THF (47.0 mL), NaH (60% in mineral oil, 1.23 g, 0.03 mol) was added at 0 °C under vigorous stirring. When the evolution of H_2 had ceased, a soln of propargyl bromide (6.0 mL of 80% wt in toluene, 8.01 g, 0.054 mol) and then solid KI (5 mg) were added. The mixture was stirred overnight at r.t., the precipitate was filtered off, and the solvent was removed under reduced pressure. The crude mixture

was purified chromatographically (silica gel, hexanes–EtOAc, 8:2) to yield **5** as yellow oils.

4,10-Dioxa-7-thiatrideca-1,12-diyne (5a)
Yellow oil; yield: 1.4 g (85%).

IR (film): 3289, 2922, 2857, 2116, 1443, 1096 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.45 (t, *J* = 2.4 Hz, 2 H), 2.79 (t, *J* = 6.7 Hz, 4 H), 3.72 (t, *J* = 6.7 Hz, 4 H), 4.18 (d, *J* = 2.4 Hz, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.7, 58.1, 69.6, 74.7, 79.6.

Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.58; H, 7.12. Found: C, 60.26; H, 6.98.

4,13-Dioxa-7,10-dithiahexadeca-1,15-diyne (5b)
Yellow oil; yield: 2.2 g (77%).

IR (film): 3287, 2920, 2856, 2115, 1442, 1096 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.45 (t, *J* = 2.4 Hz, 2 H), 2.75 (t, *J* = 6.7 Hz, 4 H), 2.78 (s, 4 H), 3.69 (t, *J* = 6.7 Hz, 4 H), 4.18 (d, *J* = 2.4 Hz, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.4, 32.6, 58.1, 69.6, 74.8, 79.5.

Anal. Calcd for $C_{12}H_{18}O_2S_2$: C, 55.78; H, 7.02. Found: C, 55.84; H, 6.85.

Cage Diazide 8
The dibromo cage derivative **7**[14] (748 mg, 2 mmol) was dissolved in anhyd DMF (5 mL). To this soln NaN_3 (234 mg, 3.6 mmol) was added in small portions under an argon atmosphere. The mixture was stirred 24 h at r.t. After this time, 50% aq NaOH (176 mg) was added and stirring was continued for an additional 0.5 h. The mixture was washed with 2% $NaHCO_3$ soln and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvents were removed under reduced pressure. The residue was purified chromatographically (silica gel, CH_2Cl_2–petroleum ether, 7:3) to give cage diazide **8** as a pale yellow oil; yield: 357 mg (60%).

IR (film): 930, 1090, 1140, 1259, 1297, 1389, 1457, 1683, 1725, 2097, 2865, 2961 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.58 (AB, J_{AB} = 10.5 Hz, 1 H), 1.93 (AB, J_{AB} = 10.5 Hz, 1 H), 2.09–2.11 (m, 4 H), 2.44–2.47 (m, 2 H), 2.56–2.59 (m, 4 H), 2.67–2.69 (m, 2 H), 3.37– 3.45 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.6, 41.6, 43.6, 44.2, 48.0, 48.1, 58.8, 94.3.

MS (CI): *m*/*z* = 299.1 $[M + 1]^+$.

Anal. Calcd for $C_{15}H_{18}N_6O$: C, 60.37; H, 6.08; N, 28.18. Found: C, 60.11; H, 6.01: N, 27.93.

Preparation of Macrocycles

Macrocycle 9a (m = 1, n = 1); Typical Procedure under Aqueous Conditions
To a stirred soln of $CuSO_4$ (26 mg, 0.14 mmol) and sodium ascorbate (190 mg, 0.96 mmol) in a degassed mixture of H_2O–MeOH (2:1, 50 mL), a soln of diazide **3a** (0.32 mmol) and propargyl derivative **4a** (0.32 mmol) in a degassed mixture of H_2O–MeOH (2:1, 50 mL) was added dropwise at 60 °C over 6 h under a argon atmosphere, and the resulting mixture was stirred for 24 h at this temperature. The soln was cooled to r.t., and then it was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by filtration through a silica gel pad (EtOAc, then 5% MeOH–CH_2Cl_2) to give macrocycle **9a** (m = 1, n = 1) as a pale yellow oil; yield: 30 mg (27%).

Macrocycles 9a,b, 10a–d, 11a,b, and 12a; General Procedure under Nonaqueous Conditions
To a soln of CuI (6 mg, 0.032 mmol) and DIPEA (0.2 mL, 148 mg, 1.15 mmol) in anhyd, degassed MeCN (50 mL), a soln of diazide and propargyl derivative in MeCN (50 mL) was added dropwise over 6 h at 40 °C, under an argon atmosphere. The resulting mixture was stirred at this temperature for a further 24 h and cooled to r.t.; the mixture was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvents were removed. The residue was purified by filtration through a silica gel pad (EtOAc, then 5% MeOH–CH_2Cl_2).

Macrocycle 9a (m = 1, n = 1)
Diazide **3a** (0.32 mmol) and propargyl derivative **4a** (0.32 mmol) gave macrocycle **9a** (m = 1, n = 1). Pale yellow oil; yield: 85 mg (78%).

IR (KBr): 3135, 2947, 2903, 2863, 1470, 1356, 1220, 1147, 1053 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.74–3.75 (m, 4 H), 3.77–3.78 (m, 4 H), 3.86 (t, *J* = 4.8 Hz, 4 H), 4.52 (t, *J* = 4.8 Hz, 4 H), 4.78 (s, 4 H), 7.49 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 50.3, 64.9, 69.5, 69.8, 70.9, 123.4, 145.6.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{23}N_6O_4$: 339.1781; found: 339.1777.

Macrocycle 9b (m = 2, n = 2)
Diazide **3b** (0.25 mmol) and propargyl derivative **4b** (0.25 mmol) gave macrocycle **9b** (m = 2, n = 2). Pale yellow oil; yield: 41 mg (36%).

IR (KBr): 3140, 2906, 2866, 1468, 1354, 1235, 1146, 1108 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.58 (s, 4 H), 3.63 (s, 4 H), 3.67–3.68 (m, 4 H), 3.69–3.72 (m, 4 H), 3.85 (t, *J* = 5.4 Hz, 4 H), 4.53 (t, *J* = 5.4 Hz, 4 H), 4.72 (s, 4 H), 7.87 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 50.0, 64.9, 69.2, 69.7, 70.1, 70.5 70.6 123.9, 145.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{31}N_6O_6$: 427.2305; found: 427.2307.

Macrocycle 10a (m = 1, n = 1)
Diazide **3a** (0.32 mmol) and propargyl derivative **5a** (0.32 mmol) gave macrocycle **10a** (m = 1, n = 1). Pale yellow oil; yield: 40 mg (35%).

IR (KBr): 3129, 2916, 2862, 1465, 126, 1093, 1050 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.85 (t, *J* = 6 Hz, 4 H), 3.79 (t, *J* = 6 Hz, 4 H), 3.8 (t, *J* = 4.8 Hz, 4 H), 4.52 (t, *J* = 4.8 Hz, 4 H), 4.70 (s, 4 H), 7.49 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 32.1, 50.3, 64.5, 69.4, 71.2, 123.4, 145.6.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{22}N_6O_3S$: 354.1474; found: 354.1469.

Macrocycle 10b (m = 2, n = 1)
Diazide **3b** (0.32 mmol) and propargyl derivative **5a** (0.32 mmol) gave macrocycle **10b** (m = 2, n = 1). Pale yellow oil; yield: 44 mg (44%).

IR (KBr): 3138, 2919, 2867, 1463, 1359, 1223, 1104 cm^{-1}.

^1H NMR(600 MHz, $CDCl_3$): δ = 2.79 (t, *J* = 6.0 Hz, 4 H), 3.58 (s, 4 H), 3.76 (t, *J* = 6.0 Hz, 4 H), 3.86 (t, *J* = 4.8 Hz, 4 H), 4.53 (t, *J* = 4.8 Hz, 4 H), 4.69 (s, 4 H), 7.82 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 32.1, 50.3, 64.7, 69.4, 70.3, 70.8, 123.7, 145.3.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{26}N_6O_4S$: 398.1736; found: 398.1726.

Macrocycle 10c (m = 1, n = 2)
Diazide **3a** (0.32 mmol) and propargyl derivative **5b** (0.32 mmol) gave macrocycle **10c** (m = 1, n = 2). Pale yellow oil; yield: 75 mg (50%).

IR (KBr): 3134, 2915, 2862, 1448, 1366, 1219, 1113**,** 1053 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.78–2.80 (m, 4 H), 2.87 (s, 4 H), 3.80–3.85 (m, 8 H), 4.52 (t, *J* = 4.8 Hz, 4 H), 4.71 (s, 4 H), 7.54 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 50.0, 64.9, 69.2, 69.7, 70.1, 70.6, 123.9, 145.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{26}N_6O_3S_2$: 414.1508; found: 414.1513.

Macrocycle 10d (m = 2, n = 2)
Diazide **3b** (0.32 mmol) and propargyl derivative **5b** (0.32 mmol) gave macrocycle **10d** (m = 2, n = 2). Pale yellow oil; yield: 45 mg (39%).

IR (KBr): 3136, 2919, 2866, 1463, 1357, 1223, 1103 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.74 (t, *J* = 6.0 Hz, 4 H), 2.78 (s, 4 H), 3.60 (s, 4 H), 3.78 (t, *J* = 6.0 Hz, 4 H), 3.86 (t, *J* = 4.8 Hz, 4 H), 4.55 (t, *J* = 4.8 Hz, 4 H), 4.71 (s, 4 H), 7.82 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 32.7, 33.2, 50.3, 64.5, 69.2, 70.5, 70.8, 123.9, 144.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{30}N_6O_4S_2$: 458.1770; found: 458.1757.

Macrocycle 11a (n = 1)
Cage diazide **8** (0.185 mmol) and propargyl derivative **5a** (0.185 mmol) gave macrocycle **11a** (n = 1). Note: degassed MeCN was used in double amount (2 × 100 mL); time of reaction 48 h. Pale yellow oil; yield: 62 mg (75%).

IR (KBr): 2958, 2863, 1663, 1459, 1370, 1296, 1222, 1080, 1049, 931, 785 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.59 (AB, J_{AB} = 10.8 Hz, 1 H), 1.94 (AB, J_{AB} = 10.8 Hz, 1 H), 2.29–2.37 (m, 6 H), 2.38–2.43 (m, 6 H), 2.52 (t, *J* = 3.6 Hz, 4 H), 2.85 (t, *J* = 6.6 Hz, 4 H), 3.82 (t, *J* = 6.6 Hz, 4 H), 4.69 (s, 4 H), 7.71 (s, 2 H).

^{13}C NMR (600 MHz, $CDCl_3$): δ = 31.5, 32.4, 41.4, 43.7, 43.9, 46.9, 47.8, 58.5, 65.2, 71.6, 94.3, 122.9, 145.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{33}N_6O_3S$: 497.2335; found, 497.2339.

Macrocycle 11b (n = 2)
Cage diazide **8** (0.185 mmol) and propargyl derivative **5b** (0.185 mmol) gave macrocycle **11b** (n = 2). Pale yellow oil; yield: 75 mg (80%).

IR (KBr): 2957, 2862, 1654, 1458, 1296, 1221, 1100, 1049, 778 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.54 (AB, J_{AB} = 12.0 Hz, 1 H), 1.87 (AB, J_{AB} = 12.0 Hz, 1 H), 2.30–2.36 (m, 8 H), 2.36–2.40 (m, 8 H), 2.66 (t, *J* = 6.0 Hz, 4 H), 3.72 (t, *J* = 6.0 Hz, 4 H), 4.42 (t, *J* = 12.0 Hz, 4 H), 4.65 (s, 4 H), 7.65 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.6, 32.3, 32.9, 41.3, 43.6, 43.8, 46.9, 47.8, 58.7, 64.8, 71.2, 94.2, 123.4, 144.7.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{37}N_6O_3S_2$: 557.2369; found: 557.2376.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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