Synthesis of novel 18-crown-6 type ligands containing a phenothiazine 5,5-dioxide unit

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Abstract
Novel crown ethers containing a phenothiazine 5,5-dioxide unit have been synthesized. Macrocyclization reactions rendering *N*-tosyl protected crown ethers were performed in the absence of metal ion templates. These new crown ethers are useful precursors of sensor and selector molecules with wide applications.

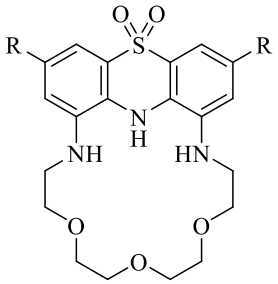
Keywords: Macrocycles, heterocycles, crown ether, phenothiazine

Introduction

Molecular recognition is a general phenomenon in Nature. There are many examples for its action such as the immunological response, enzyme–substrate interactions or selective complexation and transport of metal ions across cell membranes by ionophores. The origins of supramolecular chemistry are based on such biochemical phenomena, and modeling these phenomena using synthetic compounds has demonstrated that biological behavior can be engineered into simple molecules, such as crown ethers.[1] Since Pedersen's first crown ethers,[2] many derivatives have been prepared with different applications.[3–9] The selectivity of crown ethers can be enhanced by making the macrocycle more rigid, which can be achieved for example by incorporating tricyclic heterocycles in the macroring. Moreover the properties of the donor atoms in the heterocycle can easily be modified by substitution in the aromatic rings, and these derivatives can also be chromo- or fluorogenic, making them effective optical sensor molecules. Synthesis and molecular recognition studies of many crown ethers based on tricyclic heterocycles are reported in the literature, for example those of xanthone[10]-, dibenzofuran[11–14]-, phenanthroline[15–22]-, phenazine[23–27]-, or acridone- and acridine[23,28–37]-based macrocycles. In the continuation of our research of crown ethers based on tricyclic ring systems,[23–37] our attention turned toward phenothiazine. The properties of the nitrogen of phenothiazine can not only be

modified by substitution in the aromatic rings, but also by changing the oxidation state of the sulfur atom making it a promising building element of new macrocycles. There are some crown ethers containing phenothiazine units reported in the literature,[38–40] but there is no example in which the heteroatom (N or S atom) of the phenothiazine unit is part of the macroring.

In this paper we report the synthesis of a new class of macrocycles containing a phenothiazine unit (**1** and **2**, Fig. 1.) in which the NH group of the phenothiazine is part of the macroring. These macrocycles can be very useful intermediates in the synthesis of sensor and selector molecules with diverse applications.

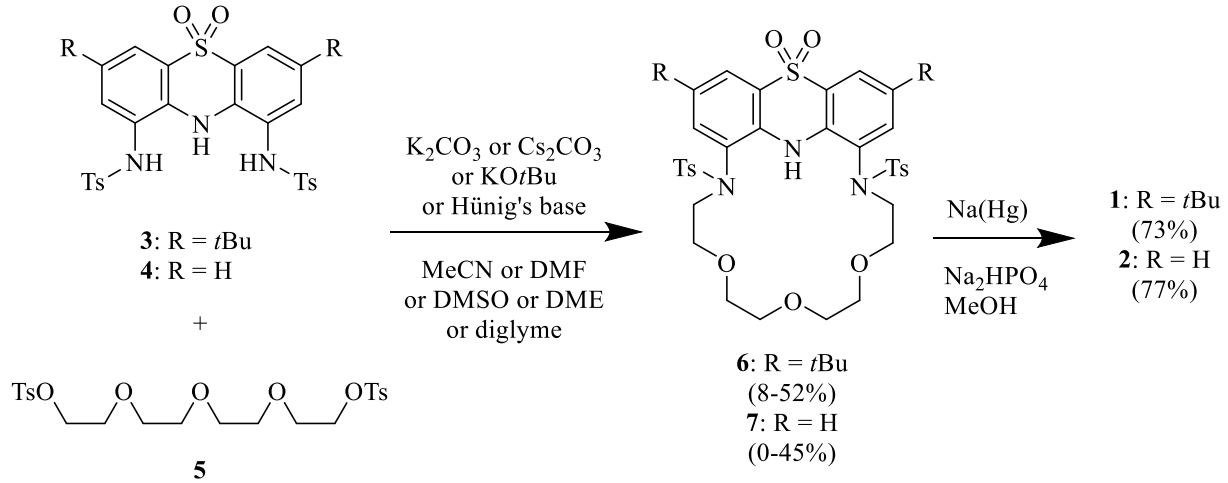


1: R = *t*Bu
2: R = H

Figure 1. Structures of new crown ethers **1** and **2**.

Results and Discussion

Crown ethers **1** and **2** were prepared starting from ditosylamides **3** and **4** in two steps (Scheme 1). Ditosylamides **3** and **4** were reacted with tetraethyleneglycol ditosylate **5**[41] in the presence of bases [potassium carbonate, cesium carbonate, potassium *tert*-butoxide or Hünig's base (*N*-ethyl-*N*,*N*-diisopropylamine)] in different solvents (acetonitrile, dimethylformamide, dimethylsulfoxide, dimethoxyethane or diglyme, see Table 1. for more details).



Scheme 1. Preparation of crown ethers **1** and **2**.

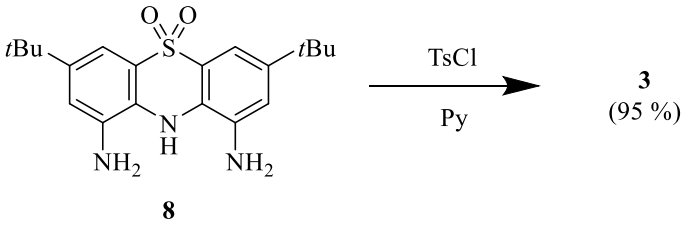
Table 1. Yields of the macrocyclization reactions in the presence of different bases in different solvents

R	base	solvent	amount of **3** or **4**	yield
*t*Bu	K_2CO_3	MeCN	0.2 g	12%
*t*Bu	K_2CO_3	MeCN	6.0 g	15%
H	K_2CO_3	MeCN	0.2 g	–
H	Cs_2CO_3	MeCN	0.2 g	–
H	K_2CO_3	DMF	0.2 g	–
H	KO*t*Bu	DMF	0.2 g	–
H	KO*t*Bu	DMSO	0.2 g	–
H	Hünig's base	dimethoxyethane	0.2 g	14%
H	Hünig's base	dimethoxyethane	2.0 g	5%
H	Hünig's base	diglyme	0.2 g	6%
H	Hünig's base	diglyme	2.0 g	2%
H	Hünig's base	MeCN	0.2 g	42%
H	**Hünig's base**	**MeCN**	**10.0 g**	**45%**
*t*Bu	Hünig's base	dimethoxyethane	0.2 g	8%
***t*Bu**	**Hünig's base**	**MeCN**	**4.0 g**	**52%**

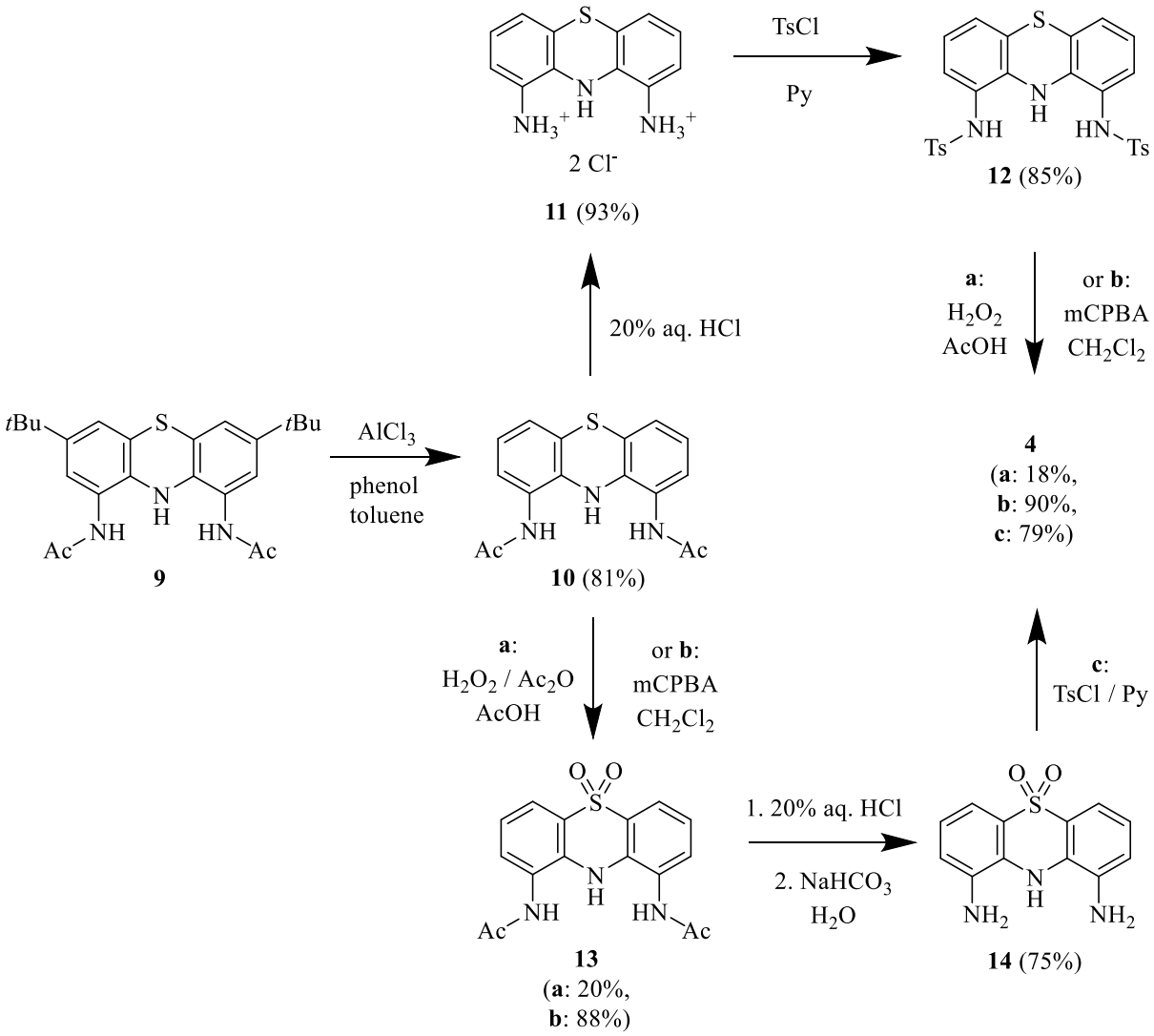
Tert-butyl substituted crown ether **6** was first prepared by a usual method using potassium carbonate as a base and acetonitrile as a solvent. The same conditions were applied for the synthesis of crown ether **7**, but the desired product could not be isolated. The formation of crown ether **7** was not observed when using other bases containing alkaline metal cations as templates (cesium carbonate or potassium *tert*-butoxide), but when Hünig's base was used in different solvents, formation of crown ether **7** did occur. Using dimethoxyethane and diglyme as solvents gave poor results, and the yield worsened in larger scales. Acetonitrile proved to be the best solvent for the reaction with reproducible yields even in larger scales. Since crown ether **7** could be prepared in the presence of Hünig's base, we examined whether the latter base could also be used in the synthesis of *tert*-butyl substituted crown ether **6**. Similar results were found as in the case of crown ether **7**, crown ether **6** could be isolated in a poor yield using dimethoxyethane and in a good yield using acetonitrile.

The tosyl protecting groups of crown ethers **6** and **7** were removed by amalgamated sodium in methanol to give crown ethers **1** and **2** in good yields (Scheme 1) using similar conditions as described for the removal of tosyl groups from a triaza-crown ether containing a pyridine unit.[42]

Ditosylamide **3** was prepared from diamine **8**[43] with tosyl chloride in pyridine in a good yield (Scheme 2). The synthesis of ditosylamide **4** was carried out as outlined in Scheme 3.



Scheme 2. Synthesis of ditosylamide **3**.



Scheme 3. Synthesis of ditosylamide **4**.

The *tert*-butyl protecting groups of the reported diacetamide **9**[43] were removed by aluminium chloride in the presence of phenol in toluene to give diacetamide **10**. Hydrolysis of diacetamide **10** with aqueous hydrochloric acid gave the hydrochloride salt **11**. As aminophenothiazines are

readily oxidized by air to methylene blue type products, the free base was liberated in the reaction medium under inert atmosphere by pyridine in the presence of tosyl chloride giving ditosylamide **12** in good yield. Ditosylamide **4** was then obtained by oxidation of ditosylamide **12** with hydrogen peroxide in acetic acid or *meta*-chloroperbenzoic acid in dichloromethane. Ditosylamide **4** was also prepared from diacetamide **10** in a different way. Diacetamide **10** was oxidized with hydrogen peroxide in acetic acid–acetic anhydride mixture or *meta*-chloroperbenzoic acid in dichloromethane to give diacetamide **13**, which was then hydrolyzed with aqueous hydrochloric acid followed by liberation of diamine **14** with sodium hydrogencarbonate. Unlike diaminophenothiazines unoxidized on the sulfur atom, diaminophenothiazine 5,5-dioxide **14** is stable in air. Ditosylamide **4** was then obtained by reacting diamine **14** with tosyl chloride in pyridine.

Conclusions

The synthesis and characterization of a new class of macrocycles containing a phenothiazine 5,5-dioxide unit **1** and **2**, and their unreported precursors have been achieved. Macrocyclization of ditosylamides **3** and **4** was performed in the absence of metal ion template rendering *N*-tosyl protected crown ethers **6** and **7**. The new crown ethers are promising precursors of sensor and selector molecules with wide applications.

Experimental Section

General. Reagents were purchased from Sigma–Aldrich Corporation unless otherwise noted. Silica gel 60 F_{254} (Merck) plates were used for TLC. Silica gel 60 (70-230 mesh, Merck) was used for column chromatography. Ratios of solvents for the eluents are given in volumes (mL/mL). Solvents were dried and purified according to well-established methods.[44] Evaporations were carried out under reduced pressure unless otherwise noted.
Infrared spectra were recorded on a Bruker Alpha-T FT-IR spectrometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained on a Bruker 300 Avance spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro-melting point apparatus and were uncorrected. Mass spectra were recorded on an Agilent 6410 TQMS instrument using ESI method.

General procedure for the synthesis of crown ethers 1 and 2. To a mixture of crown ether **6** or **7** and disodium hydrogenphosphate (5 equiv.) in MeOH was added finely powdered sodium amalgam (4 w/w% Na, 15 equiv.) under Ar at rt. After addition of the sodium amalgam, the

mixture was stirred for 3 h at reflux temperature. After the reaction was completed, the cooled reaction mixture was diluted with CH_2Cl_2, and then it was removed from the mercury by decantation. The solvent was evaporated, and the crude product was suspended in water, the pH was adjusted to 7 using acetic acid, the solid material was filtered, washed with water and triturated with hot MeOH to give **1** or **2** as offwhite crystals.

17,23-Di-*tert*-butyl-5,8,11-trioxa-20λ^6-thia-2,14,26-triazatetracyclo[13.9.3.0^{19,27}.0^{21,25}]-heptacosa-1(25),15(27),16,18,21,23-hexaene-20,20-dione (1). Starting materials: **6** (0.5 g, 0.595 mmol), Na_2HPO_4 (0.53 g, 2.98 mmol), sodium amalgam (4 w/w% Na, 5.13 g, 8.93 mmol), MeOH (10 mL). Yield: 0.231 g (73%). mp 275–277 °C ; R_f 0.87 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3385, 3266, 2960, 2903, 2867, 1615, 1527, 1489, 1420, 1295, 1279, 1242, 1141, 1088, 620, 564 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31 (s, 18H), 3.41–3.47 (m, 4H), 3.55–3.61 (m, 8H), 3.67–6.72 (m, 4H), 5.74 (br s, 2H, NH), 6.87 (d, *J* 2 Hz, 2H), 7.10 (d, *J* 2 Hz, 2H), 8.61 (br s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 31.01, 34.47, 43.34, 68.13, 69.56, 70.00, 104.15, 109.99, 120.99, 124.78, 136.75, 144.93; Ms: 532.2 $(M+H)^+$; Anal. Calcd for $C_{28}H_{41}N_3O_5S$: C, 63.25; H, 7.77; N, 7.90; S, 6.03. Found: C, 62.97; H, 7.91; N, 7.58; S, 6.15.

5,8,11-Trioxa-20λ^6-thia-2,14,26-triazatetracyclo[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15(27),-16,18,21,23-hexaene-20,20-dione (2). Starting materials: **7** (5.0 g, 6.87 mmol), Na_2HPO_4 (6.11 g, 34.3 mmol), sodium amalgam (4 w/w% Na, 59.2 g, 103 mmol), MeOH (100 mL). Yield: 2.22 g (77%). mp 257–260 °C ; R_f 0.80 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3477, 3371, 3299, 2908, 2869, 1606, 1529, 1504, 1475, 1463, 1452, 1434, 1348, 1297, 1281, 1169, 1134, 1114, 1096, 1073, 721, 552 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.38–3.44 (m, 4H), 3.54–3.62 (m, 8H), 3.65–6.71 (m, 4H), 5.86 (br s, 2H, NH), 6.91 (d, *J* 7 Hz, 2H), 7.13–7.21 (m, 4H), 8.65 (br s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.32, 68.19, 69.59, 69.95, 108.65, 112.26, 121.82, 122.52, 126.42, 136.96; Ms: 420.1 $(M+H)^+$; Anal. Calcd for $C_{20}H_{25}N_3O_5S$: C, 57.26; H, 6.01; N, 10.02; S, 7.64. Found: C, 56.98; H, 6.27; N, 9.87; S, 7.95.

General procedure for the synthesis of ditosylamides 3, 4 and 12 by reaction of diamines 8, 11 and 14 with tosyl chloride. To a solution of diamines **8**[43], **11** or **14** in pyridine was added tosyl chloride (2.2 equiv.) under Ar at 0 °C and the mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into water–ice mixture and the pH was adujsted to 3 with hydrochloric acid. The solid material was filtered, washed with water, and the crude product was triturated with MeOH to give ditosylamides **3**, **4** or **12** as offwhite crystals.

(3,7-Di-*tert*-butyl-5,5-dioxo-5,10-dihydro-5λ^6-phenothiazine-1,9-diyl)bis(4-methylbenzene-sulfonamide) (3). Starting materials: **8**[43] (4.86 g, 13.0 mmol), tosyl chloride (5.21 g, 27.3 mmol) and pyridine (50 mL). Yield: 8.40 g (95%). mp 254–257 °C , R_f 0.68 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3364, 3278, 3229, 2968, 2956, 1606, 1598, 1498, 1456, 1396, 1366, 1334, 1296, 1185, 1165, 1152, 1141, 1089, 814, 736, 658, 558 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 18H), 2.35 (s, 6H), 6.95 (d, *J* 2 Hz, 2H), 7.23 (d, *J* 8 Hz, 4H), 7.52 (s, 2H, NH), 7.71 (d, *J* 8 Hz, 4H), 7.85 (d, *J* 2 Hz, 2H), 8.92 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.65, 30.97, 34.68, 118.64, 122.27, 122.79, 128.15, 129.91, 129.99, 133.44, 134.82, 144.77,

145.30; Anal. Calcd for $C_{34}H_{39}N_3O_6S_3$: C, 59.89; H, 5.76; N, 6.16; S, 14.11. Found: C, 59.67; H, 5.96; N, 5.84; S, 13.92.

(5,5-Dioxo-5,10-dihydro-5λ^6-phenothiazine-1,9-diyl)bis(4-methylbenzenesulfonamide) (4). Starting materials: **14** (0.185 g, 0.708 mmol), tosyl chloride (0.283 g, 1.49 mmol) and pyridine (2 mL). Yield: 0.318 g (79%). mp 297–300 °C , R_f 0.52 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3376, 3303, 3273, 3065, 1604, 1510, 1483, 1460, 1395, 1381, 1346, 1331, 1308, 1296, 1185, 1161, 1126, 1090, 589, 810, 794, 671, 560 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.39 (s, 6H), 6.80 (d, *J* 7 Hz, 2H), 7.13 (t, *J* 7 Hz, 2H), 7.42 (d, *J* 8 Hz, 4H), 7.67 (d, *J* 8 Hz, 4H), 7.88 (d, *J* 7 Hz, 2H), 9.58 (s, 1H, NH), 10.23 (s, 2H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.02, 121.78, 121.81, 121.93, 123.70, 127.40, 129.74, 131.67, 135.26, 135.30, 143.83; Anal. Calcd for $C_{26}H_{23}N_3O_6S_3$: C, 54.82; H, 4.07; N, 7.38; S, 16.89. Found: C, 54.54; H, 3.82; N, 7.02; S, 16.78.

(5,10-Dihydrophenothiazine-1,9-diyl)bis(4-methylbenzenesulfonamide) (12). Starting materials: **11** (3.36 g, 11.1 mmol), tosyl chloride (4.45 g, 23.4 mmol) and pyridine (50 mL). Yield: 5.26 g (85%). mp 250–252 °C , R_f 0.75 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3384, 3251, 3211, 1597, 1489, 1463, 1452, 1416, 1401, 1320, 1306, 1159, 1090, 813, 743, 731, 570, 562 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 6H), 6.15 (d, *J* 7 Hz, 2H), 6.60 (t, *J* 7 Hz, 2H), 6.88 (d, *J* 7 Hz, 2H), 7.40 (d, *J* 7 Hz, 4H), 7.67 (d, *J* 7 Hz, 4H), 8.06 (s, 1H, NH), 9.60 (s, 2H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.06, 117.94, 121.74, 122.00, 125.60, 126.68, 127.39, 129.61, 136.22, 139.41, 143.38; Anal. Calcd for $C_{26}H_{23}N_3O_4S_3 \cdot H_2O$: C, 56.20; H, 4.53; N, 7.56; S, 17.31. Found: C, 56.55; H, 4.38; N, 7.26; S, 17.05.

Synthesis of tosylamide 4 starting from tosylamide 12.

A. Using hydrogen peroxide. To a solution of ditosylamide **12** (0.1 g, 0.186 mmol) in acetic acid (2 mL) was added 30% aqueous hydrogen peroxide (0.19 mL, 1.86 mmol). The reaction mixture was stirred at rt for 1 day, then the crystals were filtered. The crude product was triturated with hot MeOH to give ditosylamide **4** (20 mg, 18%) as offwhite crystals. Ditosylamide **4** had the same physical properties and spectral data as the one prepared above from diamine **14**.

B. Using *meta*-chloroperbenzoic acid. To a suspension of ditosylamide **12** (3.8 g, 7.07 mmol) in dichloromethane (80 mL) was added *meta*-chloroperbenzoic acid (70 w/w%, wet with water, 8.71 g, 35.3 mmol) at 0 °C . The reaction mixture was stirred at 0 °C for 15 min and then at rt for 7 days. The solid material was filtered. This crude product was suspended in water, the pH was adjusted to 7 with $NaHCO_3$, the solid material was filtered and then triturated with MeOH to give ditosylamide **4** (3.67 g, 90%) as offwhite crystals. Ditosylamide **4** had the same physical properties and spectral data as the one prepared above from diamine **14**.

General procedure for the synthesis of crown ethers 6 and 7. (Table 2.)

Table 2. Conditions and yields of the macrocyclization reactions

ditosylamide **3** or **4**			**5**		base[a]			solvent[b]		T	yield	
	g	mmol	g	mmol		g	mmol		ml	°C	g	%
3	0.2	0.293	0.162	0.323	KC	0.405	2.93	MeCN	20	82	0.030	12
3	6.0	8.79	4.86	9.67	KC	12.15	87.9	MeCN	600	82	1.11	15
4	0.2	0.351	0.194	0.386	KC	0.485	3.51	MeCN	20	82	–	–
4	0.2	0.351	0.194	0.386	CsC	1.14	3.51	MeCN	20	82	–	–
4	0.2	0.351	0.194	0.386	KC	0.485	3.51	DMF	20	70	–	–
4	0.2	0.351	0.194	0.386	K*t*B	0.394	3.51	DMF	20	70	–	–
4	0.2	0.351	0.194	0.386	K*t*B	0.394	3.51	DMSO	20	70	–	–
4	0.2	0.351	0.194	0.386	Hb	0.454	3.51	DME	20	85	0.035	14
4	2.0	3.51	1.94	3.86	Hb	4.54	35.1	DME	200	85	0.128	5
4	0.2	0.351	0.194	0.386	Hb	0.454	3.51	DG	20	120	0.015	6
4	2.0	3.51	1.94	3.86	Hb	4.54	35.1	DG	200	120	0.051	2
4	0.2	0.351	0.194	0.386	Hb	0.454	3.51	MeCN	20	82	0.107	42
4	10.0	17.6	9.70	19.3	Hb	22.7	176	MeCN	1000	82	5.74	45
3	0.2	0.293	0.162	0.323	Hb	0.378	2.93	DME	20	85	0.020	8
3	4.0	5.86	3.24	6.45	Hb	7.58	58.6	MeCN	400	82	2.57	52

[a] KC: K_2CO_3, CsC: Cs_2CO_3, K*t*B: KO*t*Bu, Hb: Hünig's base. [b] DME: dimethoxyethane, DG: diglyme

A mixture of ditosylamide **3** or **4**, tetraethyleneglycol ditosylate **5**[41] (1.1 equiv.) and a base (10 equiv.) was heated in a solvent under Ar with stirring for 1 week (see Table 2. for other reaction conditions). After the reaction was completed, the solvent was removed, and the residue was taken up in a mixture of CH_2Cl_2 and water. The phases were shaken well, separated, and the aqueous phase was extracted 3 times with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using acetone–CH_2Cl_2 (1:50) mixture as eluent to give **6** as white crystals or **7** as pale yellow crystals.

17,23-Di-*tert*-butyl-2,14-bis-(4-methylbenzenesulfonyl)-5,8,11-trioxa-20λ^6-thia-2,14,26-triazatetracyclo[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15(27),16,18,21,23-hexaene-20,20-dione (6). mp 218–221 °C , R_f 0.84 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3392, 2957, 2937, 2902, 2877, 1600, 1506, 1351, 1312, 1301, 1183, 1160, 1144, 1074, 1067, 969, 742, 732, 680, 669, 538 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 18H), 2.44 (s, 6H), 3.11–3.16 (m, 2H), 3.28–3.38 (m, 4H), 3.41–3.46 (m, 2H), 3.52–3.61 (m, 4H), 4.21–4.28 (m, 2H), 6.85 (d, *J* 2 Hz, 2H), 7.32 (d, *J* 8 Hz, 4H), 7.70 (d, *J* 8 Hz, 4H), 7.97 (d, *J* 2 Hz, 2H), 8.94 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.54, 30.81, 34.57, 51.65, 69.23, 70.56, 72.00, 119.38, 121.84,

127.26, 128.79, 129.72, 129.84, 133.51, 134.10, 144.38, 144.40; Ms: 840.2 $(M+H)^+$; Anal. Calcd for $C_{42}H_{53}N_3O_9S_3$: C, 60.05; H, 6.36; N, 5.00; S, 11.45. Found: C, 59.88; H, 6.28; N, 4.67; S, 11.36.

2,14-Bis-(4-methylbenzenesulfonyl)-5,8,11-trioxa-20λ^6-thia-2,14,26-triazatetracyclo-[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15(27),16,18,21,23-hexaene-20,20-dione (7). mp 189–190 °C , R_f 0.77 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3388, 3066, 2918, 2866, 1596, 1509, 1469, 1447, 1362, 1292, 1197, 1185, 1163, 1135, 1089, 1075, 946, 816, 802, 733, 652, 593, 546 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 6H), 3.09–3.14 (m, 2H), 3.25–3.30 (m, 2H), 3.31–3.36 (m, 2H), 3.37–3.43 (m, 2H), 3.48–3.53 (m, 2H), 3.54–3.60 (m, 2H), 3.78–3.84 (m, 2H), 4.19–4.26 (m, 2H), 6.90 (dd, J_o 8 Hz, J_m 1 Hz, 2H), 7.07 (t, J 8 Hz, 2H), 7.32 (d, J 8 Hz, 4H), 7.70 (d, J 8 Hz, 4H), 8.02 (dd, J_o 8 Hz, J_m 1 Hz, 2H), 9.13 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.78, 51.61, 69.30, 70.70, 72.07, 121.22, 122.85, 123.82, 127.81, 129.00, 129.91, 131.88, 133.37, 136.37, 144.76; Ms: 728.1 $(M+H)^+$; Anal. Calcd for $C_{34}H_{37}N_3O_9S_3$: C, 56.10; H, 5.12; N, 5.77; S, 13.22. Found: C, 55.97; H, 5.30; N, 5.50; S, 12.96.

(5,10-Dihydrophenothiazine-1,9-diyl)diacetamide (10). To a suspension of diacetamide **9**[43] (4.0 g, 9.40 mmol), phenol (2.65 g, 28.2 mmol) in toluene (40 mL) was added aluminium chloride (7.52 g, 56.4 mmol) under Ar at 0 °C , and this mixture was stirred at reflux temperature for 6 h. After the reaction was completed, the mixture was poured into a mixture of ice–water (75 mL) and EtOAc (75 mL). The crude product was filtered and washed with MeOH to give **10** (2.39 g, 81%) as a grey solid material. mp 292–295 °C , R_f 0.22 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3396, 3249, 3046, 1646, 1605, 1535, 1504, 1464, 1447, 1368, 1309, 1275, 764, 732, 720 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.09 (s, 6H), 6.82 (t, J 7 Hz, 2H), 6.90 (d, J 7 Hz, 2H), 6.97 (d, J 7 Hz, 2H), 7.26 (s, 1H, NH), 9.58 (s, 2H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 23.11, 119.24, 121.82, 123.75, 124.49, 125.41, 136.18, 168.99; Anal. Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.31; H, 4.82; N, 13.41; S, 10.23. Found: C, 61.04; H, 4.78; N, 13.19; S, 9.96.

5,10-Dihydrophenothiazine-1,9-diaminium chloride (11). A suspension of diacetamide **10** (10.0 g, 31.9 mmol) in 20% aqueous HCl (500 mL) was stirred under Ar at reflux temperature for 4 h. After the reaction was completed, the mixture was cooled to rt, and the solid material was filtered, washed with water and MeOH. The crystals were dried under reduced pressure over P_2O_5 to give **11** as an off-white solid material (9.0 g, 93%). mp: >360 °C (decomp.), R_f 0.39 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3422, 2847 (br), 1596, 1514, 1461, 1319, 1091, 1047, 762, 756, 721, 481, 452 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.94 (t, J 8 Hz, 2H), 6.99 (d, J 8 Hz, 2H), 7.11 (d, J 8 Hz, 2H), 7.42 (br s, 6H, NH), 8.40 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 121.91, 122.34, 122.83, 123.44, 124.87, 133.96; Anal. Calcd for $C_{12}H_{13}Cl_2N_3S$: C, 47.69; H, 4.34; N, 13.90; S, 10.61. Found: C, 47.43; H, 4.39; N, 13.73; S, 10.63.

(5,5-Dioxo-5,10-dihydro-5λ^6-phenothiazine-1,9-diyl)diacetamide (13).

A. Using hydrogen peroxide. To a suspension of diacetamide **10** (0.1 g, 0.319 mmol) in a mixture of acetic anhydride (3 mL) and acetic acid (1 mL) was added 30% aqueous hydrogen

peroxide (0.196 mL, 1.92 mmol) at 0 °C . The reaction mixture was stirred at 0 °C for 10 min and then at rt for 1 h. After the reaction was completed, the mixture was poured into ice–water (30 mL), and the solid material was filtered to give **13** (22 mg, 20%) as white crystals. mp 303–305 °C , R_f 0.16 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3375, 3266, 3042, 1652, 1612, 1528, 1456, 1372, 1340, 1285, 1194, 1169, 1133, 779, 731, 718, 612, 535 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.18 (s, 6H), 7.31 (t, *J* 8 Hz, 2H), 7.59 (d, *J* 8 Hz, 2H), 7.84 (d, *J* 8 Hz, 2H), 9.08 (s, 1H, NH), 10.10 (s, 2H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.14, 119.73, 121.78, 122.35, 125.90, 130.24, 132.53, 169.65; Anal. Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17; S, 9.28. Found: C, 55.39; H, 4.21; N, 11.81; S, 9.02.

B. Using *meta*-chloroperbenzoic acid. To a suspension of **10** (4.0 g, 12.8 mmol) in dichloromethane (80 mL) was added *meta*-chloroperbenzoic acid (70 w/w%, wet with water, 15.72 g, 63.8 mmol) at 0 °C . The reaction mixture was stirred at 0 °C for 10 min, at rt for 7 days, then the solid material was filtered. This crude product was suspended in water, the pH was adjusted to 7 using $NaHCO_3$, the solid material was filtered and then triturated with MeOH to give diacetamide **13** (3.87 g, 88%) as offwhite crystals. Diacetamide **13** had the same physical properties and spectral data as the one prepared above using hydrogen peroxide.

1,9-Diamino-5,10-dihydro-5λ^6-phenothiazine-5,5-dione (14). A suspension of diacetamide **13** (1.84 g, 5.34 mmol) in 20% aqueous HCl (100 mL) was stirred under Ar at reflux temperature for 4 h. After the reaction was completed, the mixture was cooled to rt, and the solid material was filtered and washed with water. The crystals were suspended in water, and the pH was adjusted to 7 using $NaHCO_3$, the solid material was filtered and washed with water to give **14** (1.04 g, 75%) as off-white crystals. mp 281–284 °C , R_f 0.30 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3375, 2924, 1644, 1601, 1518, 1485, 1463, 1434, 1286, 1242, 1174, 1163, 1115, 1064, 763, 717, 707, 580, 534 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 5.74 (s, 4H, NH), 6.98 (d, *J* 8 Hz, 2H), 7.04 (t, *J* 8 Hz, 2H), 7.16 (d, *J* 8 Hz, 2H), 8.01 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 109.28, 116.79, 121.49, 122.01, 125.86, 136.68; Anal. Calcd for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08; S, 12.27. Found: C, 55.02; H, 3.95; N, 15.81; S, 12.03.

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