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A novel approach to conformationally strained 2,2′-bipyridine thiacrown ethers and their chiral sulfoxides by sequential homo-coupling/DA–rDA reaction of 5,5′-bi-1,2,4-triazine-containing thiamacrocycles

Justyna Ławecka, Zbigniew Karczmarzyk *, Ewa Wolińska, Ewa Olender, Danuta Branowska, Andrzej Rykowski *

Siedlce University, Department of Chemistry, 08-110 Siedlce, Poland

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ABSTRACT

The synthesis of conformationally strained 2,2′-bipyridine thiamacrocycles **5**, **6**, **9**, **10** and their chiral sulfoxides **11**–**14** is elaborated using, (1) homo-coupling of 1,2,4-triazine sulfide **3** with potassium cyanide and (2) Diels–Alder/retro Diels–Alder (DA–rDA) with 2,5-norbornadiene or 1-pyrrolidino-1-cyclopentene as the key steps. The crystal structure determinations of **4**–**6** and the theoretical calculations at DFT/B3LYP/6-311G** level were conducted thus establishing conformational preferences of the target thiamacrocycles.

1. Introduction

The synthesis and properties of 2,2′-bipyridine (bpy) based macrocycles has attracted a considerable attention of chemists for many years owing to their applications in a wide range of fields.[1] They have been the subject of numerous studies in areas, such as supramolecular chemistry,[2] catalysis,[3] electrochemistry,[4] photochemistry,[5] and molecular recognition.[6] Consequently, new and efficient methods for the preparation of bpy containing macrocycles with an appropriate ring size and predictable function remain an attractive challenge in organic chemistry, particularly in the synthesis of C_2-symmetric 2,2′-bipyridine-containing crown ethers that have been developed recently for the enantiomeric recognition of amino acids derivatives and chiral organic ammonium salts.[6c] The most common synthesis of 2,2′-bipyridine based crown[7] and thiacrown ethers[8] involves the direct nucleophilic displacement of 6,6′-bifunctional-2,2′-bipyridines by the dianions of oligomeric glycolates or thioglycolates. The procedure afforded variable 3–21% yields of desired 1:1 crown or thiacrown macrocycles accompanied by a large amount of noncyclic compounds and larger oligomers.[7] One drawback of this strategy, depending on the length of glycolate chain, is thermal oligomerization of polyethylene glycols[9] and failure in nucleophilic displacement of 6,6′-disubstituted-2,2′-bipyridines by the diethylene glycol under the reaction conditions.[7] This last result may be due to the high ring strain of the cyclization product.[10] In most macrocycle synthesis the ring closing reactions are usually performed at a late stage of the synthetic route.[11] Such intramolecular macrocyclization has been applied recently for the preparation of expanded crown ether based macrocycles using copper(I)-catalyzed azide–alkyne cycloaddition.[12] This reaction, which exemplifies the click chemistry philosophy,[13] has been performed on tailor-made linear precursors leading to a range of novel macrocycles. Utilizing this concept we have elaborated a new and efficient route for preparing biheterocycle-containing thiacrown ethers, starting from the corresponding ethylene glycol oligomers bearing 1,2,4-triazine sulfides tethered to poly(ethylene glycol) chains as end groups.[14] The construction of 16-, 19- and 22-membered bpy thiacrown ethers involved sequential homo-coupling of these 1,2,4-triazine sulfides by potassium cyanide-catalyzed intramolecular cyclization and the inverse electron demand Diels–Alder/retro Diels–Alder (DA–rDA) reaction of resulting bi-1,2,4-triazine-containing thiamacrocycles.[15] From our preliminary findings[14] and theoretical calculations one may assume that the approach is also suitable for the rings of 13 or less members. Here we report a full report on application of this approach to the synthesis of such conformationally strained

* Corresponding authors. Tel.: +48 25 6431093; fax: +48 25 6442095; e-mail address: rykowski@ap.siedlce.pl (A. Rykowski).

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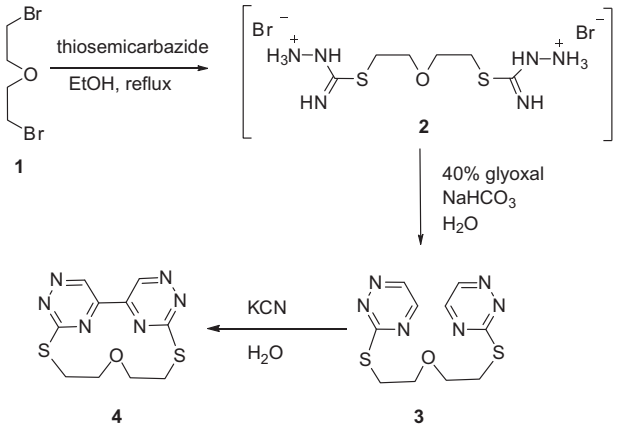
thiamacrocycles **5**, **6**, and **9**, **10** (Schemes 3 and 4) and their chiral sulfoxides **11**–**14** (Scheme 5). The crystal structures determinations and the theoretical calculations at DFT/B3LYP/6-311G** level were conducted thus establishing conformational preferences of the target compounds.

2. Results and discussion

The first step of the synthetic protocol presented in Scheme 1, required an easily access to an appropriate 1,2,4-triazine bis-sulfide **3**.



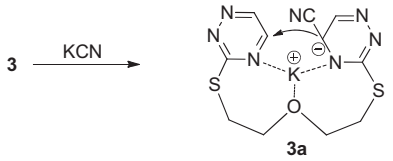
Scheme 1. Synthesis of 1,2,4-triazine bis-sulfide **3** and thiamacrocycle **4**.

The synthesis of **3** was prepared via a two-step one-pot procedure, which involved S-alkylation of thiosemicarbazide with 0.5 equiv of diethylene glycol dibromide **1** to give the intermediary diquaternary salt **2**, followed by the condensation of the latter with 40% glyoxal in the presence of sodium bicarbonate. With bis-sulfide **3** in hand we next evaluated its intramolecular homo-coupling reaction leading to 5,5′-bi-1,2,4-triazine thiamacrocycle **4** by using potassium cyanide. According to our previous report the process was carried out in water at room temperature under relatively high dilution conditions to avoid unwanted intermolecular side reactions, prior to the desired cyclization step. The reaction was completed within 15 min giving thiamacrocycle **4** exclusively (monitored by TLC). After the reaction, pure product could be easily recovered in good yield by extraction with dichloromethane (see Table 1). The efficiency of this purification procedure was confirmed by NMR and HRMS spectra of the product. It seems likely that fast and efficient formation of **4** may be attributed to a favorable conformation of the linear precursor **3** resulting in low activation energy and favorable entropy for cyclization. On the basis of our previous studies[14] we assume that potassium cyanide-catalyzed cyclization occurs via a primary cyanide addition to C(5) of 1,2,4-triazine ring leading to a cation **3a** as a result of template reaction which proceeds between its coordination sites and an alkaline metal ion (Scheme 2). The 1,2,4-triazine-acceptor and 1,2,4-triazine-donor end groups in cation **3a** can recognize each other and get close enough, thus increasing the rate of the cyclization step.

Table 1
Yields of compounds **3**–**7** and **9**–**14**

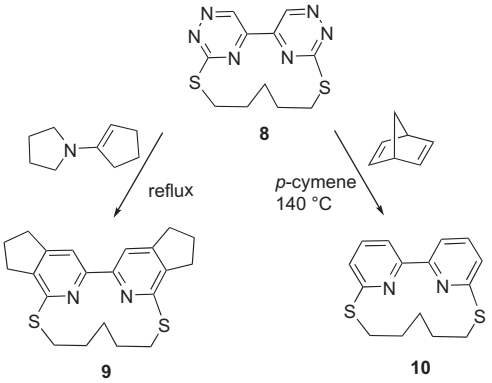
Compound	Yield %
3	38
4	73
5	64
6[a]	63
7	12
9	57
10[a]	60
11	63
12	46
13	36
14	35

[a] In sealed Carius tube.



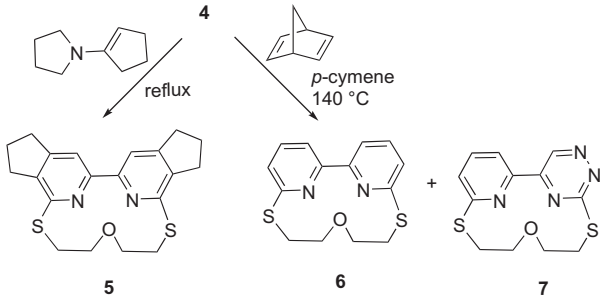
Scheme 2. Formation of the cyclization intermediate.

The preparation of bpy thiacrown ethers **5**, **6**, could involve the double DA–rDA reaction of **4** with an electron-rich dienophile or reactive strained olefine.[15] To establish optimal conditions for the cycloaddition, the reaction of its analog **8** without oxygen in the tether[14] with 1-pyrrolidino-1-cyclopentene was investigated first. Earlier, we have reported that DA–rDA reactions of 5,5′-bi-1,2,4-triazines with 1-pyrrolidino-1-cyclopentene without solvent at 150 °C led to bis-annulated 2,2′-bipyridines exclusively.[16] The reaction of **8** with 1-pyrrolidino-1-cyclopentene was carried out under the same reaction conditions for 17 h to afford cyclopenteno [*c*]2,2′-bipyridine based cyclophane **9** in 57% yield (Scheme 3).



Scheme 3. Synthesis of cyclophanes **9** and **10**.

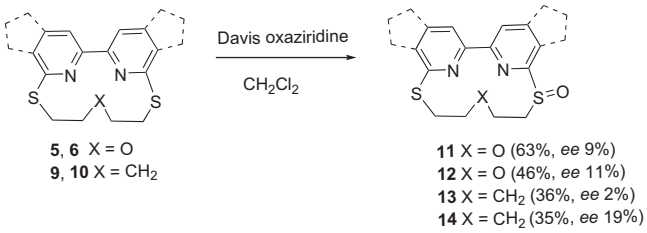
Also the reaction of **4** with the same enamine showed the generality of this process, since conformationally strained thiacrown ether **5** with cyclopenteno[*c*]2,2′-bipyridine unit in the cyclic backbone was obtained as the sole product in 64% yield. The formation of uncondensed, double bpy thiacrown ether **6** was initially attempted via the DA–rDA reaction of **4** with 2,5-norbornadiene in boiling *p*-cymene. Under these conditions the expected thiacrown ether **6** was obtained in 38% yield together with some amount of monoadduct **7** (Scheme 4). The structure of **7** is based on its NMR



Scheme 4. Synthesis of macrocycles **5**–**7**.

and ms spectra clearly showing the chemical shifts and multiplicity pattern characteristic for pyridine and 1,2,4-triazine rings (see Experimental). When the above reaction was followed by TLC, it was evident that intermediate **7** was slowly converted into **6** during extended heating. However, when **4** was reacted with 2,5-norbornadiene in a sealed Carius tube at an elevated temperature under higher pressure, the only product was the corresponding diadduct **6**, obtained in good yield (see Table 1). Compound **8** also reacts efficiently with 2,5-norbornadiene under the conditions mentioned above giving directly compound **10** in 60% yield (Scheme 3).

Finely, we have evaluated the asymmetric sulfoxidation of compounds **5**, **6**, and **9**, **10** using chiral oxaziridine developed by Davis.[17] The reactions were performed in methylene chloride at room temperature (Scheme 5).



Scheme 5. Asymmetric sulfoxidation of cyclophanes **5**, **6** and **9**, **10**.

Under these conditions the monosulfoxides **11**–**14** could be obtained in reasonable or good yield (see Table 1). The preliminary use of these monosulfoxides as chiral auxiliary was tested in asymmetric addition of the diethylzinc to benzaldehyde, however their catalytic efficiency was poor and the ee values (3–7%) of the chiral alcohol **15** (Fig. 1) thus obtained were much lower than the values observed for other catalysts.[18]

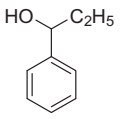


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Fig. 1. 1-Phenyl-1-propanol.

The spectroscopic properties of the bpy cyclophanes **5**, **6** and **9**, **10** are entirely consistent with the functional group present. The preferred conformations of these macrocycles are determined by analyzing the chemical shifts of 3-pyridyl hydrogens[7] and X-ray analysis. The resonances of such hydrogens in compounds **5**, **6** and **9**, **10** (range from 7.15 to 7.35 ppm) indicate cis arrangement for these biheterocycles. This is consistent with the chemical shifts of pyridine protons (7.36–7.47 ppm) in the annulated 16- and 19-membered bpy thiacrown ethers having cis conformation. In contrast, the chemical shifts of bipyridine protons in 22-membered thiacrown ether (7.85 ppm) show trans conformation exclusively.[14] These data also prove that 13-membered macrocyclic system **4** containing 5,5′-bi-1,2,4-triazine skeleton also exist in cis conformation.

In order to establish the conformational preferences of the title thiamacrocycles in the crystalline state the crystal structure determinations of **4**–**6** were undertaken. The X-ray structure analysis of **4** revealed, that the asymmetric part of the unit cell of its crystal contains two independent molecules AB and CD (Fig. 2). The structures of the molecules **5** and **6** are shown in Fig. 3. One can see that the molecules **5** and **6** containing, respectively, annulated 2,2′-bipyridine and 2,2′-bipyridine ring systems exist in the crystal in the cis (*syn*) conformation with the torsion angle N1A–C2A–C2B–N2B about the central bond of the bipyridyl system of −11.7 (3)° for **5** and −19.67(18)° for **6**. In the molecules AB and CD of **4** the 5,5′-bi-1,2,4-triazine system adopts also cis (*syn*) conformation with the torsion angle N4A–C5A–C5B–N4B and N4C–C5C–C5D–N4D of 2.5(3) and 19.1(3)°, respectively. The cis conformation of the bi-heterocyclic systems in **4**–**6** is forced by the strain effect in the nine-membered thiaethereal chain during the cyclization process. The problem of the change of conformation of bi-heterocyclic system from cis to trans conformation depending on the length of thiaethereal chain was discussed by us earlier for 2,2′-bipyridine thiamacrocyles.[14]

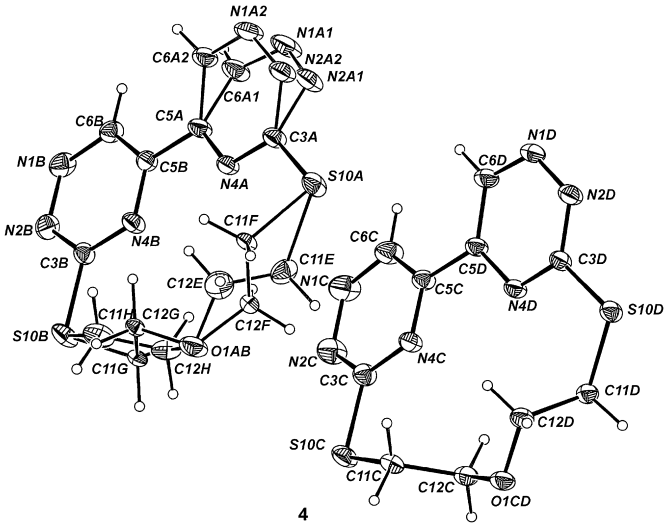

Fig. 2. A view of the X-ray molecular structures of two independent molecules AB and CD of 4 with the atomic labeling.

In molecules **5** and **6** and molecule CD of **4** the bond lengths and angles are in normal ranges[19] and they are very similar to those found in previously reported related structures of annulated 2,2′-bipyridine thiamacrocycles.[14] The statistically significant differences in the bond lengths and angles appear in the thiaethereal bridge in molecule AB of **4** mainly due to positional disorder of C11 and C12 atoms and their large thermal motions. The C_2 symmetry of the macrocycles **4**–**6** is not retained in their crystals because the molecules occupy an asymmetric position in the unit cell. However, the torsion angles around following bonds of thiaethereal chains in **5** and **6** (Table 1 in Supplementary data) show practically the same *cis-gauche-trans-gauche* conformation of the symmetry related left (A) in **5** and **6** and (C) in **4** and right (B) in **5** and **6** and (D) in **4** parts of molecules. The split of C11 and C12 atoms into two sites in molecule AB of **4** gives four different conformations of its thiaethereal chain indicated as AE–BG, AE–BH, AF–BG, and AF–BH. These conformations are also *cis-gauche-trans-gauche* for (A) and (B) parts differing in C11–C12–O1–C12′ torsion angle (two pairs AE–BG, AF–BH, and AE–BH, AF–BG) and signs of respective torsion angles (Table 2 in Supplementary data). The theoretical calculation on DFT/B3LYP/6-311++G(d,p) level showed that the analyzed conformations of the molecules **4**–**6** obtained after energy minimization and geometry optimization do not differ significantly from those observed in crystalline state and the pairs of conformations AE–BG, AF–BH, and AE–BH, AF–BG of molecule **4** are equi-energetically ($E_{AE-BG}=E_{AF-BH}=-1587.34188$ and $E_{AE-BH}=E_{AF-BG}=-1587.34463$ a.u.) with small difference of energy between them of $\Delta E=1.73$ kcal/mol. The conformations of molecules **4**–**6** in the crystals are stabilized by the pairs of short intramolecular contacts C12A–H···N1A and C12B–H···N1B in **5** and **6**, C12C···N4C and C12D–H···N4D in molecule CD and C12G–H···N4B in molecule AB of **4** with H···N distances in the range from 2.50 to 2.60 Å.

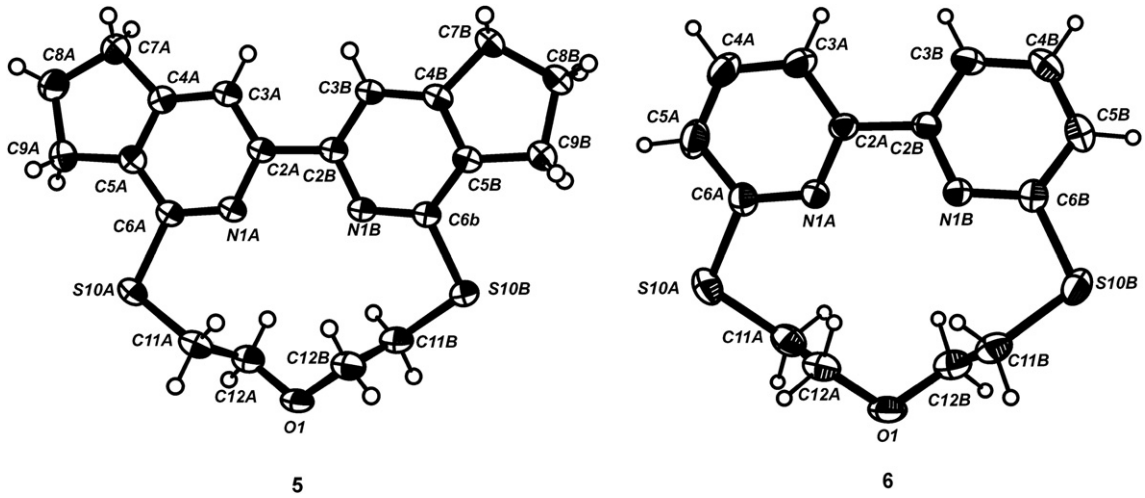

Fig. 3. A view of the X-ray molecular structures of **5** and **6** with the atomic labeling.

The analysis of the cyclic molecules obtained from 2,2′-bipyridyl and polyoxyethylene oligomers (x-mers) showed that the cyclization is impossible for x=2, barely possible for x=3, and most readily achieved with x=5–7.[10] However, replacement of the O atoms with the S atoms in the linkages of the ethereal chain to the pyridine and triazine rings in **4**–**6** makes the cyclization possible for x=2. Assuming the bond lengths C_{ar}–O=1.370(11), C_{sp3}–O=1.431(13), C_{ar}–S=1.773(9) and C_{sp3}–S=1.817(13) Å[19] the implementation of the S atom in the place of O atom extends the thiaethereal (**4**–**6**) and thiaalkyl (**8**–**10**) chains for 1.578 Å in comparison with analogous ethereal chains. Theoretical calculations on DFT/B3LYP/6-311++G(d,p) level predict that in the case of thiaalkyl chain the cyclization is also possible for four CH_2 groups. The structure of modeled appropriate 5,5′-bi-1,2,4-triazine macrocycle with reasonable geometry and conformation obtained after geometrical parameters optimization and energy minimization is shown in Fig. 4. The 5,5′-bi-1,2,4-triazine system adopts cis conformation with the torsion angle N–C–C′–N′ of 28.4°. The bond lengths and angles have acceptable values. The only small constrains within the biheterocycle system appearing with deformation of exocyclic valency angles at C5 and C5′ atoms (127.4 and 113.2°) are observed. The experimental trials of synthesis this compound are in progress.

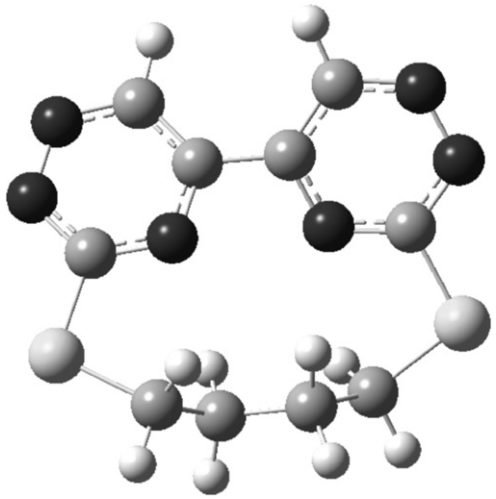

Fig. 4. The structure of 5,5′-bi-1,2,4-triazine thiamacrocyle with four CH_2 groups in thiaalkyl chain obtained after theoretical calculation on DFT/B3LYP/6-311++G(d,p) level.

3. Conclusions

We have demonstrated a facile approach to conformationally strained 2,2′-bipyridine based thiamacrocycles by sequential homo-coupling/DA–rDA reaction of resulting 5,5′-bi-triazine thiamacrocycles. The method should be of general use for the synthesis of related macrocycles and analogs.

4. Experimental section

4.1. General methods

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were determined at 200 and 50 MHz, respectively, with a Varian Gemini spectrometer. Chemical shifts (δ) are given in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ=7.26). Coupling constants are given as absolute values expressed in Hertz. Mass spectra were obtained by using AMD 604 (AMD Intectra GmbH, Germany) and GC/MS QP 5050 Shimadzu (30 m×0.25 mm ID-BPX 5 0.25 mm) spectrometers. Elemental analyses were recorded with a Perkin–Elmer 2400-CHN analyzer and the results for indicated elements were within 0.3% of the calculated values. Optical rotation values were measured at room temperature with a JASCO P-2000 polarimeter. The ee values were determined by HPLC analysis by using a chiral stationary phase column (Chirobiotic T or Chiralpac AS). Thin layer chromatography (TLC) was carried out on aluminum sheets percolated with silica gel 60 F_{254} (Merck). Column chromatography separations were performed by using Merck Kieselgel 60 (0.040–0.060 mm). Solvents were dried and distilled according to standard procedures. Synthesis of 1,7-dithia[7]3,3′-5,5′-bis(1,2,4-triazine)cyclophane (**8**) was performed according to our published procedure.[14]

4.2. Procedure for the preparation of 1,5-bis(1,2,4-triazin-3-ylsulfanyl)-3-oxapentane (3)

A solution of thiosemicarbazide (5.9 g, 14.28 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (**1**) (1.68 g, 7.28 mmol) in absolute ethanol (40 mL) was stirred at reflux until thiosemicarbazide was consumed (TLC control). The ethanol was then evaporated and a solution of glyoxal (2.1 mL, 40% solution in water, 14.28 mmol) and sodium bicarbonate (1.2 g, 14.28 mmol) in ice water (40 mL) was added to the brown residue containing hydrobromide salt **2**. After stirring at room temperature for 30 min, methanol (55 mL)

was added and the mixture was stirred at room temperature for 24 h. Methanol was evaporated at vacuo and the water layer was extracted with CH_2Cl_2 (5×10 mL). After evaporation of the solvent from the combined extracts, the remaining residue was purified by column chromatography (CH_2Cl_2/acetone, 10:1) to give pure compound **3** as white solid (0.84 g, 38%); mp 56–58 °C; R_f (CH_2Cl_2/acetone, 10:1) 0.42; UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=321 (3.43); δ_H (200 MHz, $CDCl_3$) 3.44 (4H, t, J=6.4 Hz, SCH_2), 3.80 (4H, t, J=6.4 Hz, OCH_2), 8.36 (2H, d, J=2.4 Hz, triazine hydrogen atoms), 8.91 (2H, d, J=2.4 Hz, triazine hydrogen atoms); δ_C (50 MHz, $CDCl_3$) 30.1 (SCH_2), 69.0 (OCH_2), 145.4, 148.1, 173.7 triazine carbon atoms; HRMS (EI): M^+, found 296.0509. $C_{10}H_{12}N_6OS_2$ requires 296.0514.

4.3. Synthesis of 4-oxa-1,7-dithia[7](3,3′)-5,5′-bis(1,2,4-triazine)cyclophane (4)

A suspension of compound **3** (0.175 g, 0.59 mmol) in water (134 mL) was stirred at 40 °C until complete dissolution. After cooling to room temperature, potassium cyanide (0.137 g, 2.12 mmol) was added as a solid, and the resulting mixture was stirred for 15 min. The mixture was extracted with CH_2Cl_2 (5×50 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (CH_2Cl_2/acetone, 10:1) to give pure compound **4** (0.127 g, 73%) as a yellow solid (mp 210–211 °C); R_f (CH_2Cl_2/acetone, 10:1) 0.39; UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=375 (3.38); δ_H (200 MHz, $CDCl_3$) 3.30 (4H, t, J=6.4 Hz, SCH_2), 4.06 (4H, t, J=6.4 Hz, OCH_2), 9.55 (2H, s, triazine H); δ_C (50 MHz, $CDCl_3$) 30.0 (SCH_2), 68.9 (OCH_2), 145.3, 148.1, 173.7 triazine carbon atoms; HRMS (EI): M^+, found 294.0348. $C_{10}H_{10}N_6OS_2$ requires 294.0357.

4.4. General procedure for the preparation of cyclophanes 5 and 9

Cyclophane **4** or **8** (2.96 mmol) was added to freshly distilled 1-pyrrolidine-1-cyclopentene (2.43 g, 17.75 mmol). The mixture was heated at 150 °C for 17 h, and then evaporated in vacuo. The residue was purified by column chromatography (CH_2Cl_2/acetone, 50:1) to give pure compounds **5** or **9**.

*4.4.1. 4-Oxa-1,7-dithia[7](6,6′)-2,2′-bis(cyclopenta[c]pyridine)cyclophane (**5**).* (0.70 g, 64%) as a yellow solid; mp 269–270 °C; R_f (CH_2Cl_2/acetone, 50:1) 0.59; UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=319 (4.04); δ_H (200 MHz, $CDCl_3$) 2.15 (4H, J=7.4 Hz, CH_2), 2.80 (4H, J=7.4 Hz, CH_2), 2.95 (4H, J=7.6 Hz, CH_2), 3.29–3.38 (4H, m, SCH_2), 4.06–4.14 (4H, m, OCH_2), 7.37 (2H, s, pyridine hydrogen atoms); δ_C (50 MHz, $CDCl_3$) 24.3 (CH_2), 27.4 (CH_2), 29.5 (CH_2), 32.8 (SCH_2), 66.3 (OCH_2), 112.8, 136.1, 153.2, 153.6, 154.1 pyridine carbon atoms; HRMS (EI): M^+, found 370.1183. $C_{20}H_{22}N_2OS_2$ requires 370.1173.

*4.4.2. 1,7-Dithia[7](6,6′)-2,2′-bis(cyclopenta[c]pyridine)cyclophane (**9**).* (0.62 g, 57%); mp 191–192 °C; R_f (CH_2Cl_2/acetone, 100:1) 0.62; δ_H (200 MHz, $CDCl_3$) 1.50–1.59 (3H, m, CH_2), 1.99–2.21 (8H, m, CH_2), 2.76–2.83 (4H, m, CH_2), 2.89–2.97 (4H, m, CH_2), 3.14–3.22 (3H, m, CH_2), 7.32 (2H, s, pyridine hydrogen atoms); δ_C (50 MHz, $CDCl_3$) 24.4 (CH_2), 27.8 (CH_2), 28.9 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 32.9 (SCH_2), 112.77, 135.9, 153.4, 153.8 pyridine carbon atoms; HRMS (EI): M^+, found 368.1369. $C_{21}H_{24}N_2S_2$ requires 368.1381.

4.5. General procedure for the preparation of cyclophanes 6, 7, and 10

Method A. A solution of 2,5-norbornadiene (1.8 mL) in *p*-cymene (4 mL) containing compound **4** or **8** (0.59 mmol) was heated for 20 h at 140 °C. The solvent was evaporated in vacuo and the mixture was separated by column chromatography (CH_2C_2/acetone, 20:1) to give compounds **6** (0.07 g, 38%), followed by CH_2Cl_2/acetone (10:1) to afford monoadduct **7** (0.02 g, 12%). Compound **10** was isolated as the only product (0.10 g, 60%).

Method B. A solution of norbornadiene (1.8 mL) in *p*-cymene (4 mL) was added to a Carius tube containing **4** (0.173 g, 0.59 mmol). The tube was tightly closed and the mixture was heated for 86 h at 140 °C. The solvent was evaporated in vacuo and the product was purified by column chromatography (CH_2Cl_2/acetone, 20:1) to give pure compound **6** (0.11 g, 63%).

*4.5.1. 4-Oxa-1,7-dithia[7](6,6′)-2,2′-bis(pyridine)cyclophane (**6**).* Mp 132–133 °C; R_f(CH_2Cl_2/acetone, 100:1) 0.55; UV/vis ($CHCl_3$): UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=327 (4.03); δ_H (200 MHz, $CDCl_3$) 3.29–3.37 (4H, m, SCH_2), 4.05–4.14 (4H, OCH_2), 7.17 (2H, d, J=8.0 Hz, pyridine hydrogen atoms), 7.46 (2H, d, J=8.0 Hz, pyridine hydrogen atoms), 7.57 (2H, t, J=7.6 Hz, pyridine hydrogen atoms); δ_C (50 MHz, $CDCl_3$) 27.9 (SCH_2), 66.2 (OCH_2), 116.2, 121.5, 136.5, 155.2, 158.5 pyridine carbon atoms; Anal. Calcd for $C_{14}H_{14}N_2OS_2$: C, 57.93; H, 4.83; N, 9.66%. Found: C, 57.89; H, 4.83; N, 9.62.

*4.5.2. 10-Oxa-7,13-dithia-4,5,18,19-tetraaza-tricyclo[12.3.1.1^{2,6}]nonadeca-1(18),2,4,6(19),14,16-hexaene (**7**).* (0.02 g, 12%); mp 236–237 °C; R_f (CH_2Cl_2/acetone, 100:1) 0.19; UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=357 (3.70); δ_H (200 MHz, $CDCl_3$) 3.25–3.33 (4H, m, CH_2), 4.02–4.15 (4H, m, CH_2), 7.34 (1H, dd, J=1.8 Hz, J=7.0 Hz, pyridine hydrogen atom), 7.61–7.69 (2H, m, pyridine hydrogen atoms), 9.41 (1H, s, triazine hydrogen atom); δ_C (50 MHz, $CDCl_3$) 28.6 (SCH_2), 29.1 (SCH_2), 65.4 (OCH_2), 65.8 (OCH_2), 117.9, 124.4, 136.8, 141.6, 150.1 pyridine carbon atoms, 153.0, 160.9, 174.4 triazine carbon atoms; HRMS (EI): M^+, found 292.0464. $C_{12}H_{12}N_4OS_2$ requires 292.0452.

*4.5.3. 1,7-Dithia[7](6,6′)-2,2′-bis(pyridine)cyclophane (**10**).* Yield (0.10 g, 60%), mp 151–152 °C; R_f (CH_2Cl_2/acetone, 100:1) 0.92; UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=330 (4.01); δ_H (200 MHz, $CDCl_3$) 1.59–1.73 (2H, m, CH_2), 1.99–2.19 (4H, m, CH_2), 3.14–3.23 (4H, m, CH_2), 7.18 (2H, d, J=7.8 Hz, pyridine hydrogen atoms), 7.43 (2H, d, J=7.3 Hz, pyridine hydrogen atoms), 7.56 (2H, t, J=7.6 Hz, pyridine hydrogen atoms); δ_C (50 MHz, $CDCl_3$) 27.6 (CH_2), 28.7 (CH_2), 29.9 (SCH_2), 116.0, 121.4, 136.2, 155.2, 159.1 pyridine carbon atoms. Anal. Calcd for $C_{15}H_{16}N_2S_2$: C, 62.50; H, 5.56; N, 9.72%. Found: C, 62.43; H, 5.56; N, 9.71.

4.6. General procedure for the preparation of sulfoxides 11, 12, 13, and 14 (Davis method)

To a solution of sulfide **5**, **6**, **9** or **10** (1 mmol) in anhydrous methylene chloride (30 mL), was added (+)-(8,8′-dichlorocamphorylsulfonyl)oxaziridine (0.75 mmol) and the reaction mixture was stirred at room temperature for 24 h. Afterward, the solvent was evaporated, and the residue was purified by flash chromatography (CH_2Cl_2/acetone, 10:1.5) to yield pure monosulfoxides **11**–**14**.

*4.6.1. 4-Oxa-1,7-dithia[7](6,6′)-2,2′-bis(cyclopenta[c]pyridine)cyclophane sulfoxide (**11**).* Yield (0.24 g, 63%), oil, ee 9%, $[\alpha]_D^{20}$ −8.1 (*c* 0.7, CH_2Cl_2); R_f (CH_2Cl_2/adetone, 10:1) 0.22; IR (KBr): ν 1032 cm^{-1} (S=O); UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=315 (3.91); δ_H (200 MHz, CDCl3) 2.10–2.40 (4H, m), 2.78–2.82 (2H, m), 2.93–3.06 (4H, m), 3.11–3.62 (6H, m), 3.92–4.09 (4H, m), 7.42 (1H, s, pyridine hydrogen atom), 7.72 (1H, m, pyridine hydrogen atom); δ_C (50 MHz, $CDCl_3$) 24.3 (CH_2), 25.0 (CH_2), 27.6 (CH_2), 29.6 (CH_2), 32.5 (CH_2), 32.9 (SCH_2), 47.6 (CH_2SO), 61.5, 66.6 (OCH_2), 113.2, 118.4, 137.0, 153.0, 154.0, 155.6, 158.2, 168.8, 179.3 pyridine carbon atoms; HRMS (EI): M^+, found 386.1114. $C_{20}H_{22}N_2O_2S_2$ requires 386.1123. HPLC

analysis (Chiralpac AS, hexane/(ether/2-propoanol 4:1) 60:30, flow rate 0.5 mL min^{-1}): t_R=36.17 min (54.5%), 48.82 min (45.5%).

*4.6.2. 4-Oxa-1,7-dithia[7](6,6′)-2,2′-bis(pyridine)cyclophane sulfoxide (**12**).* Yield (0.14 g, 46%); 149–150 °C, ee 11%, $[\alpha]_D^{20}$ +8.9 (*c* 0.64, CH_2Cl_2); R_f (CH_2Cl_2/acetone, 10:1) 0.17; IR (KBr): ν 1038 cm^{-1} (S=O); UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=324 (3.84); δ_H (200 MHz, $CDCl_3$) 3.12–3.21 (1H, m), 3.41–3.55 (2H, m), 3.80–3.97 (2H, m), 4.12–4.36 (2H, m), 4.47–4.61 (1H, m), 7.17–7.29 (1H, m), 7.56–7.67 (2H, m), 7.85–7.86 (1H, m), 7.89–8.09 (2H, m); δ_C (50 MHz, $CDCl_3$) 28.6 (SCH_2), 52.5 ($SOCH_2$), 62.6, 66.9 (OCH_2), 116.3, 121.5, 121.6, 122.2, 136.8, 138.8, 153.8, 154.9, 159.5, 164.9 pyridine carbon atoms; HRMS (EI): M^+, found. 306.0492 $C_{14}H_{14}N_2O_2S_2$ requires 306.0497. HPLC analysis (Chirobiotic T, hexane/(ether/2-propoanol 4:1) 60:40, flow rate 0.5 mL min^{-1}): t_R=21.98 min (44.4%), 24.70 min (55.5%).

*4.6.3. 1,7-Dithia[7](6,6′)-2,2′-bis(cyclopenta[c]pyridine)cyclophane sulfoxide (**13**).* Yield (0.14 g, 36%); mp 190–191 °C; ee 2%, $[\alpha]_D^{20}$ +10.0 (*c* 0.7, CH_2Cl_2); R_f (CH_2Cl_2/acetone, 10:1) 0.33; IR (KBr): ν 1020 cm^{-1} (S=O); UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=313 (3.93); δ_H (200 MHz, $CDCl_3$) 2.10–2.25 (9H, m, CH_2), 2.78 (2H, t, *J*=7.6 Hz, CH_2), 2.82–3.02 (5H, m, CH_2), 3.10–3.50 (5H. m, CH_2), 3.80–3.94 (1H, m, CH_2), 7.35 (1H, s, pyridine hydrogen atom), 7.65 (1H, s, pyridine hydrogen atom); δ_C (50 MHz, $CDCl_3$) 19.3 (CH_2), 24.3 (CH_2), 25.0 (CH_2), 27.7 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.5 (CH_2), 32.9 (SCH_2), 50.27 ($SOCH_2$), 112.9, 118.3, 136.6, 140.9, 153.2, 153.6, 154.0, 154.6, 155.5, 157.8 pyridine carbon atoms; HRMS (EI): M^+, found 384.13259. $C_{21}H_{24}N_2OS_2$ requires 384.133009. HPLC analysis (Chiralpac AS, hexane/(ether/2-propoanol 4:1) 60:30, flow rate 0.5 mL min^{-1}): t_R=30.25 min (51.0%), 37.65 min (49.0%).

*4.6.4. 1,7-Dithia[7](6,6′)-2,2′-bis(pyridine)cyclophane sulfoxide (**14**).* Yield (0.10 g, 35%), ee 19%, $[\alpha]_D^{20}$ −8.34 (*c* 1.0, CH_2Cl_2); R_f (CH_2Cl_2/acetone, 10:1) 0.26; IR (KBr): ν 1027 cm^{-1} (S=O); UV/vis ($CHCl_3$, nm): λ_{max} (log ε)=324 (3.79); δ_H (200 MHz, $CDCl_3$) 1.56–1.71 (3H, m, CH_2), 1.92–2.09 (1H, m, CH_2), 2.18–2.40 (2H, m, CH_2), 2.79–2.95 (1H, m, CH_2), 3.13–3.41 (2H, m, CH_2), 3.64–3.78 (1H, m, CH_2), 7.17–7.21 (1H, m, pyridine hydrogen atom), 7.43–7.68 (2H, m, pyridine hydrogen atoms), 7.80–7.84 (1H, m, pyridine hydrogen atom), 7.94–8.04 (2H, m, pyridine hydrogen atoms); δ_C (50 MHz, $CDCl_3$) 21.1 (CH_2), 27.4 (CH_2), 27.7 (CH_2), 30.5 (SCH_2), 54.7 ($SOCH_2$), 116.1, 121.3, 121.4, 122.1, 136.4, 138.5, 153.9, 155.2, 160.3, 165.1 pyridine carbon atoms; HRMS (EI): M^+, found 304.0700. $C_{15}H_{16}N_2OS_2$ requires 304.0704. HPLC analysis (Chirobiotic T, hexane/(ether/2-propoanol 4:1) 15:20(60), flow rate 0.5 mL min^{-1}): t_R=31.32 min (40.5%), 33.48 min (59.5%).

*4.6.5. Asymmetric addition of diethylzinc to benzaldehyde in the presence of ligands **11**–**14**.* To a solution of **11**–**14** (2.5 mol %) in anhydrous benzene (5 mL) was added diethylzinc (3 mmol, 1.0 M solution in hexane) under argon and the reaction was stirred for 10 min at room temperature. The solution was cooled at 0 °C, and benzaldehyde (1 mmol) was added slowly. After being stirred for 2 h at 0 °C, and 12 h at room temperature, the reaction was quenched with 1 M aqueous HCl (20 mL). The mixture was extracted with Et_2O, and the combined organic layer dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate, 10:1) to afford 1-phenyl-1-propanol (**15**) as a colorless liquid in 43–74% yield. The ee values of **15** range from 3 to 7%.

4.7. X-ray structure determinations

X-ray data of **5** were collected on the Kuma KM4 diffractometer; crystal sizes 0.40×0.40×0.10 mm, Cu Kα (λ=1.54178 Å) radiation, $\omega/2\theta$ scans. Data collections for **4** and **6** were performed on the Bruker SMART APEX II CCD diffractometer; crystal sizes 0.18×0.14×0.09 mm (**4**) and 0.28×0.19×0.09 mm (**6**), Mo Kα (λ=0.71073 Å) radiation, ω scans. All structures were solved by direct methods using SHELXS97[20] and refined by full-matrix least-squares with SHELXL97.[20] The H atoms were positioned geometrically and treated as riding on their parent C atoms with C–H distances of 0.93 Å (aromatic) and 0.97 Å (CH_2). All H atoms were refined with isotropic displacement parameters taken as 1.5 times those of the respective parent atoms. All calculations were performed using WINGX version 1.64.05 package.[21] CCDC 791625 (**4**), CCDC 791626 (**5**), CCDC 791627 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

*4.7.1. Crystal data of **4**.* $C_{10}H_{10}N_6OS_2$, *M*=294.36, monoclinic, space group *C*2/*c*, *a*=30.5580 (4), *b*=10.0847 (2), *c*=16.4199 (4) Å, β=95.813 (1)°, *V*=1141.24 (7) Å^3, *Z*=16, d_{calcd}=1.554 Mg m^{-3}, *F* (000)=2432, μ(Mo Kα)=0.424 mm^{-1}, *T*=293 K, 44,408 measured reflections (θ range 2.13–25.76°), 4829 unique reflections (R_{int}=0.033), final *R*=0.035, *wR*=0.091, *S*=1.007 for 3786 reflections with $I>2\sigma(I)$. The final residual electron-density maps showed that the N1A, N2A and C6A atoms of 1,2,4-triazine ring and C11 and C12 atoms of thiaethereal chain are disordered over two sites. The occupancy factors (s. o. f.) for the split nitrogen and carbon atoms were refined and finally fixed at 0.5.

*4.7.2. Crystal data of **5**.* $C_{20}H_{22}N_2OS_2$, *M*=350.52, triclinic, space group $P\bar{1}$, *a*=8.232 (1), *b*=9.367 (1), *c*=13.027 (2) Å, α=81.59 (1), β=79.13 (1), γ=62.92 (1)°, *V*=876.2 (2) Å^3, *Z*=2, d_{calcd}=1.404 Mg m^{-3}, *F*(000)=392, μ(Cu Kα)=2.831 mm^{-1}, *T*=293 K, 3881 measured reflections (θ range 3.46–80.25°), 3460 unique reflections (R_{int}=0.036), final *R*=0.048, *wR*=0.138, *S*=1.092 for 2974 reflections with $I>2\sigma(I)$. The crystal of **5** used in X-ray diffractometer measurement was non-merohedral twin. The structure was easily solved by direct methods and all non-H atoms were found. However the refinement only converged to *R* of 0.27 and the refinement statistics showed that the K=mean(F_o^2)/mean(F_c^2) was systematically high for reflections with low intensity. Additionally, for all of the disagreeable reflections F_o is much greater than F_c. The Laue symmetry $\bar{1}$ gives a respectably low value for *R*(merge) of 0.042 and the value for all other Laue classes is larger since 0.8. Above mentioned features are typical of non-merohedral twins, where the reciprocal lattices do not overlap exactly and only some of the reflections are affected by the twinning.[22] Therefore, after refinement of the structure to *R* of 0.27, the 69 reflections with $F_o^2>>F_c^2$ were removed from the intensity data file assuming that they are affected by the twinning and the remaining reflections are contributed to a single twin domain. The refinement on the modified intensity data file gave *R* of 0.048 and acceptable values of other refinement parameters.

*4.7.3. Crystal data of **6**.* $C_{14}H_{14}N_2OS_2$, *M*=290.39, triclinic, space group $P\bar{1}$, *a*=8.2719 (7), *b*=9.1916 (8), *c*=10.2434 (9) Å, α=67.289 (1), β=78.987 (1), γ=83.799 (1)°, *V*=704.70 (11) Å^3, *Z*=2, d_{calcd}=1.369 Mg m^{-3}, *F*(000)=304, μ(Mo Kα)=0.370 mm^{-1}, *T*=293 K, 11,741 measured reflections (θ range 2.18–24.84°), 2423 unique reflections (R_{int}=0.013), final *R*=0.029, *wR*=0.082, *S*=1.075 for 2231 reflections with $I>2\sigma(I)$.

4.8. Theoretical calculations

The theoretical calculations at the DFT/B3LYP level with 6-311++G(d,p) basis set implemented in GAUSSIAN 03[23] were

carried out via Natural Bond Order (NBO) analysis to investigate the conformational preferences of **4**–**6**. The structures were fully optimized without any symmetry constraint and the initial geometries were built from their crystallographic data. The total energies and dipole moments for molecules **4**–**6** are summarized in Table 2 in Supplementary data. The structure of 5,5′-bi-1,2,4-triazine thiamacrocyle with four CH_2 groups in thiaalkyl chain was modeled de novo and its total energy, dipole moment and geometrical parameters (bond lengths, angles and torsion angles) obtained after energy minimization and geometry optimization are presented in Table 3 in Supplementary data.

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Supplementary data

Selected torsion angles. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.081.

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