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Synthesis of redox active large macrocyclic hosts and the recognition of secondary ammonium salts

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Abstract—Interconvertible macrocyclic hosts containing thiol groups or a disulfide linkage in the binding cavity have been synthesized. The binding affinities of the reduced and oxidized forms toward benzylammoium derivatives are completely reverse. Formation of pseudorotaxane is suggested upon the host–guest complexation.

1. Introduction

Recently, large macrocyclic compounds have been utilized to synthesize topologically interesting molecules such as catenanes and rotaxanes.[1] Application of these compounds to molecular machines and devices has also attracted much attention.[2] In general, a host bearing a large binding cavity shows much lower affinity toward small guests such as a metal ion than small hosts like 18-crown-6.[3] If an external stimulus conducts interconversion between a large host and a small one, the host-binding ability would be regulated coincidentally. Redox reactions between thiol and disulfide are very useful to control molecular structures and functions simultaneously.[4] In the artificial recognition systems, all-or-none regulation of Ag^+ binding is carried out by the redox reactions.[4e] Formation of the disulfide bond closes the binding site to diminish the binding affinity to metal ions, whereas the thiol form as an open state provides a very selective site for Ag^+. This strategy can be extended to the size regulation of a binding site of hosts, because intramolecular disulfide formation would divide the large cavity into the two corresponding half-sized cavities which bind a small ion. Preliminary study on regulation of paraquat recognition by these redox active hosts has been reported.[4g] Herein we report the synthesis of the macrocyclic hosts **1** in detail and regulation of their unique binding behaviour toward secondary ammonium salts by the redox reactions.

2. Results and discussion

The synthesis of crown ethers $\mathbf{1a}_{red}$ and $\mathbf{1b}_{red}$ is shown in Scheme 1. Reaction of tosylates **2a** and **2b** with excess catechol in the presence of K_2CO_3 gave **3a** and **3b** in 77 and 90% yield, respectively. **3a** and **3b** thus obtained were treated with **4a** and **4b** in CH_3CN to afford polyethers **5a** and **5b**. Removal of the benzyl group from **5a** and **5b** produced the corresponding alcohols **6a** and **6b**. The compounds **6a** and **6b** were also prepared from diols **7a** and **7b** by using 3,4-dihydro-2*H*-pyran. The protection of the hydroxy group is necessary because the 1:1 cyclization product instead of the desired 2:2 macrocycle was obtained from **7a** and **8** (Scheme 2). Alcohols **6a** and **6b** reacted with **8** in dry THF using NaH as a base to afford **9a** and **9b** in 88 and 89% yield. Deprotection of **9a** and **9b** proceeded under acidic conditions to give diols **10a** and **10b**. Reaction of **10a** and **10b** with **8** under high dilution conditions afforded cyclic dibromides **11a** and **11b** in 50%. Lithiation of **11a** and **11b** followed by addition of S_8 gave dithiol hosts $\mathbf{1a}_{red}$ and $\mathbf{1b}_{red}$ in 70 and 50% yield, respectively.

Interconversion between dithiol hosts ($\mathbf{1a}_{red}$ and $\mathbf{1b}_{red}$) and disulfide hosts ($\mathbf{1a}_{ox}$ and $\mathbf{1b}_{ox}$) was successfully performed. Oxidation of $\mathbf{1a}_{red}$ and $\mathbf{1b}_{red}$ with H_2O_2 produced $\mathbf{1a}_{ox}$ and $\mathbf{1b}_{ox}$ in 96 and 91%, respectively. $\mathbf{1a}_{ox}$ and $\mathbf{1b}_{ox}$ were reverted to $\mathbf{1a}_{red}$ (86%) and $\mathbf{1b}_{red}$ (83%) by the reduction with $NaBH_4$ (Scheme 3).

The structures of **1a** and **1b** were identified by ^1H NMR, ^{13}C NMR, IR, MS spectroscopies and/or elemental analysis. Furthermore, X-ray crystallographic analysis reveals that $\mathbf{1a}_{ox}$ has two independent cavities separated by the disulfide bond.[5]

Ion recognition ability of **1** to secondary ammonium ion **12**–**14** (Fig. 1) was examined by ^1H NMR spectroscopy. Addition of $\mathbf{1b}_{ox}$ (1 equiv.) to **12** caused downfield shift ($\Delta\delta$=0.09 ppm) of the benzyl protons of **12** in $CDCl_3$/CD_3CN (10:1, Fig. 2).[6] However, the corresponding

Keywords: redox reactions; crown ethers; thiol; disufide.

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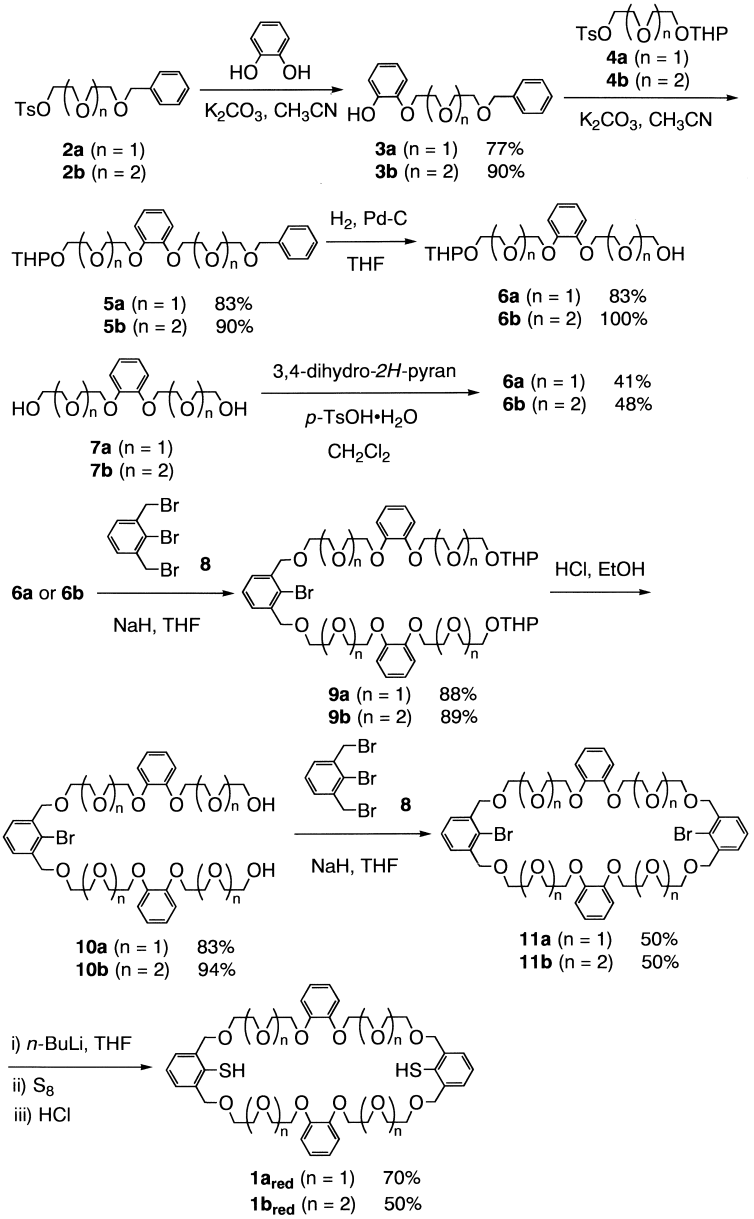
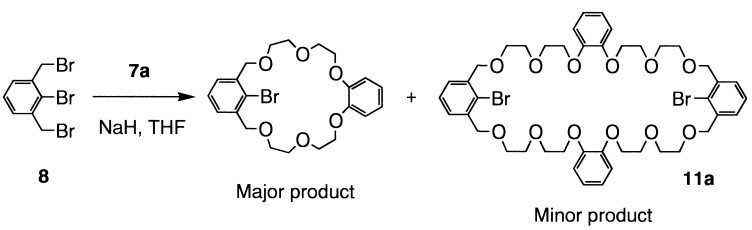
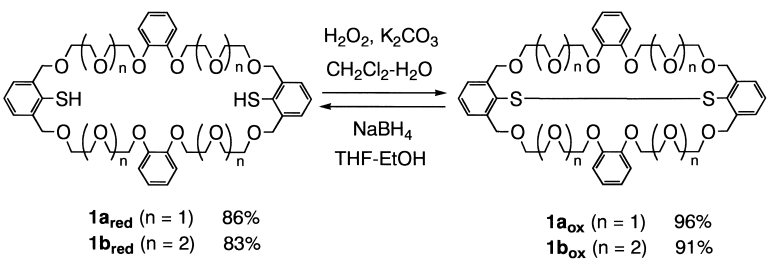


Scheme 1. Synthesis of $\mathbf{1a}_{red}$ and $\mathbf{1b}_{red}$.



Scheme 2. Cyclization reaction of **8** and **7a**.



Scheme 3. Interconversion between the reduced and oxidized forms of **1** by the redox reactions.

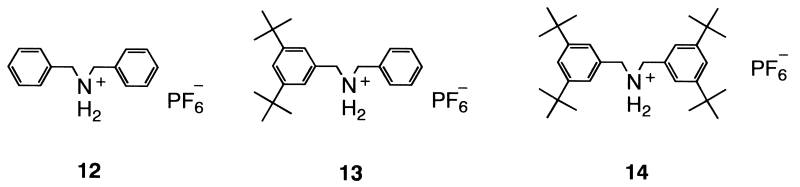


Figure 1. Structure of guests **12**–**14**.

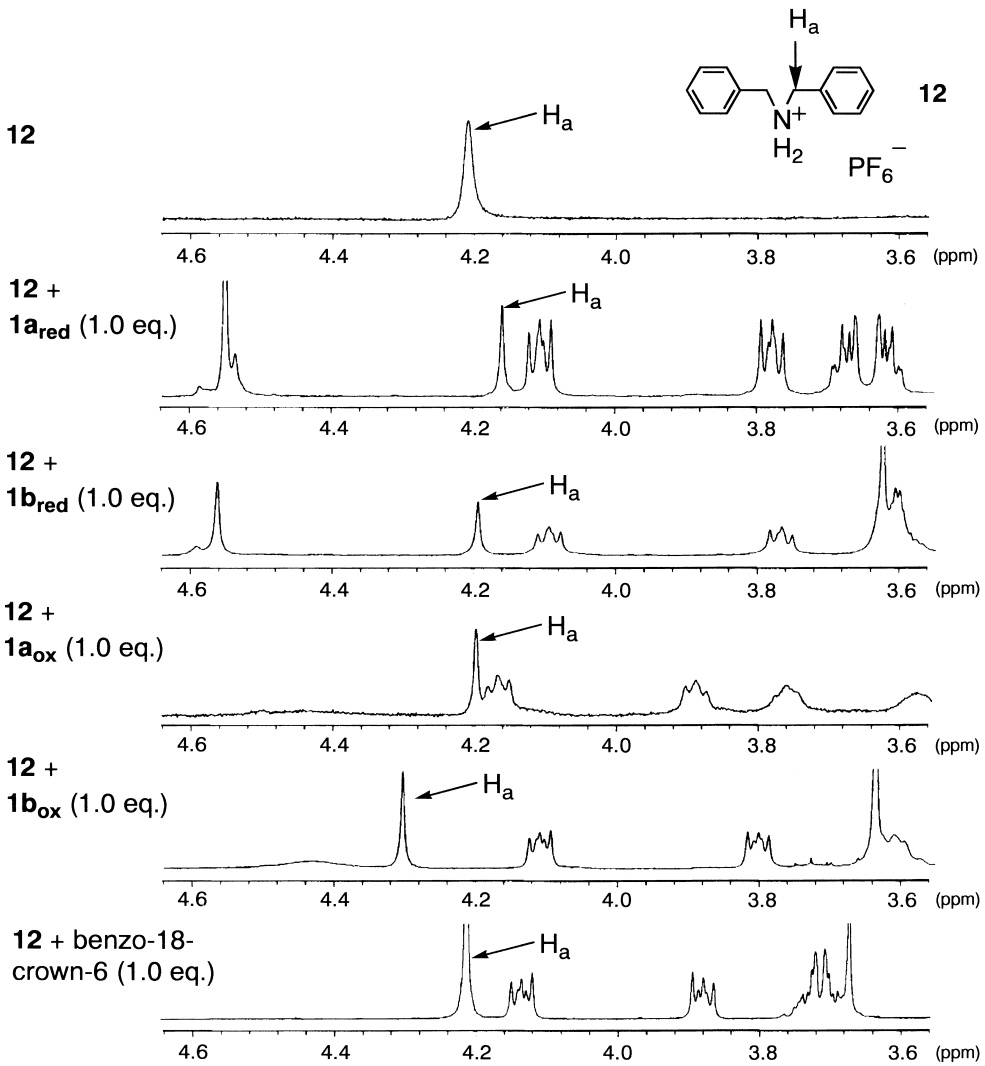


Figure 2. ^{1}H NMR spectral changes of **12** by the addition of **1** or benzo-18-crown-6 (300 MHz, $CDCl_3/CD_3CN$=10:1, [**12**]=2.0×10^{-3} M).

Table 1. Association constants of hosts **1** with ammonium salts **12**–**14**

Host	K_1 (M^{-1})[a]		
	12[b]	**13**[c]	**14**[c]
$\mathbf{1a}_{red}$	250±30	140±10	260±30
$\mathbf{1a}_{ox}$	–[d]	–[d]	–[d]
$\mathbf{1b}_{red}$	170±30	130±10	160±20
$\mathbf{1b}_{ox}$	850±250 (K_2=75±25)	675±125 (K_2=125±55)	–[d]

[a] K_1=[Host·Guest]/[Host][Guest], K_2=[Host·$Guest_2$]/[Host·Guest][Guest], determined by ^{1}H NMR spectroscopy ($CDCl_3/CD_3CN$=10:1).
[b] [**12**]=2.0×10^{-3} M.
[c] [Host]=2.0×10^{-3} M.
[d] Not determined due to very small change in chemical shifts.

reduced form $\mathbf{1b}_{red}$ resulted in much smaller effect on the signal of the benzyl protons. In contrast, $\mathbf{1a}_{red}$ gave rise to an upfield shift of the protons. Very small upfield shifts of H_a were performed by $\mathbf{1a}_{ox}$. 18-Crown-6 shows practically no affinity to **12**. ^{1}H NMR titration provided the binding constants (K_1) for the 1:1 complexation between **1** and the guests (**12**–**14**) by using non-linear-least-squares regression (Table 1). $\mathbf{1b}_{ox}$ shows the largest K_1 values for **12** and **13** among the hosts **1**. Interestingly, the 1:2 complexation between $\mathbf{1b}_{ox}$ and **12** (or **13**) is suggested, although K_2 for the second binding step is significantly smaller than K_1. On the other hand, $\mathbf{1b}_{red}$ has a much lower affinity to **12** and **13** probably because the cavity is too large and flexible for effective host–guest interactions. $\mathbf{1a}_{red}$ and $\mathbf{1a}_{ox}$ exhibit

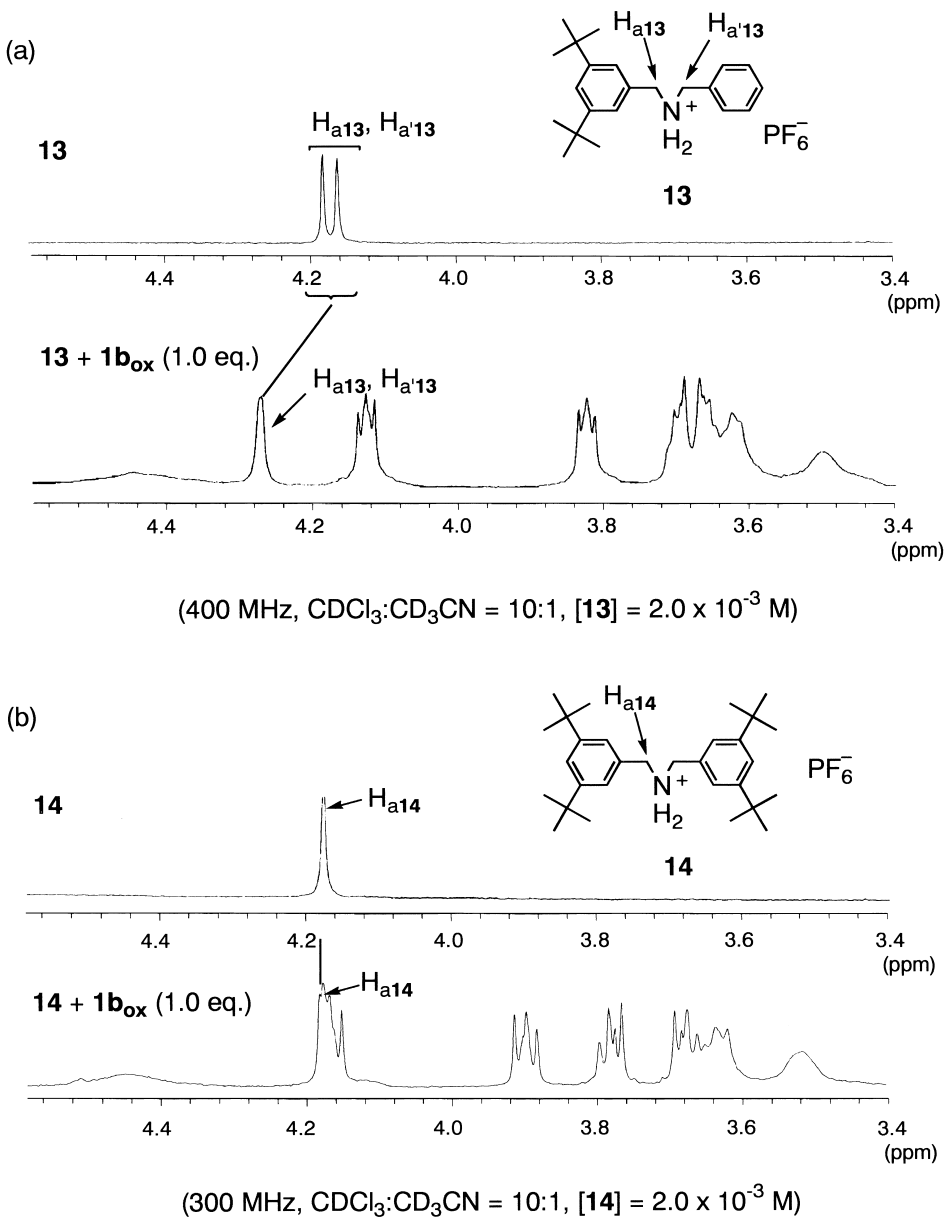


Figure 3. ^{1}H NMR spectral changes of ammonium salts **13**, **14** by the addition of **1b**$_{ox}$.

lower or no affinity to the guests. From the CPK model inspection and the X-ray analysis, the two cavities of **1a**$_{ox}$ are too small to bind **12**. Similarly to **1b**$_{red}$, **1a**$_{red}$ provides a large binding cavity for the guests. ESI-MS confirms the 1:1 complexation between **1b**$_{ox}$ and **12**, although the peaks assigned to the 1:2 complex were not observed. The ^{1}H NMR study points out that **1a**$_{red}$, **1b**$_{red}$ and **1b**$_{ox}$ bind **13** with the K_1 values similar to those for **12**, but that only **1a**$_{red}$ and **1b**$_{red}$ bind **14** in a similar fashion. In contrast, **1a**$_{ox}$ and **1b**$_{ox}$ causes no chemical shift change of the benzyl protons in **14** (Fig. 3). The lack of affinity of **1a**$_{ox}$ and **1b**$_{ox}$ to **14** suggests that the complexation between **1b**$_{ox}$ and **12** makes pseudorotaxane. The CPK model examination indicates that the bulky *t*-Bu groups of **14** prevents the penetration of **14** into the cavities of **1a**$_{ox}$ and **1b**$_{ox}$ (Fig. 4). The cavities of the reduced forms **1a**$_{red}$ and **1b**$_{red}$ are large enough to bind **14** without the steric hindrance. Thus, the K_1 values for **14** are nearly the same as those for **12** and **13**. The guest **13**, however, passes through the cavity because **13** consists of benzyl and 3,5-di-*t*-Bu-phenylmethyl moieties. These results strongly suggest that **1b**$_{ox}$ binds **13** to give the corresponding pseudorotaxane.

Solid–liquid extraction experiment clearly indicated the affinity of the hosts **1a**$_{ox}$, **1b**$_{ox}$, **1b**$_{red}$ to **12** (Fig. 5). ^{1}H NMR spectroscopy shows the guest **12** is sparingly soluble in $CDCl_3$. In the presence of the hosts, however, the amount of **12** extracted into the $CDCl_3$ phase is remarkably enhanced. As the binding constant suggested, the hosts solubilize **12** efficiently into the $CDCl_3$ layer due to the formation of the host–guest complex.

3. Conclusion

In summary, recognition of the secondary ammonium

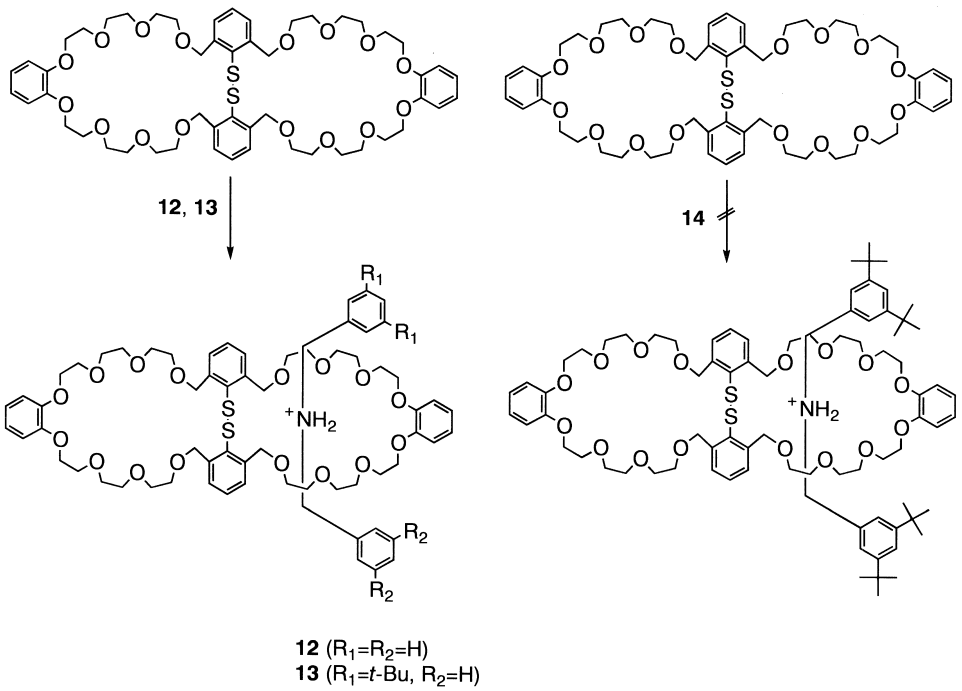


Figure 4. Plausible complexation mode.

guests is finely controlled by using the redox active hosts **1**. $\mathbf{1a}_{red}$ binds the guests more strongly than $\mathbf{1a}_{ox}$, while $\mathbf{1b}_{ox}$ exhibits much higher affinity to **12** and **13** than $\mathbf{1b}_{red}$. These results clearly indicate that regulation of the size of the binding sites is very useful to control molecular recognition ability. Thus, we believe that this strategy can be applied to construction of molecular machines and devices such as a molecular shuttle and a motor by an external stimulus.

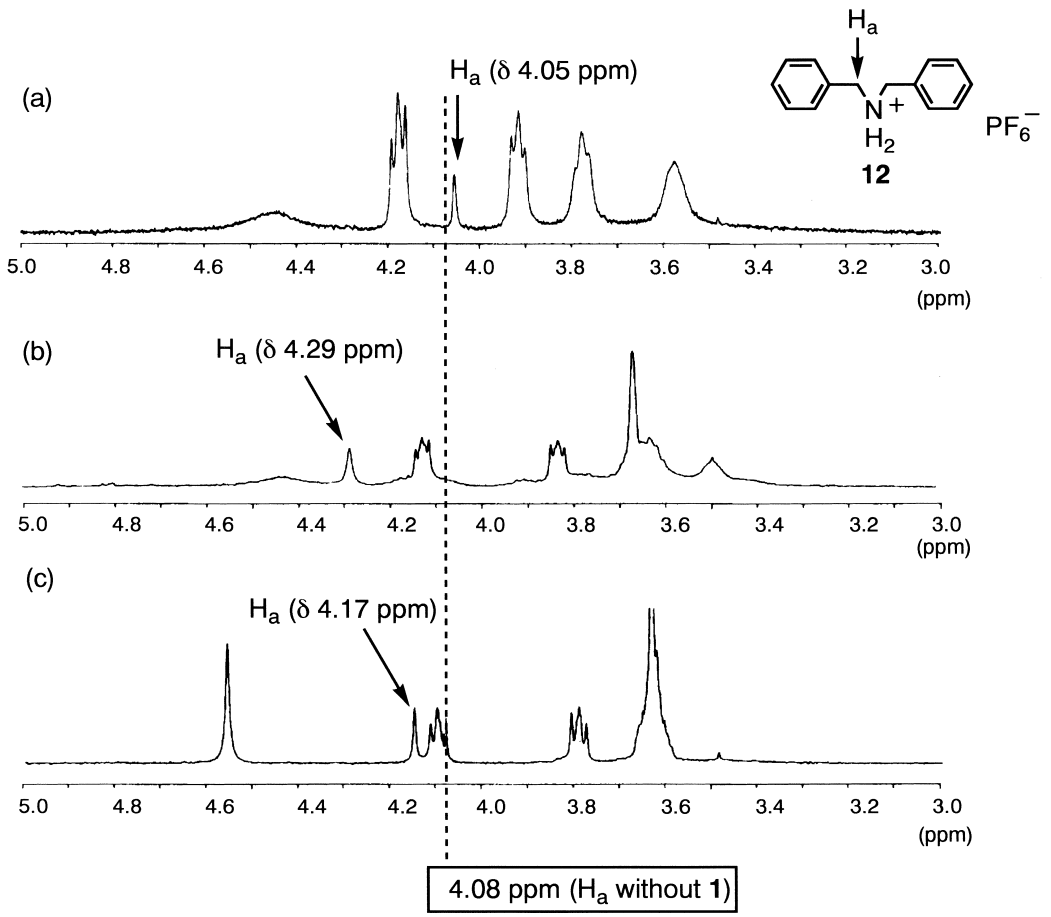


Figure 5. Solid-liquid extraction of **12** by (a) $\mathbf{1a}_{ox}$, (b) $\mathbf{1b}_{ox}$, (c) $\mathbf{1b}_{red}$ (300 MHz, $CDCl_3$, [Host]=2.0 mM).

4. Experimental

4.1. General methods

All chemical reagents were purchased and used without further purification. THF was distilled from benzophenone ketyl under nitrogen atmosphere prior to use. Tosylates **2a**[7] and **2b**,[8] phenol **3a**,[7] tosylates **4a**[9] and **4b**,[10] diols **7a**[11] and **7b**,[4b] and tribromide **8**[12] were prepared by previously described methods. ^{1}H NMR spectra were recorded on a Bruker ARX400 at 400 MHz or a Bruker AC300 at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker ARX400 at 100 MHz. Coupling constants (J) were reported in Hz. NMR chemical shifts were reported in ppm downfield from a tetramethylsilane peak. NMR solvents were purchased and used without further purification. IR spectra were recorded on a JASCO FT/IR-5000 spectrometer using KBr pellets or NaCl plates, and only partial data are reported. Melting points were determined on a Yanaco melting point apparatus, and not corrected. ESI-MS spectra were recorded with a Perkin-Elmer Sciex API-100 spectrometer. Elemental analyses were performed at Chemical Analysis Center, University of Tsukuba.

4.2. Preparation of crown ethers 1a and 1b

4.2.1. Synthesis of 3b. A solution of **2b** (15.00 g, 38.0 mmol) in CH_3CN (50 ml) was added dropwise to a refluxing mixture of catechol (20.95 g, 0.190 mol) and K_2CO_3 (6.85 g, 49.6 mmol) in CH_3CN (300 ml) over 30 min. After the mixture was refluxed for 14 h, the solvent was evaporated and then the residue was poured into H_2O (150 ml) and $CHCl_3$ (150 ml). The mixture was acidified (pH 3) with 3 M hydrochloric acid, and the aqueous phase was extracted with $CHCl_3$ (2×150 ml). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. After removal of excess catechol by sublimation at ca. 130°C in vacuo, the crude product was purified by column chromatography (SiO_2, $CHCl_3$/EtOAc=10:1) to afford **3b** as a yellow oil (11.36 g, 34.2 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.34–7.27 (m, 5H), 7.03 (brs, 1H), 6.92–6.85 (m, 3H), 6.81–6.77 (m, 1H), 4.57 (s, 2H), 4.15 (t, 2H, J=4.4 Hz), 3.83 (t, 2H, J=4.4 Hz), 3.74–3.63 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 147.4 (s), 146.1 (s), 137.9 (s), 128.4 (d), 127.9 (d), 127.7 (d), 122.6 (d), 119.7 (d), 115.9 (d), 114.4 (d), 73.2 (t), 70.50 (t), 70.48 (t), 70.4 (t), 69.5 (t), 69.3 (t), 69.1 (t). Anal. calcd for $C_{19}H_{24}O_5$·0.33H_2O: C, 67.44; H, 7.35. Found: C, 67.38; H, 7.49.

4.2.2. Synthesis of 5a. To a solution of **3a** (9.930 g, 34.4 mmol) in CH_3CN (150 ml) were added K_2CO_3 (5.22 g, 37.8 mmol) and a solution of **4a** (12.05 g, 35.0 mmol) in CH_3CN (50 ml), and then the resulting mixture was refluxed for 12 h. After removal of the solvent, H_2O (150 ml) was added to the residue. The mixture was extracted with $CHCl_3$ (3×150 ml), and the organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc=10:1) to afford **5a** as a yellow oil (13.11 g, 28.5 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.4–7.3 (m, 5H), 7.0–6.8 (m, 4H), 4.64–4.61 (m, 1H), 4.58 (s, 2H), 4.20–4.15 (m, 4H), 3.90–3.83 (m, 6H), 3.78–3.72 (m, 4H), 3.66–3.59 (m, 3H), 3.51–3.47 (m, 1H), 1.85–1.48 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.0 (s), 138.2 (s), 128.3 (d), 127.7 (d), 127.5 (d), 121.6 (d), 114.9 (d), 98.9 (d), 73.2 (t), 70.8 (t), 70.7 (t), 69.8 (t), 69.7 (t), 69.4 (t), 68.9 (t), 66.7 (t), 62.1 (t), 30.5 (t), 25.4 (t), 19.4 (t). Anal. calcd for $C_{26}H_{36}O_7$·0.25H_2O: C, 67.15; H, 7.91. Found: C, 67.14; H, 7.84.

4.2.3. Synthesis of 5b. To a solution of **3b** (18.65 g, 56.1 mmol) in CH_3CN (300 ml) were added K_2CO_3 (9.405 g, 68.0 mmol) and a solution of **4b** (21.75 g, 56.1 mmol) in CH_3CN (50 ml), and the mixture was refluxed for 14 h. After removal of the solvent, H_2O (150 ml) was added to the residue. The mixture was extracted with $CHCl_3$ (3×150 ml), and the organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc=10:1) to afford **5b** as a yellow oil (11.36 g, 34.2 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.34–7.27 (m, 5H), 6.94–6.90 (m, 4H), 4.64–4.61 (m, 1H), 4.56 (s, 2H), 4.16 (t, 4H, J=5.1 Hz), 3.89–3.83 (m, 6H), 3.76–3.59 (m, 15H), 3.53–3.47 (m, 1H), 1.88–1.48 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.0 (s), 138.2 (s), 128.3 (d), 127.7 (d), 127.6 (d), 121.6 (d), 114.9 (d), 98.9 (d), 73.2 (t), 70.8 (t), 70.71 (t), 70.66 (t), 70.6 (t), 69.8 (t), 69.4 (t), 68.8 (t), 66.6 (t), 62.2 (t), 30.6 (t), 25.4 (t), 19.5 (t). Anal. calcd for $C_{30}H_{44}O_9$·0.25H_2O: C, 65.14; H, 8.11. Found: C, 65.14; H, 8.07.

4.2.4. Synthesis of 6a. To a solution of **5a** (16.02 g, 34.8 mmol) in THF (100 ml) was added 10% Pd-C (1.648 g), and the mixture was stirred under H_2 atmosphere (1 atm) for 60 h. The catalyst was removed by filtration, and the solvent was evaporated. The residue thus obtained was purified by column chromatography (SiO_2, EtOAc) to afford **6a** as a pale yellow oil (10.67 g, 28.5 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.90–6.87 (m, 4H), 4.62–4.60 (m, 1H), 4.16–4.12 (m, 4H), 3.89–3.44 (m, 14H), 1.9–1.4 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 148.9 (s), 148.7 (s), 121.7 (d), 121.5 (d), 114.6 (d), 114.4 (d), 98.9 (d), 72.7 (t), 70.7 (t), 69.7 (t), 69.5 (t), 68.9 (t), 68.6 (t) 66.7 (t), 62.1 (t), 61.6 (t), 30.5 (t), 25.4 (t), 19.4 (t). Anal. calcd for $C_{19}H_{30}O_7$·0.4H_2O: C, 60.43; H, 8.22. Found: C, 60.53; H, 8.32.

4.2.5. Synthesis of 6b. To a solution of **5b** (22.48 g, 38.4 mmol) in THF (120 ml) was added 10% Pd-C (1.011 g), and the mixture was stirred under H_2 atmosphere (1 atom) for 72 h. The catalyst was removed by filtration and the solvent was evaporated to give **6b** as a pale yellow oil (17.73 g, 38.7 mmol, 100%), which was used in the following reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.91 (s, 4H), 4.63 (t, 1H, J=3.6 Hz), 4.17 (t, 4H, J=4.6 Hz), 3.89–3.85 (m, 6H), 3.77–3.67 (m, 12H), 3.62–3.57 (m, 3H), 3.52–3.47 (m, 1H), 2.82 (brs, 1H), 1.86–1.49 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 148.84 (s), 148.75 (s), 121.64 (d), 121.57 (d), 114.5 (d), 98.9 (d), 72.7 (t), 70.83 (t), 70.78 (t), 70.6 (t), 70.5 (t), 70.3 (t), 69.8 (t), 69.7 (t), 68.7 (t), 66.6 (t), 62.2 (t), 61.7 (t), 30.5 (t), 25.4 (t), 19.5 (t). Anal. calcd

for $C_{23}H_{38}O_9 \cdot 0.5H_2O$: C, 59.08; H, 8.41. Found: C, 58.73; H, 8.44.

4.2.6. Synthesis of 9a. To a solution of **6a** (12.48 g, 33.7 mmol) in dry THF (200 ml) were added NaH (60% dispersion in oil, 1.498 g, 37.5 mmol) and **8** (5.722 g, 17.3 mmol), and then the mixture was refluxed for 51 h. After removal of the solvent, H_2O (200 ml) was added to the residue. The mixture was extracted with $CHCl_3$ (3×200 ml), and the organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated, and the crude product was purified by column chromatography (SiO_2, $CHCl_3$/EtOAc=1:1) to afford **9a** as a yellow oil (13.69 g, 14.9 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (d, 2H, J=7.8 Hz), 7.28 (t, 1H, J=7.8 Hz), 6.95–6.88 (m, 8H), 4.647 (s, 4H), 4.64–4.60 (m, 2H), 4.19–4.16 (m, 8H), 3.91–3.85 (m, 12H), 3.81–3.79 (m, 4H), 3.76–3.73 (m, 8H), 3.64–3.59 (m, 2H), 3.50–3.47 (m, 2H), 1.83–1.48 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.1 (s), 149.0 (s), 137.9 (s), 127.9 (d), 127.2 (d), 122.6 (s), 121.7 (d), 121.6 (d), 115.1 (d), 115.0 (d), 98.9 (d), 72.7 (t), 70.83 (t), 70.78 (t), 70.3 (t), 69.9 (t), 69.8 (t), 69.0 (t), 68.9 (t), 66.7 (t), 62.2 (t), 30.6 (t), 25.4 (t), 19.5 (t). Anal. calcd for $C_{46}H_{65}BrO_{14}$: C, 59.93; H, 7.11. Found: C, 59.81; H, 7.27.

4.2.7. Synthesis of 9b. To a solution of **6b** (6.002 g, 13.1 mmol) in dry THF (100 ml) were added NaH (60% dispersion in oil, 0.680 g, 17.0 mmol) and **8** (2.249 g, 6.56 mmol), and then the mixture was refluxed for 51 h. After removal of the solvent, H_2O (100 ml) was added to the residue. The mixture was extracted with $CHCl_3$ (3×100 ml), and the organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated, and the crude product was purified by column chromatography (SiO_2, $CHCl_3$/EtOAc=1:1) to afford **9b** as a yellow oil (6.354 g, 5.79 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (d, 2H, J=7.6 Hz), 7.28 (t, 1H, J=7.6 Hz), 6.93–6.88 (m, 8H), 4.64–4.61 (m, 6H), 4.18–4.15 (m, 8H), 3.88–3.84 (m, 12H), 3.77–3.67 (m, 28H), 3.63–3.58 (m, 4H), 1.89–1.45 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.0 (s), 137.9 (s), 127.9 (d), 127.2 (d), 122.6 (s), 121.7 (d), 115.0 (d), 98.9 (d), 72.7 (t), 70.9 (t), 70.8 (t), 70.7 (t), 70.63 (t), 70.58 (t), 70.2 (t), 69.83 (t), 69.81 (t), 68.9 (t), 66.7 (t), 62.2 (t), 30.6 (t), 25.4 (t), 19.5 (t). Anal. calcd for $C_{54}H_{81}BrO_{18} \cdot H_2O$: C, 58.11; H, 7.50. Found: C, 58.34; H, 7.49.

4.2.8. Synthesis of 10a. To a solution of **9a** (3.412 g, 3.70 mmol) in EtOH (20 ml) was added 3 M hydrochloric acid (10 ml), and the mixture was stirred for 16 h at rt. After addition of saturated aq. $NaHCO_3$ (15 ml), the organic solvent was evaporated. The mixture was poured into H_2O (10 ml), extracted with $CHCl_3$ (3×20 ml), and the organic phase was dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, EtOAc to EtOAc/EtOH=10:1) to afford **10a** as a yellow oil (2.311 g, 3.07 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (d, 2H, J=7.6 Hz), 7.27 (t, 1H, J=7.6 Hz), 6.92–6.90 (m, 8H), 4.64 (s, 4H), 4.19–4.14 (m, 8H), 3.92 (t, 4H, J=5.0 Hz), 3.87–3.85 (m, 4H), 3.81–3.79 (m, 4H), 3.77–3.71 (m, 8H), 3.67–3.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 148.7 (s), 148.5 (s), 137.8 (s), 128.0 (d), 127.2 (d), 122.8 (s), 121.6 (d), 121.4 (d), 114.0 (d), 113.9 (d), 72.9 (t), 72.7 (t), 70.7 (t), 70.1 (t), 69.7 (t), 69.4 (t), 68.6 (t), 68.3 (t), 61.6 (t). Anal. calcd for $C_{36}H_{49}BrO_{12}$: C, 57.37; H, 6.55. Found: C, 57.09; H, 6.73.

4.2.9. Synthesis of 10b. To a solution of **9b** (5.581 g, 5.08 mmol) in EtOH (20 ml) was added 3 M hydrochloric acid (10 ml), and the mixture was stirred for 48 h at rt. After addition of saturated aq. $NaHCO_3$ (15 ml), the organic solvent was evaporated. The mixture was poured into H_2O (30 ml), extracted with $CHCl_3$ (3×40 ml), and the organic phase was dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, EtOAc to EtOAc/EtOH=5:1) to afford **10b** as a yellow oil (4.440 g, 4.78 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (d, 2H, J=8.0 Hz), 7.29 (t, 1H, J=8.0 Hz), 6.91 (s, 8H), 4.63 (s, 4H), 4.17 (t, 4H, J=5.0 Hz), 3.89–3.85 (m, 4H), 3.77–3.66 (m, 36H), 3.61–3.59 (m, 4H), 2.72 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 148.7 (s), 148.6 (s), 137.9 (s), 127.9 (d), 127.2 (d), 122.6 (s), 121.6 (d), 121.5 (d), 114.4 (d), 114.3 (d), 72.71 (t), 72.66 (t), 70.8 (t), 70.7 (t), 70.5 (t), 70.2 (t), 70.1 (t), 69.70 (t), 69.66 (t), 68.6 (t), 68.5 (t), 61.6 (t). Anal. calcd for $C_{44}H_{65}BrO_{16} \cdot H_2O$: C, 55.75; H, 7.12. Found: C, 55.76; H, 7.17.

4.2.10. Synthesis of 11a. A solution of **8** (2.293 g, 6.69 mmol) and **10a** (5.019 g, 6.67 mmol) in dry THF (100 ml) was added dropwise to a refluxing suspension of NaH (60% dispersion in oil, 0.587 g, 14.7 mmol) in dry THF (250 ml) over 24 h, and then the mixture was refluxed for 48 h. After removal of the solvent, H_2O (50 ml) was added and the mixture was extracted with $CHCl_3$ (3×50 ml). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude product thus obtained was purified by column chromatography (SiO_2, $CHCl_3$ to $CHCl_3$/Et_2O/EtOH=10:10:1) and recrystallization from EtOAc to afford **11a** as a white powder (3.117 g, 3.34 mmol, 50%). Mp 106.5–108.5°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.36 (d, 4H, J=7.8 Hz), 7.24 (t, 2H, J=7.8 Hz), 6.91 (s, 8H), 4.57 (s, 8H), 4.17 (t, 8H, J=4.8 Hz), 3.88 (t, 8H, J=4.8 Hz), 3.78 (t, 8H, J=4.6 Hz), 3.68 (t, 8H, J=4.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.0 (s), 137.9 (s), 127.9 (d), 127.2 (d), 122.6 (s), 121.6 (d), 114.7 (d), 72.7 (t), 70.8 (t), 70.2 (t), 69.9 (t), 69.1 (t). Anal. calcd for $C_{44}H_{54}Br_2O_{12}$: C, 56.54; H, 5.82. Found: C, 56.36; H, 5.92. ESI-MS m/z found: $[M+Na]^+$, 955.2, $C_{44}H_{54}Br_2O_{12}Na^+$ requires 955.2.

4.2.11. Synthesis of 11b. A solution of **8** (1.498 g, 4.37 mmol) and **10b** (4.078 g, 4.39 mmol) in dry THF (50 ml) was added dropwise to a refluxing suspension of NaH (60% dispersion in oil, 0.472 g, 11.8 mmol) in THF (300 ml) over 24 h, and then the mixture was refluxed for 48 h. After removal of the solvent, H_2O (50 ml) was added and the mixture was extracted with $CHCl_3$ (3×50 ml). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, $CHCl_3$ to $CHCl_3$/Et_2O/EtOH=10:10:1) and recrystallization from EtOAc to afford **11b** as a white powder (2.427 g, 2.19 mmol, 50%). Mp 84.0–85.5°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.39 (d, 4H, J=7.8 Hz), 7.26 (t, 2H, J=7.8 Hz), 6.89 (s, 8H), 4.61 (s, 8H), 4.15 (t, 8H, J=4.8 Hz), 3.86 (t, 8H, J=5.0 Hz), 3.76–3.67 (m, 32H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ (ppm) 149.0 (s), 137.9 (s), 127.9 (d), 127.2 (d), 122.6 (s), 121.6 (d), 114.8 (d), 72.7 (t), 70.9 (t), 70.8 (t), 70.6 (t), 70.2 (t), 69.8 (t), 69.0 (t). Anal. calcd for $C_{52}H_{70}Br_2O_{16}$: C, 56.22; H, 6.35. Found: C, 56.30; H, 6.44. ESI-MS *m/z* found: $[M+Na]^+$, 1131.5, $C_{52}H_{70}Br_2O_{16}Na^+$ requires 1131.3.

4.2.12. Synthesis of $\mathbf{1a_{red}}$. To a solution of **11a** (0.600 g, 6.42×10^{-4} mol) in dry THF (100 ml) was added *n*-BuLi (1.54 M) in hexane (1.50 ml, 2.31 mmol) dropwise at −75°C. After stirring for 5 min, elemental sulfur (0.150 g, 4.69 mmol as S) was added by using an additional flask and then the reaction mixture was stirred at −75°C for 8 h. The mixture was poured into 3 M hydrochloric acid and the organic solvent was evaporated. The mixture was extracted with $CHCl_3$ (3×30 ml), and the organic phase was dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, $CHCl_3$ to $CHCl_3$/Et_2O/EtOH=10:10:1) and recrystallization from EtOAc to afford $\mathbf{1a_{red}}$ as a white powder (0.457 g, 4.49×10^{-4} mol, 70%). Mp 91.5–93.0°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25 (d, 4H, *J*=7.2 Hz), 7.09 (t, 2H, *J*=7.2 Hz), 6.90 (s, 8H), 4.58 (s, 8H), 4.52 (s, 2H), 4.15 (t, 8H, *J*=4.8 Hz), 3.84 (t, 8H, *J*=4.8 Hz), 3.74–3.72 (m, 8H), 3.64–3.61 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.1 (s), 136.9 (s), 132.4 (s), 129.2 (d), 125.1 (d), 121.6 (d), 114.9 (d), 72.5 (t), 70.7 (t), 69.8 (t), 69.5 (t), 69.1 (t). IR: (NaCl) 2537 cm^{-1} (–SH). Anal. calcd for $C_{44}H_{56}O_{12}S_2{\cdot}0.5H_2O$: C, 62.17; H, 6.76. Found: C, 61.90; H, 6.64. ESI-MS *m/z* found: $[M+Na]^+$, 863.5, $C_{44}H_{56}O_{12}S_2Na^+$ requires 863.3.

4.2.13. Synthesis of $\mathbf{1a_{ox}}$. 5% aq. H_2O_2 (5 ml, 7.35 mmol) and K_2CO_3 (88.5 mg, 6.40×10^{-4} mol) were added to a solution of $\mathbf{1a_{red}}$ (0.179 g, 2.13×10^{-4} mol) in CH_2Cl_2 (20 ml), and the mixture was stirred for 30 min at rt. The organic layer was dried over anhydrous $MgSO_4$. After removal of the solvent, $\mathbf{1a_{ox}}$ was obtained as a white powder (0.172 g, 2.05×10^{-4} mol, 96%), which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (brs, 4H), 7.32 (t, 2H, *J*=7.6 Hz), 6.90 (s, 8H), 4.44 (brs, 8H), 4.17 (t, 8H, *J*=4.6 Hz), 3.91 (t, 8H, *J*=4.2 Hz), 3.78 (brs, 8H), 3.59 (brs, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 148.9 (s), 143.1 (s), 131.8 (s), 130.2 (d), 127.6 (d), 121.5 (d), 114.2 (d), 70.9 (t), 70.6 (t), 70.2 (t), 69.7 (t), 69.2 (t). Anal. calcd for $C_{44}H_{54}O_{12}S_2{\cdot}0.25H_2O$: C, 62.65; H, 6.51. Found: C, 62.64; H, 6.56. ESI-MS *m/z* found: $[M+Na]^+$, 861.4, $C_{44}H_{54}O_{12}S_2Na^+$ requires 861.3.

4.2.14. Synthesis of $\mathbf{1b_{red}}$. To a solution of **11b** (1.088 g, 9.79×10^{-4} mol) in dry THF (90 ml) was added *n*-BuLi (2.47 M) in hexane (2.00 ml, 4.94 mmol) dropwise at −75°C. After stirring for 10 min, elemental sulfur (0.197 g, 6.16 mmol as S) was added by using an additional flask, and the mixture was stirred for 8 h at −75°C. The mixture was poured into 3 M hydrochloric acid, and the organic solvent was evaporated. The mixture was extracted with $CHCl_3$ (3×30 ml), and the organic phase was dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, $CHCl_3$ to $CHCl_3$/Et_2O/EtOH=10:10:1) and recrystallization from EtOAc to afford $\mathbf{1b_{red}}$ as a white powder (0.502 g, 4.93×10^{-4} mol, 50%). Mp 67.0–68.0°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.27–7.25 (m, 4H), 7.09 (t, 2H, *J*=7.6 Hz), 6.90 (s, 8H), 4.60 (s, 8H), 4.58 (s, 2H), 4.15 (t, 8H, *J*=5.0 Hz), 3.85 (t, 8H, *J*=5.0 Hz), 3.80–3.60 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.2 (s), 137.1 (s), 132.7 (s), 129.5 (d), 125.3 (d), 121.8 (d), 115.0 (d), 72.8 (t), 71.1 (t), 71.0 (t), 70.7 (t), 70.0 (t), 69.8 (t), 69.1 (t). IR: (NaCl) 2530 cm^{-1} (–SH). Anal. calcd for $C_{52}H_{72}O_{16}S_2$: C, 61.40; H, 7.13. Found: C, 61.33; H, 7.62. ESI-MS *m/z* found: $[M+Na]^+$, 1039.4, $C_{52}H_{72}O_{16}S_2Na^+$ requires 1039.4.

4.2.15. Synthesis of $\mathbf{1b_{ox}}$. 5% aq. H_2O_2 (5 ml, 7.35 mmol) and K_2CO_3 (78.4 mg, 5.67×10^{-4} mol) were added to a solution of $\mathbf{1b_{red}}$ (0.148 g, 1.45×10^{-4} mol) in CH_2Cl_2 (20 ml), and the mixture was stirred for 20 min at rt. The organic layer was dried over anhydrous $MgSO_4$. After removal of the solvent, $\mathbf{1b_{ox}}$ was obtained as a yellow oil (0.135 g, 1.33×10^{-4} mol, 91%), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.43–7.35 (m, 6H), 6.90 (s, 8H), 4.46 (brs, 8H), 4.17 (t, 8H, *J*=4.7 Hz), 3.91 (t, 8H, *J*=4.8 Hz), 3.81–3.78 (m, 8H), 3.70–3.65 (m, 16H), 3.52 (brs, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.0 (s), 143.1 (s), 131.5 (s), 130.2 (d), 127.2 (d), 121.6 (d), 114.7 (d), 71.0 (t), 70.79 (t), 70.75 (t), 70.5 (t), 70.0 (t), 69.9 (t), 69.2 (t). Anal. calcd for $C_{52}H_{70}O_{16}S_2$: C, 61.52; H, 6.95. Found: C, 61.36; H, 7.11. ESI-MS *m/z* found: $[M+Na]^+$, 1037.5, $C_{52}H_{70}O_{16}S_2Na^+$ requires 1037.4.

4.2.16. Synthesis of $\mathbf{1a_{red}}$ (reduction of $\mathbf{1a_{ox}}$). To a solution of $\mathbf{1a_{ox}}$ (78.2 mg, 9.32×10^{-5} mol) in 20% EtOH/THF (10 ml) was added $NaBH_4$ (52.1 mg, 1.38 mmol) and the mixture was stirred for 1 h at rt. The mixture was poured into 3 M hydrochloric acid and the organic solvent was removed under reduced pressure. H_2O (10 ml) was added to the residue and the mixture was extracted with $CHCl_3$ (3×10 ml). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated to give $\mathbf{1a_{red}}$ as a white powder (67.2 mg, 7.99×10^{-5} mol, 86%).

4.2.17. Synthesis of $\mathbf{1b_{red}}$ (reduction of $\mathbf{1b_{ox}}$). To a solution of $\mathbf{1b_{ox}}$ (70.0 mg, 6.89×10^{-5} mol) in 20% EtOH/THF (5 ml) was added $NaBH_4$ (0.110 g, 2.91 mmol) and the mixture was stirred for 1 h at rt. The mixture was poured into 3 M hydrochloric acid and the organic solvent was removed under reduced pressure. H_2O (20 ml) was added to the residue and the mixture was extracted with $CHCl_3$ (2×20 ml). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated to give $\mathbf{1b_{red}}$ as a white powder (58.0 mg, 5.70×10^{-5} mol, 83%).

4.2.18. Synthesis of 6a (from 7a). To a mixture of **7a** (18.011 g, 62.9 mmol) and *p*-toluenesulfonic acid monohydrate (1.148 g, 6.04 mmol) in CH_2Cl_2 (100 ml) was added a solution of 3,4-dihydro-2*H*-pyran (5.332 g, 63.4 mmol) in CH_2Cl_2 (10 ml) dropwise over 10 min at 4°C, and the solution was stirred at 4°C for 5 h. Excess K_2CO_3 was added, and then the mixture was stirred for further 3 h. The solution was washed with 5% aq. $NaHCO_3$ (100 ml), and the organic layer was dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, EtOAc) to afford **6a** as a pale yellow oil (9.576 g, 25.9 mmol, 41%).

4.2.19. Synthesis of 6b (from 7b). To a mixture of **7b** (27.421 g, 73.2 mmol) and *p*-toluenesulfonic acid monohydrate (1.486 g, 7.81 mmol) in CH_2Cl_2 (100 ml) was added a solution of 3,4-dihydro-2*H*-pyran (6.164 g, 73.7 mmol) in CH_2Cl_2 (30 ml) dropwise over 15 min at 4°C, and then the solution was stirred at 4°C for 12 h. Excess K_2CO_3 was added, and the mixture was stirred for further 3 h. The solution was washed with 5% aq. $NaHCO_3$ (100 ml), and the organic layer was dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, EtOAc) to afford **6b** as a pale yellow oil (16.113 g, 35.1 mmol, 48%).

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