Synthesis M. Stefaniak, J. Romański Paper

Facile Synthesis of Hydroxy-Substituted Thiacrown Ethers via Nucleophilic Ring Opening of Epoxides

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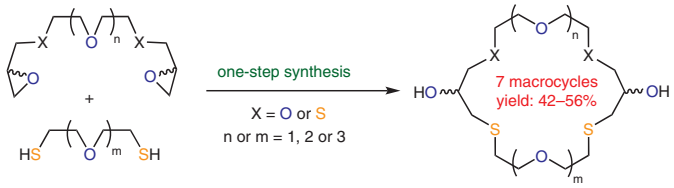

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Abstract The title thiacrown ethers were prepared in a one-step procedure to give a series of unique macrocycles possessing two unsubstituted hydroxy groups that can be easily functionalized. In addition, epoxides and macrocycles derived from Cookson's birdcage diketone, were prepared. The nucleophilic ring opening of epoxides synthesis can be classified in the frame of click chemistry. Surprisingly, some of the prepared allyl substituted polyglycols as well as bis-epoxides, especially sulfur analogues, were prepared for the first time.

Key words thiacrown ethers, click chemistry, epoxides, macrocycles, cage compounds

Since 1934, when the first synthesis of thiacrown macrocycles was developed by Meadow and Reid,[1] sulfur-containing crown ethers have become an important class of compounds in coordination chemistry, showing excellent complexing ability toward transition-metal cations.[2] Representative reports dealing with examples of polymeric, luminescent, chemosensory, and dye material applications underline the recent interest in this area.[3]

Though there are many papers on the synthesis of crown ethers, sulfur-containing macrocycles possessing reactive groups are important intermediates for a variety of further functionalized derivatives.[4] In spite of their structural diversity, thiacrown ethers functionalized with lipophilic moieties, for example, terpene-derived molecules,[5] or with simple reactive groups still represents a rather unique class of macrocycles. In particular, a special interest is focused on the hydroxyl group, which can be easily transformed into various derivatives by using well-established methods. Selected examples[6] of hydroxy-substituted macrocycles depicted in Figure 1 are based on 1,2-ethanedithiol or its derivatives. However, among the synthetic methods available to date for the preparation of thiacrown ethers, the ring-opening epoxide strategy was applied to only a limited extent.[6a,d,f]

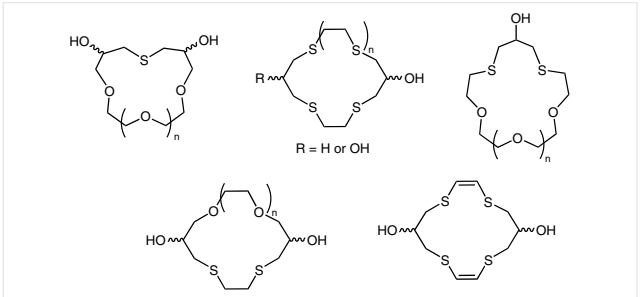

Figure 1 Examples of bis-hydroxy substituted macrocycles

Derivatives of epoxides are very powerful compounds and constitute an important starting point for the synthesis of optically active amino alcohols,[7] sulfides,[8] azidoalcohols,[9] and hydroxy nitrates.[10] In many cases, this is a very easy and rapid way to obtain a series of useful linkers that can be used to prepare libraries of various compounds.[11] The application of this reaction demonstrates its possible use in the synthesis of novel macrocyclic systems.

In addition, some reports exploiting polycyclic cage diketone **4**[12] for the preparation of hydrocarbon-enriched (lipophilic) thiacrown ethers were published by Marchand and co-workers.[13] Recently, we utilized copper-catalyzed azide-alkyne cycloaddition[14] for the synthesis of a series of macrocyclic systems containing sulfur and oxygen atoms with a built-in lipophilic cage moiety as hydrocarbon skeleton for rigid macrocyclic ethers.[15] This kind of approach for the synthesis of macrocycles has been applied as a click chemistry pathway.[16] Taking into account this concept, the opening of small heterocyclic rings fits perfectly with the presented results in which bis-epoxides, in a one-step reac-

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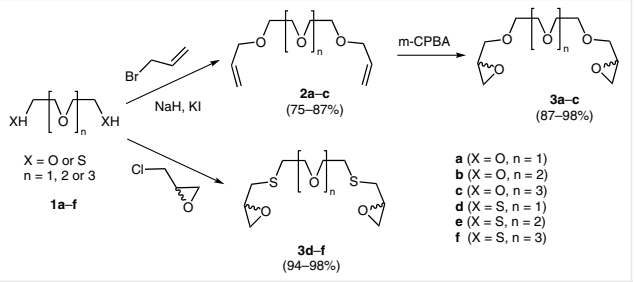
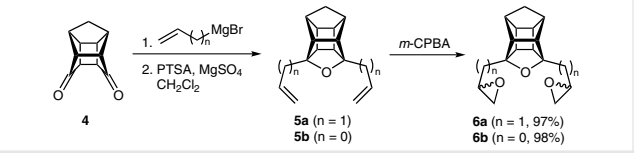
tion with dithiols, provide a series of unique macrocyclic systems containing various sizes of complexation cavity and functionalized by hydroxy groups. This work expands our previous study on the synthesis of thiacrown-like compounds.

Initial experiments were performed using di-, tri-, and tetraethylene glycols selected as model substrates. By following classical protocols,[17] starting materials **1a–c** (X = O) were reacted with allyl bromide to give, after standard chromatographic purification, the corresponding bis-allyl derivatives **2a–c** in good yields (71–95%). To our surprise, bis-allyl compounds **2a–c** were used only sporadically and neither the synthetic details nor spectral data have been described in the literature. As depicted in Scheme 1, for **2a–c**, the corresponding bis-epoxides **3a–c** were prepared using *m*-CPBA for oxidation, according to a known method.[18] In the case of sulfur-containing glycols, an alternative protocol was applied to obtain bis-epoxides **3d–f**. Given the presence of sulfur atoms, which can also be oxidized to either sulfoxide or sulfone, the oxidizing step should be omitted and the bis-epoxides were prepared using (±)-epichlorohydrin as a source of the epoxide ring. Substitution of the hydroxyl group in glycols **1d–f** with an epichlorohydrin was done by using two approaches. The first included the use of sodium hydroxide at 65 °C.[19] In the second approach, which is more common, the epichlorohydrin reacted with alcohols in the presence of sodium hydroxide and tetrabutylammonium chloride.[20] Both methods led to unknown bis-epoxides **3d–f**, but only the second approach, under phase-transfer catalysis conditions and, in our hands, supported by ultrasound, give excellent yields.



Scheme 1 Synthesis of bis-epoxides **3a–f**

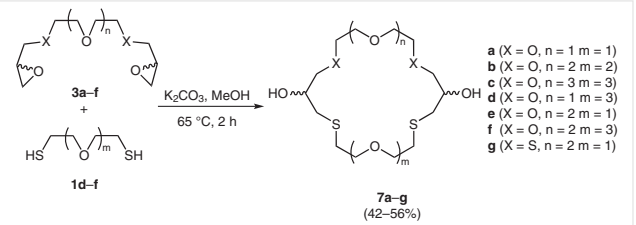
Cookson's birdcage dione **4** was also used to introduce a rigid and lipophilic motif to the studied macrocyclic system, which is well described elsewhere.[21] According to a reported procedure, cyclopentadiene reacts with benzoquinone in Diels–Alder cycloaddition to give the cycloadduct and subsequent [2+2]-photocycloaddition led to diketone **4** in excellent yield.[22] As depicted in Scheme 2, the reaction of diketone **4** with two equivalents of Grignard reagent, after dehydration in the presence of PTSA, gave oxygen bridged allyl and vinyl derivatives **5a** and **5b**.[23] The latter compounds were easily transformed into the preliminary described[24] bis-epoxides **6a** and **6b**. It is important to note that in all bis-epoxides, two stereogenic centers were generated and a mixture of *meso* and *d*,*l* stereoisomers was obtained.



Scheme 2 Synthesis of cage-derived bis-epoxides **6a** and **6b**

Interestingly, analysis of the ^{13}C NMR spectra of the carefully purified bis-epoxides **6a** and **6b** indicated that, in the case of vinyl derivative **6b**, the rotation between epoxide rings is limited. Comparison of characteristic signals in the range of 94–96 ppm showed two signals for **6a** and four signals for **6b**. For both bis-epoxides, two diagnostic signals should be expected (*meso* and *d*,*l* mixture). This phenomenon is still under investigation using temperature-dependent NMR and computation methods.

Having in hand the series of bis-epoxides **3a–f**, **6a–b** and dithiols **1d–f** as suitable starting materials, a first experiment was performed in the presence of a methanolic solution of potassium or sodium hydroxide. After 24 hours, new compounds of type **7** were obtained, albeit in low yields (below 10%). For this reason, different methods to merge starting epoxides **3**, **6** and thiols **1** were explored. Thus, different carbonates (sodium, potassium or cesium) in methanol solution were applied. The reaction was carried out on 1 mmol scale and under high dilution conditions (ca. 1 mg/mL) to avoid formation of linear and/or polymeric side products. The choice of appropriate carbonate led to a difference in size of the resulting macrocyclic cavity (Scheme 3). The structures are summarized in Table 1.



Scheme 3 One-step cyclization toward bis-hydroxy crowns **7a–g**

Several new thiacrown macrocycles **7a–g** were obtained with various sizes of cavity from 18- to 36-membered rings and possessing unsubstituted hydroxyl groups that are amenable to further modification. Flash chromatography was used for purification of crude reaction mixtures, eluting with chloroform with addition 1–5% methanol. All macrocycles were obtained as mixtures of *d*,*l* and *meso* stereo-

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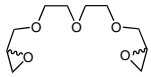
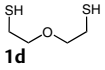
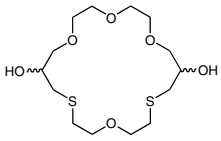
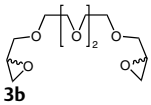
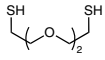
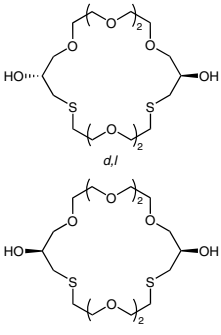
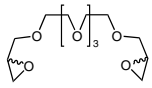
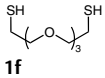
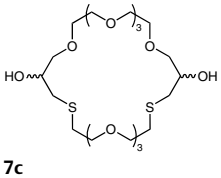
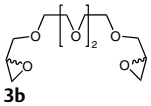
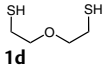
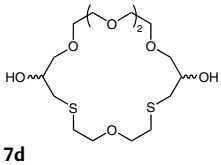
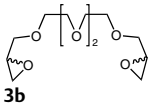
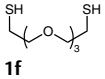
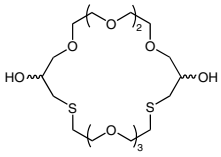
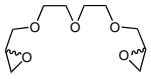
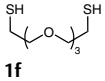
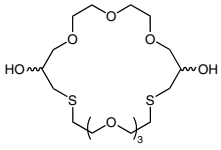
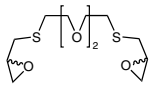
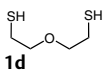
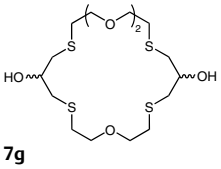
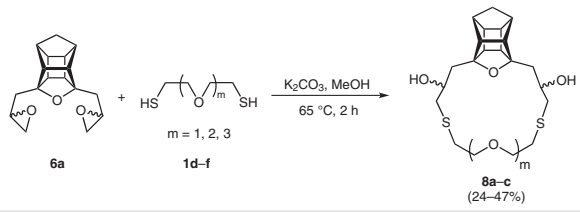
Table 1 Structures and Yields of Macrocycles **7a–g**

Bis-epoxide	Dithiol	Macrocycle	Yield (%)
 **3a**	 **1d**	 **7a**	42
 **3b**	 **1e**	 *d,l* *meso* **7b**	54
 **3c**	 **1f**	 **7c**	56
 **3b**	 **1d**	 **7d**	48
 **3b**	 **1f**	 **7e**	45
 **3a**	 **1f**	 **7f**	52
 **3e**	 **1d**	 **7g**	45

isomers. The attempted separation of stereoisomers was performed using preparative thin-layer chromatography. Only in the case of macrocycle **7b** was the separation successful. Furthermore, for both separated fractions of **7b** with R_f = 0.2 and R_f = 0.3 the MS spectra showed the same molecular mass peak, which confirm our expectations, but we did not attribute which fraction belongs to *d*,*l* or *meso* isomer. Unfortunately, the other examples of new macrocycles of type **7** were obtained as mixtures of stereoisomers, and attempts at separation were unsuccessful.

Subsequently, bis-epoxides **6a** and **6b**, containing a cage moiety, were used for the ring-opening reaction under the same conditions (Scheme 4). However, for **6b**, all attempts completely failed. In the case of product **8b**, in the NMR spectrum of the crude reaction mixture we found signals that correspond to the desired macrocyclic structure. However, despite several trials to obtain pure material, the final product was not obtained in good quality (see the Supporting Information). Moreover, in the case of expected macrocycle **8c** (*m* = 3) the product was not detected. Only macrocyclic product **8a** was obtained as a pure material in acceptable yield of 47%.



Scheme 4 Preparation of cage-containing macrocycles **8a–c**

Taking into account the problem with the preparation of target cage macrocycles, we suspect that the reason lies in the rigid structure of the cage bis-epoxides **6a** and **6b**, especially in the case of **6b**, for which the epoxides rings are connected directly to the polycyclic cage unit.

In conclusion, the application of the nucleophilic ring-opening process leading, in a one-step protocol, to novel macrocycles **7a–g** containing hydroxyl groups, based on the series of bis-epoxides **3a–c** and sulfur analogues **3d–f** has been developed. Some of the simple bis-epoxides derivatives based on polyglycols and its sulfur analogous were prepared for the first time as well as cage bis-epoxides (previously disclosed without spectral data[24]). All macrocycles were obtained as mixtures of *d*,*l* and *meso* isomers and, in the case of **7b**, the diastereoisomers could be separated by using preparative thin-layer chromatography. In extension, the newly obtained bis-epoxides **6a** and **6b**, containing a lipophilic cage moiety, were used for the preparation of thiacrown macrocycles. However, only for **8a** was preparation of pure material achieved. The free hydroxyl group can be modified into, for example, ditosylate derivatives and further modification opens the way to new classes of crypt-

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ands with a bridgehead carbon atom. In further studies the application of diamines is planned for the preparation of nitrogen-containing macrocycles.

All reagents and solvents were purchased from commercial sources and were used as received. Bis-epoxides **3b–c**[25] and dithiols **1d–f**[15b] were prepared according to reported protocols. NMR spectra were recorded with Bruker Avance III 600 instruments in $CDCl_3$; chemical shifts are reported relative to solvent residual peak (^{1}H: δ = 7.26 ppm [$CDCl_3$]; ^{13}C: δ = 77.0 ppm [$CDCl_3$]). IR spectra were measured with a Nexus FT-IR spectrophotometer. HRMS and elemental analyses were recorded with a Finnigan MAT 95 (EI, FAB) or MaldiSYNAPT G2-S HDMS (ESI) instrument and Elementar Super Vario Micro Cube, respectively.

Preparation of Starting Materials

Allyl Derivatives of Type 2; General Procedure

To a stirred solution of the corresponding glycol **1a–c** (45 mmol) in anhydrous tetrahydrofuran (50 mL), sodium hydride (60% in mineral oil, 90 mmol, 2.15 g) was added at 0 °C under argon atmosphere. To the reaction flask, allyl bromide (90 mmol, 11.0 g, 7.87 mL) was added and the resulting mixture was stirred at r.t. overnight. Water (5 mL) was then added carefully to decompose the excess of sodium hydride. The resulting solution was extracted with diethyl ether (3 × 50 mL). After evaporation of solvent, the crude product was purified by column chromatography (silica gel, EtOAc). The products of type **2** were obtained as pale-yellow oils.

Compound 2a

Yield: 75% (6.3 g).

IR (film): 3081, 2923, 2871, 1732, 1647, 1456, 1377, 1351, 1296, 1251, 1128, 995, 925, 880, 722 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.86–5.79 (m, 1 H), 5.19 (dd, *J* = 1.8, 12.0 Hz, 1 H), 5.08 (dd, *J* = 1.8, 1.2 Hz, 1 H), 3.94 (d, *J* = 6.0 Hz, 2 H), 3.59–3.58 (m, 2 H), 3.53–3.52 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 134.8, 116.9, 72.2, 70.6, 69.4.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{18}O_3Na$: 209.1150; found: 209.1154.

Compound 2b

Yield: 85% (8.79 g).

IR (film): 3080, 2865, 1647, 1457, 1348, 1292, 1250, 1108, 996, 925, 880 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.81–5.74 (m, 1 H), 5.14 (d, *J* = 17.4 Hz, 1 H), 5.04 (d, *J* = 10.8 Hz, 1 H), 3.89 (d, *J* = 5.4 Hz, 2 H), 3.54–3.52 (m, 4 H), 3.48–3.46 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 134.4, 116.2, 71.6, 70.2, 70.1, 68.9.

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.33; H, 9.79.

Compound 2c

Yield: 87% (10.69 g).

IR (film): 3080, 2909, 2869, 1729, 1647, 1457, 1349, 1296, 1250, 1108, 927 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.85–5.78 (m, 1 H), 5.16 (dd, *J* = 1.2, 1.8 Hz, 1 H), 5.08 (dd, *J* = 1.2, 1.8 Hz, 1 H), 3.93–3.92 (m, 2 H), 3.57–3.55 (m, 6 H), 3.52–3.49 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 134.6, 116.6, 71.9, 70.4, 70.36, 70.3, 69.2.

Anal. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55. Found: C, 61.09; H, 9.45.

Preparation of Bis-epoxides 3a and 6a,b

To a solution of bis-allyl derivatives **2a** or **5a**,**b** (5 mmol) in methylene chloride (25 mL), *m*-chloroperbenzoic acid (*m*-CPBA) (14 mmol, 2.4 g) was added at 0 °C under argon atmosphere. The reaction was stirred at r.t. for 24 h then the mixture was filtered and washed with methylene chloride. The combined filtrates were stirred with 5% solution of $Na_2S_2O_3$ (10 mL) for 15 minutes. The solution was washed with a saturated solution of $NaHCO_3$ (10 mL) then extracted with methylene chloride (3 × 20 mL). The combined organic layer was dried and the solvent was removed. The products were obtained as pale-yellow oils.

Compound 3a

Yield: 98% (1.06 g).

IR (film): 3059, 2916, 2872, 1723, 1575, 1457, 1289, 1257, 1104, 911, 856, 755 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.15–3.12 (m, 2 H), 3.78 (d, *J* = 3.0 Hz, 1 H), 3.76 (d, *J* = 3.0 Hz, 1 H), 3.69–3.62 (m, 8 H), 3.42 (dd, *J* = 6.0, 3.6 Hz, 2 H), 2.77 (t, *J* = 4.8 Hz, 2 H), 2.58 (dd, *J* = 3.0, 2.4 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 71.9, 70.7, 70.6, 50.8, 44.2.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{18}O_5Na$: 241.1052; found: 241.1053.

Compound 6a

Yield: 97% (1.12 g).

IR (film): 2968, 2866, 1486, 1344, 1255, 941, 878 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.08–3.01 (m, 2 H), 2.79–2.78 (m, 2 H), 2.72–2.68 (m, 4 H), 2.63–2.58 (m, 2 H), 2.51–2.48 (m, 4 H), 2.13–2.05 (m, 2 H), 1.98–1.91 (m, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 94.4, 94.3, 59.2, 59.1, 58.6, 58.4, 49.4, 49.3, 48.6, 48.5, 47.9, 47.8, 46.8, 46.8, 46.7, 46.6, 6.5, 44.4, 44.4, 44.2, 44.1, 43.9, 43.7, 43.3, 41.7, 41.7, 41.6, 41.6, 35.9, 35.8.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{20}O_3Na$: 295.13102; found: 295.13108.

Compound 6b

Yield: 98% (1.10 g).

IR (film): 3050, 2965, 1410, 1348, 1296, 1258, 1138, 922, 837 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.08–3.01 (m, 2 H), 2.79–2.78 (m, 2 H), 2.72–2.68 (m, 4 H), 2.63–2.58 (m, 2 H), 2.51–2.48 (m, 4 H), 2.13–2.05 (m, 2 H), 1.98–1.91 (m, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 94.4, 94.3, 59.2, 59.1, 58.6, 58.4, 49.4, 49.3, 48.6, 48.5, 47.9, 47.8, 46.8, 46.8, 46.7, 46.6, 6.5, 44.4, 44.4, 44.2, 44.1, 43.9, 43.7, 43.3, 41.7, 41.7, 41.6, 41.6, 35.9, 35.8.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{16}O_3Na$: 267.0997; found: 267.0999.

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Sulfur-Containing Bis-epoxides 3d–f; General Procedure

To a solution of (±)-epichlorohydrin (30 mmol, 3.0 g), sodium hydroxide (30 mmol, 1.3 g) and water (1 mL), tetrabutylammonium hydrosulfate (0.62 mmol, 0.2 g) and the corresponding dithiol **1d–f** (5.5 mmol) were added. The reaction was stirred for 45 min at r.t. in an ultrasonic bath. The reaction mixture was filtered and washed with methylene chloride. The combined organic layer was dried over anhydrous magnesium sulfate and then the solvent was removed. The residue was purified by flash chromatography (silica gel, EtOAc) and bis-epoxides **3d–f** were obtained as pale-yellow oils.

Compound 3d

Yield: 94% (1.3 g).

IR (film): 2990, 2920, 2860, 1407, 1103, 837 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.64 (t, *J* = 6.0 Hz, 2 H), 3.13–3.11 (m, 1 H), 2.79–2.76 (m, 2 H), 2.74–2.67 (m, 2 H), 2.59–2.57 (q, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 70.4, 51.6, 46.5, 34.4, 31.5.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{18}O_3S_2Na$: 273.0596; found: 273.0595.

Compound 3e

Yield: 98% (1.56 g).

IR (film): 2987, 2920, 2863, 1353, 1106, 840 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.65 (t, *J* = 6.6 Hz, 2 H), 3.59 (s, 2 H), 3.12–3.09 (m, 1 H), 2.78–2.76 (m, 2 H), 2.74–2.64 (m, 2 H), 2.57–2.56 (q, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 70.8, 70.0, 51.6, 46.6, 34.4, 31.5.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{22}O_4S_2Na$: 317.0858; found: 317.0857.

Compound 3f

Yield: 97% (2.19 g).

IR (film): 2920, 2866, 1353, 1109, 837 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.56–3.52 (m, 2 H), 3.51–3.49 (m, 4 H), 3.02–2.99 (m, 1 H), 2.68–2.66 (m, 3 H), 2.63–2.55 (m, 2 H), 2.48–2.46 (q, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 70.7, 70.2, 69.9, 51.4, 46.4, 34.2, 31.3.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{26}O_5S_2Na$: 361.1120; found: 361.1119.

Preparation of Macrocycles 7a–g and 8a–b; General Procedure

To a solution of corresponding dithiol **1d–f** (1 mmol) in MeOH (50 mL) and appropriate carbonate (sodium, potassium or cesium) (1 mmol, 0.5 g) a solution of bis-epoxide of type **3** (1 mmol) in MeOH (5 mL) was added. The mixture was stirred at 65 °C for 3 h. The solution was extracted with methylene chloride (3 × 20 mL) and the combined organic layer were dried over anhydrous magnesium sulfate and then solvent was evaporated. The final product was isolated by flash chromatography (chloroform: 5% methanol) on silica gel and additionally by preparative thin-layer chromatography using chloroform as solvent. The macrocycles **7a–g** and **8a–b** were obtained as pale-yellow oils.

Compound 7a

Prepared in the presence of Na_2CO_3.

Yield: 42% (150 mg).

IR (film): 2917, 2860, 1454, 1356, 1109, 1040 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 4.02–3.92 (m, 1 H), 3.72–3.61 (m, 8 H), 3.55–3.50 (m, 1 H), 2.83–2.69 (m, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 74.7, 74.6, 71.2, 71.2, 70.7, 70.7, 70.6, 70.6, 70.5, 36.0, 35.8, 32.2, 32.1.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{28}O_6S_2Na$: 379.1225; found: 379.1226.

Compound 7b

Prepared in the presence of K_2CO_3: Yield: 42% (150 mg). The final product was isolated by flash chromatography (silica gel; chloroform/methanol, 95:5), then by preparative thin-layer chromatography on silica gel using chloroform as solvent. Two fractions were obtained (R_f = 0.2; R_f = 0.3) as pale-yellow oils.

R_f = 0.2. Yield: 54% (239.8 mg).

IR (film): 2870, 1480, 1353, 1112, 938 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.97–3.93 (m, 1 H), 3.71 (t, *J* = 6.6 Hz, 2 H), 3.68–3.59 (m, 10 H), 3.52–3.49 (m, 1 H), 2.80–2.76 (m, 2 H), 2.74–2.72 (m, 2 H), 3.96–3.94 (m, 1 H), 3.70 (t, *J* = 6.0 Hz, 2 H), 3.67–3.59 (m, 10 H), 3.53–3.49 (m, 1 H), 2.82–2.78 (m, 2 H), 2.77–2.73 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 74.4, 74.3, 71.6, 70.6, 70.5, 70.0, 35.7, 32.0.

Anal. Calcd for $C_{18}H_{36}O_8S_2$: C, 48.63; H, 8.16; S, 14.42. Found: C, 48.45; H, 8.17; S, 14.33.

R_f = 0.3. Yield: 47% (210 mg).

IR (film): 2870, 1480, 1353, 1112, 938 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.96–3.94 (m, 1 H), 3.70 (t, *J* = 6.0 Hz, 2 H), 3.67–3.59 (m, 10 H), 3.53–3.49 (m, 1 H), 2.82–2.78 (m, 2 H), 2.77–2.73 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 74.4, 74.3, 71.6, 70.6, 70.5, 70.0, 35.7, 32.0.

Anal. Calcd for $C_{18}H_{36}O_8S_2$: C, 48.63; H, 8.16; S, 14.42. Found: C, 48.50; H, 8.16; S, 14.44.

Compound 7c

Prepared in the presence of Cs_2CO_3.

Yield: 56% (298 mg).

IR (film): 2911, 2866, 1458, 1350, 1293, 1264, 1109, 1040 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.93–3.89 (m, 1 H), 3.69 (t, *J* = 6.0 Hz, 2 H), 3.65–3.58 (m, 14 H), 3.53–3.50 (m, 1 H), 2.78–2.6 (m, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 74.3, 74.2, 71.3, 70.8, 70.6, 70.6, 70.5, 70.4, 69.9, 36.0, 32.2.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{36}O_8S_2Na$: 467.1749; found: 467.1741.

Compound 7d

Prepared in the presence of K_2CO_3.

Yield: 51.8% (230 mg).

IR (film): 2917, 2863, 1356, 1293, 1116, 1043 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.99–3.95 (m, 1 H), 3.74 (t, *J* = 6.6 Hz, 2 H), 3.71–3.64 (m, 10 H), 3.56–3.53 (m, 1 H), 2.83–2.80 (m, 2 H), 2.74–2.72 (q, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 74.5, 74.4, 71.4, 71.3, 70.7, 70.5, 70.3, 70.2, 35.5, 31.9.

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HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{36}O_8S_2Na$: 467.1749; found: 467.1741.

Compound 7e

Prepared in the presence of K_2CO_3.

Yield: 47.5% (190 mg).

IR (film): 2918, 2870, 1354, 1294, 1111, 1040 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.97–3.96 (m, 1 H), 3.71–3.58 (m, 10 H), 3.54–3.50 (m, 1 H), 2.83–2.68 (m, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 32.1, 32.2, 35.9, 70.2, 70.3, 70.5, 70.6, 71.2, 71.3, 74.3, 74.4, 74.3, 71.3, 71.2, 70.6, 70.5, 70.3, 70.2, 35.9, 32.2, 32.1.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{32}O_7S_2Na$: 423.1487; found: 423.1475.

Compound 7f

Prepared in the presence of Cs_2CO_3.

Yield: 45% (220 mg).

IR (film): 2914, 2866, 1350, 1116, 1036 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.95–3.92 (m, 1 H), 3.71 (t, *J* = 6.6 Hz, 2 H), 3.68–3.59 (m, 12 H), 3.54–3.51 (m, 1 H), 2.78 (t, *J* = 6.6 Hz, 2 H), 2.72 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 74.2, 74.2, 71.2, 70.6, 70.4, 70.3, 70.2, 69.8, 35.6, 31.9.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{40}O_9S_2Na$: 511.2011; found: 511.1996.

Compound 7g

Prepared in the presence of K_2CO_3.

Yield: 45% (195 mg).

IR (film): 2920, 2863, 1261, 1103, 1036 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.91–3.88 (m, 1 H), 3.71–3.66 (m, 7 H), 2.86–2.79 (m, 6 H), 2.74–2.71 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 71.2, 70.7, 70.3, 70.0, 38.8, 38.7, 32.4, 32.3.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{36}O_8S_2Na$: 467.1749; found: 467.1740.

Compound 8a

Prepared in the presence of Na_2CO_3.

Yield: 47% (160 mg).

IR (film): 2923, 2865, 1475, 1346, 1262, 938, 872 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.97–3.83, (m, 2 H), 3.07–2.90, (m, 4 H), 2.80–2.52 (m, 10 H), 2.50–2.37 (m, 2 H), 2.08–1.98 (m, 5 H), 1.55–1.50 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 94.7, 94.6; 94.6, 71.6, 71.5, 68.5, 68.2, 67.7, 67.4, 60.8, 60.1, 58.2, 56.8, 50.3, 49.6, 47.5, 46.3, 44.2, 44.0, 43.9, 43.7, 43.6, 43.5, 41.7, 41.7, 41.6, 41.6, 41.5, 41.4, 41.2, 41.0, 37.9, 37.7, 31.4, 31.3.

ESI-MS: *m*/*z* = 411 [M$^+$+1], 433 [M$^+$+Na].

Compound 8b

Prepared in the presence of K_2CO_3.

Estimated yield = 24% (ca. 100 mg) not fully characterized (see main text).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.94–3.98 (m), 3.79–3.63 (m), 2.99–2.90 (m), 2.81–2.46 (m), 2.02–1.91 (m), 1.59–1.56 (m).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 95.4, 95.3, 95.0, 94.9, 72.9, 71.2, 71.2, 71.0, 70.5, 70.4, 70.3, 70.2, 69.7, 69.6, 68.7, 68.5, 68.3, 59.8, 59.1, 58.7, 57.9, 49.1, 48.2, 47.7, 47.2, 44.1, 43.9, 43.8, 43.4, 41.5, 41.3, 41.2, 40.9, 40.8, 40.3, 39.2, 38.4, 37.9, 37.8, 32.2, 31.7, 31.5, 31.4.

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