Bisthioxanthylidene biscrown ethers as potential stereodivergent chiral ligands†

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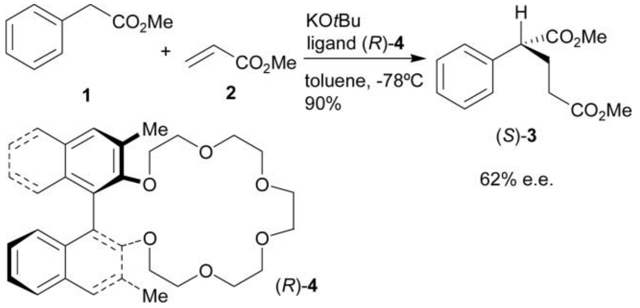
The concept of bisthioxanthylidene biscrown ethers as potential stereodivergent chiral ligands in asymmetric synthesis is introduced. Substituted bisthioxanthylidenes may be chiral and can exist as stable enantiomers due to their folded structure. As a result, both a right-handed helix (*P*) and left-handed helix (*M*) are present in this type of molecule. This offers the unique possibility to construct two crown ether moieties, attached to the same molecule, of which one exhibits (*P*)-helicity and the other (*M*)-helicity. When the crown ether moieties differ in size they can be complexed selectively with a base containing a cation of appropriate diameter. In this manner the (*P*)-helix and the (*M*)-helix can be activated selectively to serve as a chiral environment for base catalyzed asymmetric synthesis. Thus, we envisioned the new concept of a single chiral ligand to separately synthesize two enantiomers of a chiral product just by varying the added base. For this purpose, four new bisthioxanthylidene monocrown ethers and two new bisthioxanthylidene biscrown ethers were synthesized. Two biscrowns and two monocrowns were separated into their respective enantiomers (HPLC) and optical data (UV and CD) were collected to ensure stability of enantiomers at ambient temperatures. Ion complexation of one mono- and two biscrown ethers with potassium and sodium cations was investigated.

Introduction

Following the seminal discovery by C. J. Pedersen[1] in 1967 numerous applications of crown ethers, and derivatives, have been developed. These compounds have been the basis for host–guest chemistry and are at the dawn of supramolecular chemistry.[2] Cram *et al.* employed chiral crown ethers as ligands for potassium ions in base catalyzed asymmetric Michael addition reactions (Scheme 1).[3] Chiral ligand (*R*)-**4** consists of a six oxygen crown ether attached to an optically pure binaphthol moiety. The size of the crown ether was perfectly suited for 1 : 1 complexation with KO*t*Bu, which initiated the Michael addition of methyl acrylate **2** to methyl phenylacetate **1**. In this way a chiral environment was created around the reaction center which led to formation of product **3** in 90% yield, with an ee of 62%.



Scheme 1 Asymmetric Michael addition using crown ether (*R*)-**4** as chiral ligand.

Concept

This methodology inspired us to construct chiral crown ethers with bisthioxanthylidene as a chiral template (Fig. 1).

We envisioned that the combination of the unique three dimensional shape of bisthioxanthylidene[4–6] and ion complexation capabilities of crown ethers[1,2] would provide an interesting new class of chiral bifunctional structures. Bisthioxanthylidenes are proven to exhibit a folded structure due to the severe steric hindrance around the central double bond (Fig. 1, structures **A** and **B**). Unequal substituents at either side of the molecule lead to a chiral compound with both a right (*P*) and a left handed helix (*M*) in the same molecule (Fig. 1, structure **A**).[7] Equal substituents would lead to an achiral *meso* compound (Fig. 1, structure **B**). Rebek *et al.* synthesized a biphenyl which was functionalized with equally sized crown ether moieties at both sides (Fig. 1, structure **C**).[8] Cooperative binding affinity of this biscrown system[8] and related structures[9] with cations was investigated. Since biphenyls have a twisted conformation, two helices of same configuration (two (*P*)-helices or two (*M*)-helices) are present in this type of molecule. Note that, despite having equal substituents, the presence of two helices of the same configuration makes this type of structure chiral anyway, independent from its substitution pattern.

Bisthioxanthylidenes have racemization barriers ($\Delta G^{\ddagger}$) around 27.0 kcal mol^{-1} which ensure sufficient stability to preserve optical activity at ambient temperatures.[4–6] We aimed at four bisthioxanthylidene monocrown ethers **5–8** and two bisthioxanthylidene

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† Electronic supplementary information (ESI) available: Atom numbering schemes for compounds **5**, **6**, **24**, **25**, **28**, **29**, **32**, **33**, **9**, and **10**; X-ray analysis of **9**; chiroptical data of **7** and **8**; procedures for complexation experiments of compounds **5**, **9**, and **10**; ^{1}H and ^{13}C NMR-spectra of **5–10**. See DOI: 10.1039/b609271c

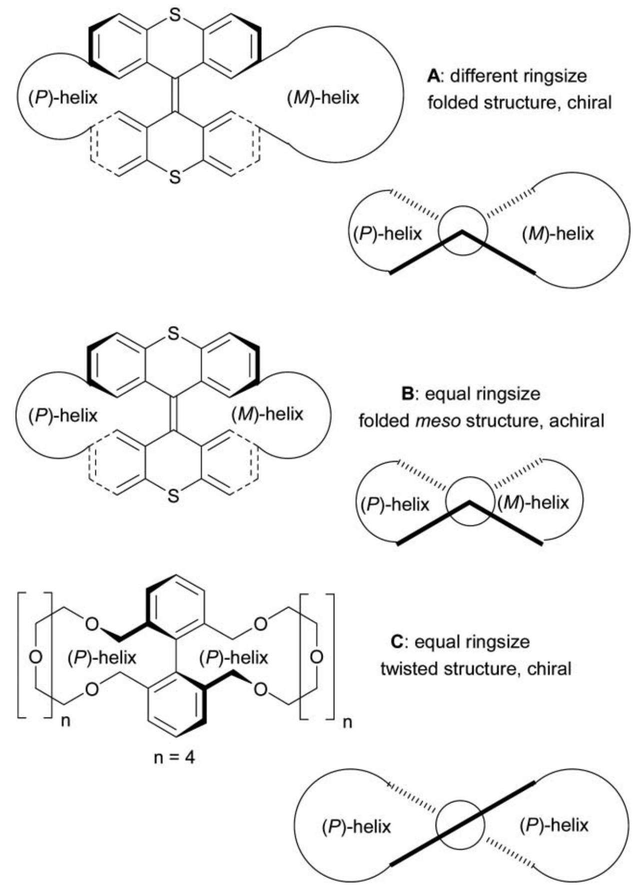


Fig. 1 Schematic presentation of: (**A**) bisthioxanthylidene with unequal crown ether moieties; (**B**) bisthioxanthylidene with equal crown ether moieties, (**C**) biphenyl with equal crown ether moieties. Right: projection viewed from top along the central double bond.

biscrown ethers **9** & **10** bearing crown ether moieties comprising four, five, and six oxygen atoms, connected by ethylene moieties (Fig. 2). Crown ethers of this composition are known to have a distinct preference for selective 1 : 1 complexation with lithium, sodium, and potassium cations, respectively, according to the 'optimal spatial concept'.[2,10]

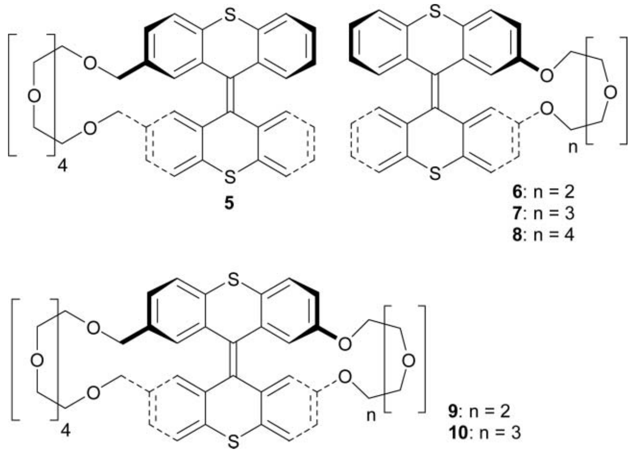


Fig. 2 New bisthioxanthylidene monocrown ethers **5–8** and bisthioxanthylidene biscrown ethers **9** and **10**.

All new bisthioxanthylidene crown ethers **5–10** are chiral since they have different substituents attached at either side of the molecule. Bisthioxanthylidene monocrowns **5–8** were intended to examine the complexation behavior of this class of compounds with metal cations. The differently sized crown ether moieties of two biscrown ethers **9** and **10** were anticipated to selectively bind a metal ion of appropriate size. In this manner the (*P*)-helix and (*M*)-helix can be complexed selectively by varying the size of the added metal ion. The (*P*)-helix and (*M*)-helix can serve as a chiral environment for base mediated asymmetric catalysis. Thus, we envisioned the new concept of a single chiral ligand which is able to control the formation of either enantiomers of a chiral product in a distinct way simply by varying the added achiral base (Fig. 3).

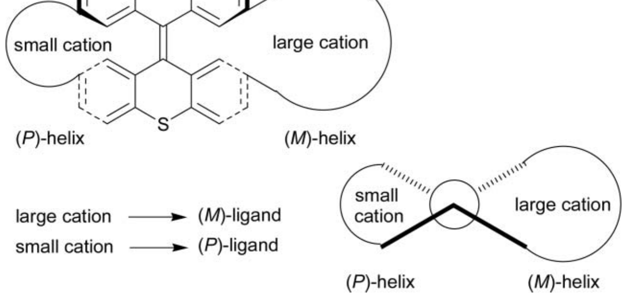
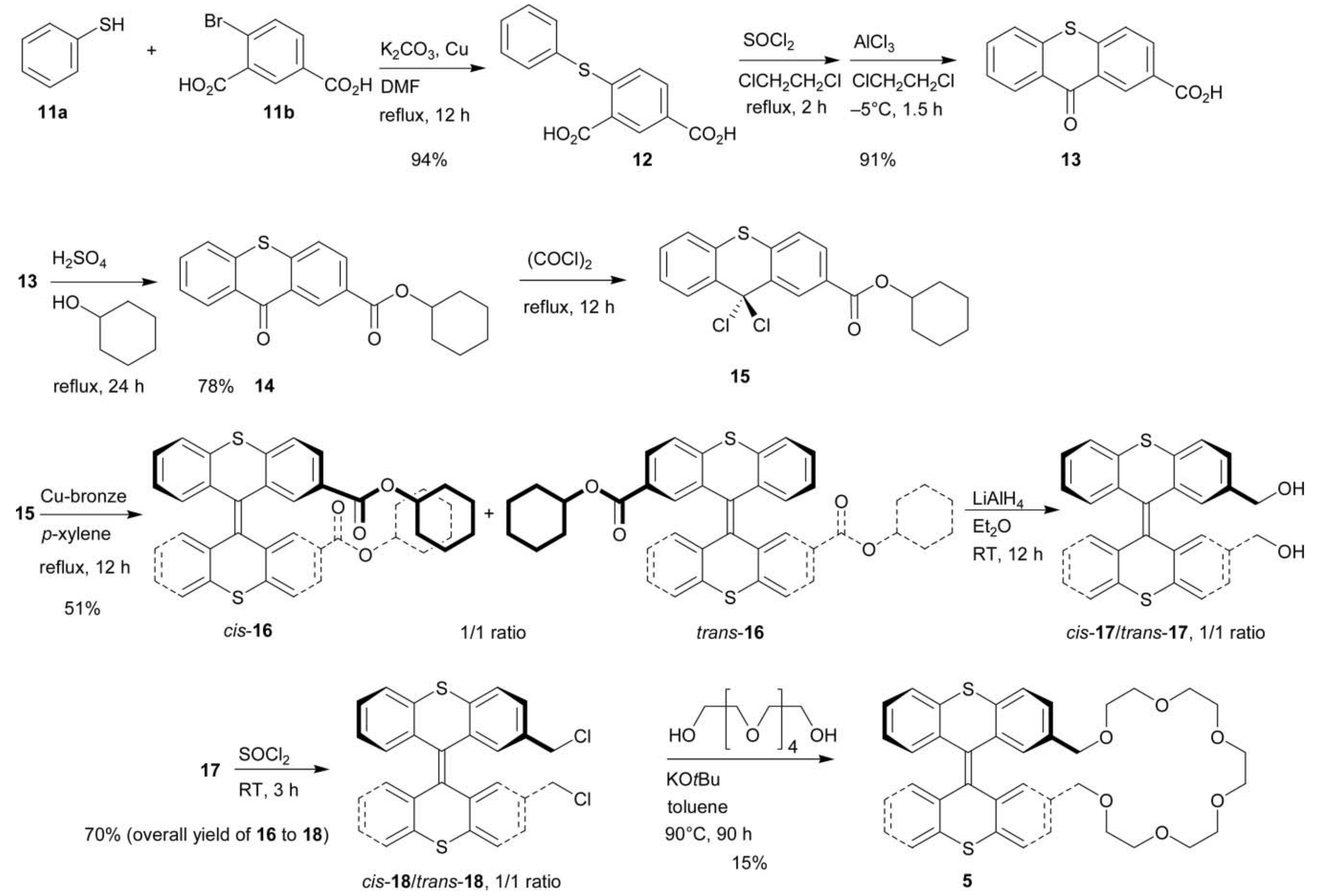


Fig. 3 Selective activation of the (*M*)-helix or (*P*)-helix of a bisthioxanthylidene biscrown ether by ion binding. Left: bisthioxanthylidene biscrown ligand. Right: schematic drawing viewed from top along central double bond.

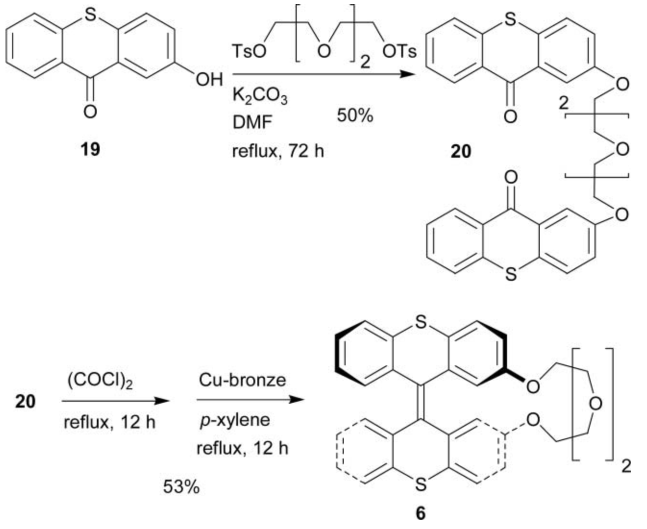
Synthesis

Monocrown **5**, with methylene groups between the bisthioxanthylidene backbone and oligoether segment, was synthesized from thiophenol **11a** and 4-bromoisophthalic acid **11b** (Scheme 2). Ketone **13** was conveniently synthesized from substrates **11a** and **11b** *via* an aromatic substitution yielding **12** followed by an intramolecular Friedel–Crafts reaction. The carboxylic acid moiety of **13** was protected by esterification with cyclohexanol to provide adduct **14**. Thioxanthone ester **14** was converted into unstable *gem*-dichloride **15** by refluxing in oxalyl dichloride to facilitate subsequent intermolecular coupling by the action of activated Cu-bronze[11] in refluxing *p*-xylene.[12] Bisthioxanthylidene **16** was obtained in 51% yield after purification by column chromatography. A mixture of *cis* and *trans*-**16**, in a 1 : 1 ratio, was obtained and separation of the two isomers was achieved by column chromatography. However, the *cis–trans* mixture was applied in the following step. The ester groups of **16** were readily converted into dichlorides *cis*-**18** and *trans*-**18** (1 : 1 ratio) by a $LiAlH_4$ reduction and subsequent reaction with $SOCl_2$. The crown ether moiety was constructed by coupling pentaethylene glycol with *cis–trans*-**18** through a twofold Williamson ether synthesis. A rather low yield of 15% was found due to extensive formation of oligomers. The *trans* isomer of **5** was not observed.

The synthesis route towards monocrown **6** is depicted in Scheme 3. Two 2-hydroxy-thioxanthylidene moieties **19**[13,14] were coupled with triethylene glycol ditosylate using K_2CO_3 in refluxing DMF providing diketone **20** in 50% yield. An intramolecular



Scheme 2 Synthesis route towards monocrown **5**.

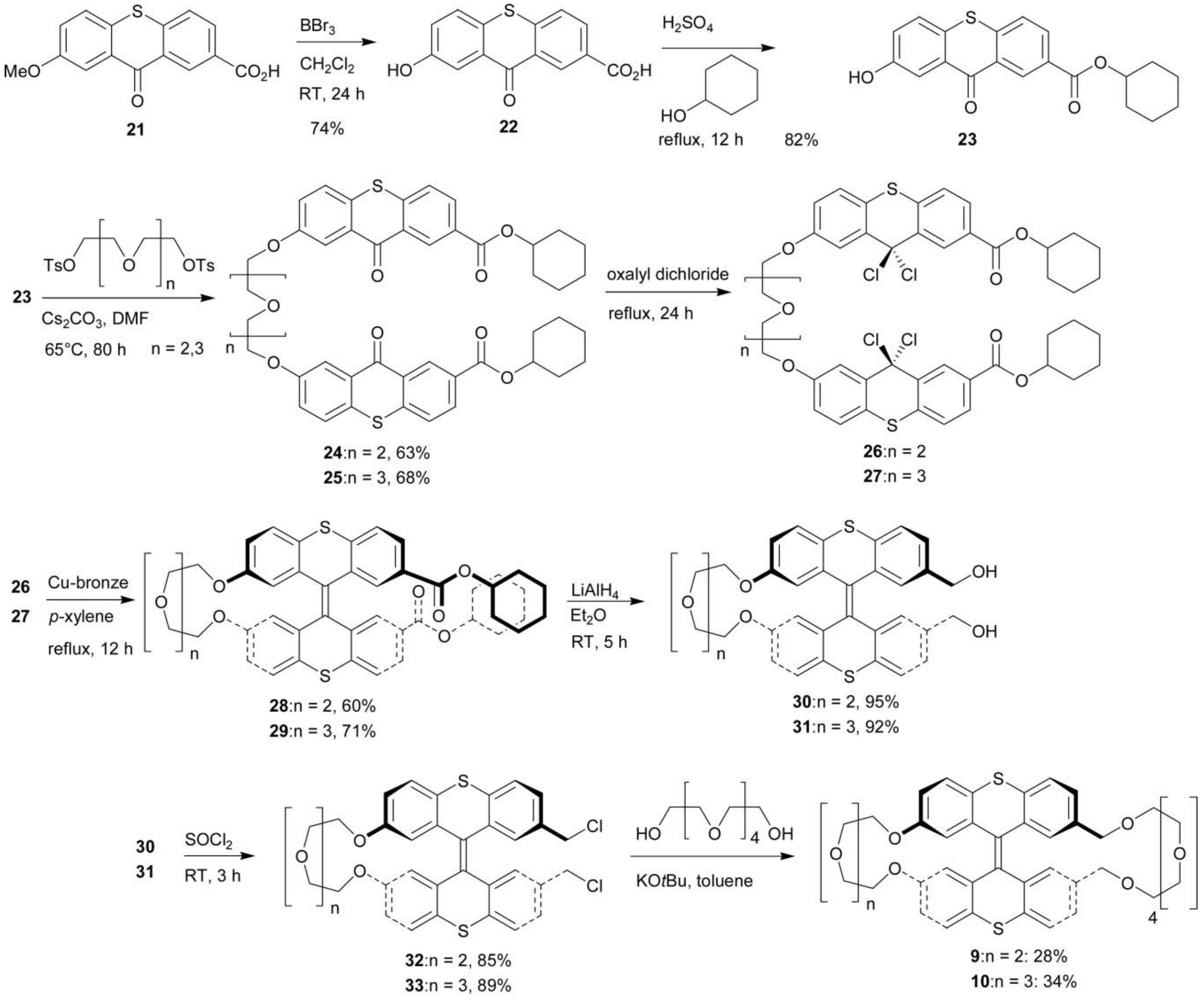


Scheme 3 Synthesis route towards monocrown **6**.

coupling reaction of **20** by oxalyl dichloride[12] and activated Cu-bronze[11] furnished bisthioxanthylidene monocrown ether **6**. Synthesis of monocrown ether compounds **7** and **8** (Fig. 2) was reported previously.[14] All four monocrowns **5–8** were characterized by ^{1}H and ^{13}C NMR as well as HRMS analysis.

Bisthioxanthylidene biscrown ethers **9** and **10** were synthesized in eight steps from 7-methoxy-9-oxo-9*H*-thioxanthene-2-carboxylic acid **21**[6] (Scheme 4). A building block with two different substituents was chosen to be able to selectively construct two unequally sized crown ether moieties. First the methoxy substituent of **21** was deprotected by BBr_3 yielding **22** after which the carboxylic acid moiety was esterified with cyclohexanol to give **23**. Two equivalents of **23** were coupled with one equivalent of ditosylate by the action of Cs_2CO_3 to give compounds **24** (n = 2, 63%) and **25** (n = 3, 68%). The reaction temperature was kept at 65 °C to prevent hydrolysis of the esters which, however, caused prolonged reaction times of up to 80 h.

A crucial intramolecular coupling reaction followed which simultaneously resulted in construction of the central double bond of the bisthioxanthylidene backbone and the first crown ether moiety. Diketones **24** and **25** were converted into their respective bis-*gem*-dichlorides **26** and **27** by heating at reflux in oxalyl dichloride for 24 h.[12] The bis-*gem*-dichlorides were unstable and therefore treated *in situ* with activated Cu-bronze[11] in refluxing *p*-xylene to furnish ring closed adducts **28** (n = 2) and **29** (n = 3) in 60% and 71% yield respectively. These were satisfactory yields given that sterically demanding overcrowded alkenes were prepared during intramolecular coupling reactions which could give oligomers. Only *cis*-isomers were found. The conversion of the two ester groups into methylene chlorides and subsequent attachment of the second crown ether moiety



Scheme 4 Synthesis route towards biscrown ethers **9** and **10**.

proceeded in a similar fashion as employed for monocrown **5** (Scheme 2). KO*t*Bu was applied as base in an attempt to exploit a template effect[15] during intramolecular crown ether formation. Thus, bisthioxanthylidene biscrown ethers **9** (n = 2) and **10** (n = 3) were obtained in gratifying yields of 28 and 34% after purification by column chromatography. These yields are doubled in comparison with the 15% yield found for intramolecular crown ether formation of dichloride *cis*–*trans*-**18** leading to **5** (Scheme 2). This is in line with the fact that dichlorides **32** and **33** are only present in the *cis*-configuration promoting intramolecular coupling. Biscrown ethers **9** and **10** were characterized by mass spectrometry, ^{1}H NMR, ^{13}C NMR, NOESY, and COSY NMR.

Chiroptical data

Optical resolution of monocrown ethers **7** and **8** (n = 3, 4) and both biscrown ethers **9** and **10** was pursued to confirm the anticipated chirality and optical stability. Separation into their respective enantiomers was readily achieved by chiral HPLC and specifications are summarized in Table 1. CD-spectra of **7–10** were recorded and displayed a pair of mirror images in all cases. Data of the (*M*) enantiomers are given in Table 2 and UV and CD-spectra of the (*P*) and (*M*) enantiomer of biscrown **9** are depicted in Fig. 4. CD-spectra of the four bisthioxanthylidene (bis) crown ethers **7–10** show similar features except for the

Table 1 Enantioresolution by chiral HPLC of crown ether compounds **7–10**

Crown ether	Chiral column	Eluent	Retention times/min	Configuration first fraction
7	AD	*n*-Hexane–*i*-propanol 120 : 1	64, 72	(*P*)
8	AD	*n*-Hexane–*i*-propanol 60 : 1	44, 56	(*M*)
9	OD	*n*-Hexane–*i*-propanol 9 : 1	13, 19	(*P*)
10	AD	*n*-Hexane–*i*-propanol–chloroform 8 : 1 : 1	15, 23	(*P*)

Table 2 CD data of (M) enantiomers of crown ethers **7–10**[a]

Crown ether	Configuration[b]	λ/nm, ε/1000 cm^2 mol^{-1}					
7	(M)	218 (+27.5)	227 (−3.6)	247 (−14.7)	268 (+12.1)	287 (−28.0)	308 (+14.1)
8	(M)	218 (+22.8)	228 (−18.4)	248 (−23.7)	268 (+9.5)	287 (−40.0)	310 (+21.8)
9	(M)	219 (+42.6)	229 (−21.4)	252 (−28.5)	270 (+19.3)	289 (−44.9)	312 (+23.9)
10	(M)	220 (+14.6)	230 (−12.5)	252 (−15.9)	271 (+12.4)	290 (−23.9)	312 (+10.3)

[a] all recordings in *n*-hexane [b] based on ref. 6.

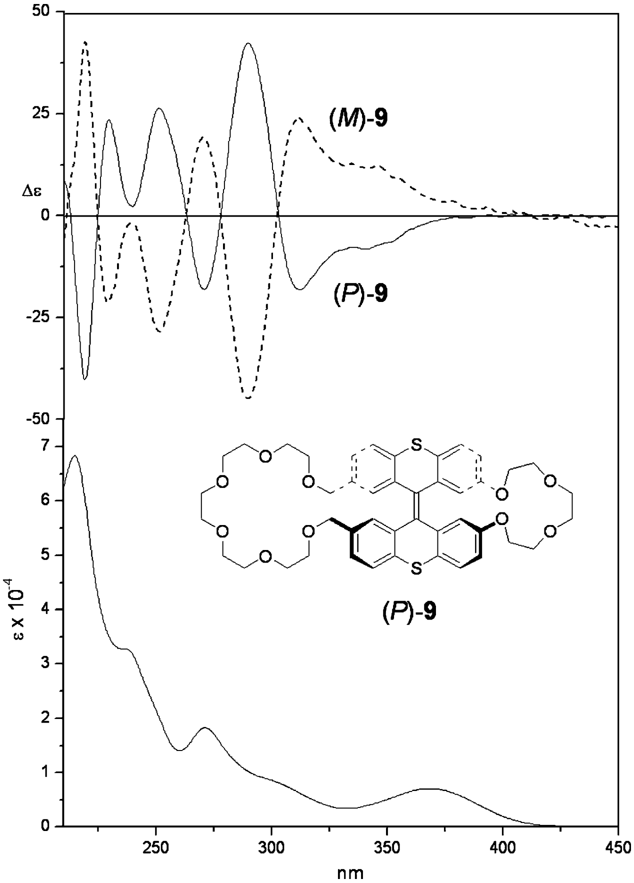


Fig. 4 UV (*n*-hexane–*i*-propanol 9 : 1) of biscrown ether (P)-**9** and CD (*n*-hexane) spectra of (P) (straight) and (M) (dashed) enantiomers of **9**.

sign which is dependent on the enantiomer. This led to the conclusion that the folded[16] bisthioxanthylidene backbone largely governed the shape and sign of the CD-spectra. Maxima, or minima, were found around 219, 228, 249, 269, 288 and 310 nm, respectively. The absolute configurations of crown ethers **7–10** were determined by comparison of CD-data with those of a similarly substituted bisthioxanthylidene backbone of which the absolute configuration was established unambiguously.[6] The collected optical data confirmed that bisthioxanthylidene crown ethers **7–10** preserve their optical activity and can exist as stable enantiomers at ambient temperatures.

Complexation studies

Previous ^{1}H NMR longitudinal relaxation time studies of monocrown **7** with lithium, sodium, potassium, rubidium, and caesium triflates in $CDCl_3$ revealed that **7** has a preference for 1 : 1 complexation with lithium cations.[14] Cation : **7** 1 : 2 sandwich complexes were observed with potassium, rubidium, and caesium. Monocrown **8** was found to favor 1 : 1 complexation with potassium and rubidium cations.[14] Monocrown **5** and biscrowns **9** and **10** were examined with respect to their complexation behavior with potassium and sodium cations in acetone-d_6.[9,17,18] Potassium and sodium thiocyanate were used as salts. Changes in chemical shift ($\Delta\delta$ (Hz)) of seven different protons [H_I (X and Y), H_{II} (A and B), H_{III}, H_{IV}, and H_V) of **5**, **9**, and **10** upon addition of metal cation was monitored with ^{1}H NMR spectroscopy (Fig. 5, Table 3). The change in chemical shift ($\Delta\delta$ (Hz)) was screened during stepwise increase of salt concentration up to 5 equivalents with respect to a constant concentration of crown ether. The changes in chemical shifts of protons H_I–H_V after addition of five equivalents of salt are given in Table 3. Protons H_I (XY part of ABXY system) and H_{II} (AB system) are aliphatic protons which are part of the large six oxygen ring. H_{III} and H_{IV} are aromatic protons attached to the bisthioxanthylidene backbone. H_V are aliphatic protons belonging to the small four and five oxygen crown ether moieties of **9** and **10**, respectively. Two of the four protons H_V were detected as clear and separate signals in ^{1}H NMR spectra of **9** and **10** recorded in acetone-d_6. Protons at either side of the molecules were examined which allowed distinction between cation complexation with the large (H_I–H_{III}) and small crown ether ring (H_{IV} and H_V).

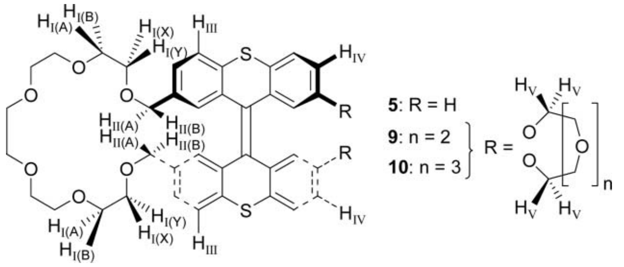


Fig. 5 Crown ethers **5**, **9**, and **10** with relevant protons H_I–H_V.

Monocrown **5** showed preference for 1 : 1 complexation with both potassium and sodium ions (entries 1 and 4, Table 3). The equilibrium constants (K) for the favored 1 : 1 complexes were determined straightforwardly[18,19] although other dynamic processes upon addition of potassium ions to **5** cannot be excluded.

As anticipated complexation of potassium ions ($K = 5.9 \times 10^3$ M) with the six oxygen crown ether of **5** is favored over sodium ions ($K = 1.4 \times 10^3$ M). These equilibrium constants are of identical magnitude compared to values found for complexation of 15-crown-5 with sodium and potassium ions respectively.[2b,20] However, they are much smaller than values found for complexation of sodium and potassium with 18-crown-6.[2b,20] This can

Table 3 Complexation behavior of crown ethers **5**, **9**, and **10**. Chemical shifts (δ) of protons H_I–H_V (δ), change in chemical shift (Δδ) upon addition of five equivalents of salt, crown : salt ratio of favored complex, equilibrium constant of favored complex $(K)^a$, and complexation energy of favored complex $(-\Delta G^0)^b$

		Proton, splitting pattern, chemical shift (δ) (ppm)						Proton, splitting pattern downfield change in chemical shift (Δδ) (Hz)							
Entry	Crown	H_I XY	H_{II} AB	H_{III} d	H_{IV} dd	H_V ddd	Salt	H_I XY	H_{II} AM	H_{III} d	H_{IV} dd	H_V ddd	Ratio crown : salt	K^a / $\times 10^{-3}$ M	$-\Delta G^0$/kcal $mol^{-1\,b}$
1	**5**	3.48	4.41	7.73	7.36	—	KSCN	71.8, 54.2	67.7, −5.5	9.9	4.2	—	1 : 1	5.9	5.1
2	**9**	3.45	4.39	7.70	7.04	4.18[c]	KSCN	77.8, 57.5	67.7, −6.2	9.9	7.1	2.9[c]	1 : 1	6.3	5.2
3	**10**	3.46	4.40	7.71	7.04	4.02	KSCN	82.0, 56.6	67.9, −3.5	10.2	12.0	13.1	2 : 3	—	—
4	**5**	3.48	4.41	7.73	7.36	—	NaSCN	65.5, 8.8	31.0, −6.0	6.6	2.7	—	1 : 1	1.4	4.3
5	**9**	3.45	4.39	7.70	7.04	4.18[c]	NaSCN	57.5, 9.9	21.8, 0.7	6.3	6.9	2.1[c]	1 : 1	2.0	4.4
6	**10**	3.46	4.40	7.71	7.04	4.02	NaSCN	57.9, 9.5	24.5, −0.9	6.2	9.9	3.8	1 : 1	1.1	4.1

[a] ref. 18. [b] ref. 19. [c] Multiplet. All experiments in acetone-d_6.

be explained by the observation that increased rigidity in the crown ether ring system, for example by replacing ethylene by benzo moieties, reduces equilibrium constants for complexation with metal cations.[2b,21] The folded bisxanthylidene backbone[4,5,6,16] features severe rigidity indeed and diminishes complexation ability. Upon stepwise addition of 5 equivalents of salt the AB system of protons $H_{II(AB)}$ gradually changed into an AM system[22] while the chemical environment of $H_{I(X)}$ changed considerably more than that of $H_{I(Y)}$ (Table 3). The downfield shift of $H_{II(A)}$ of 67.7 (entry 1) and 31.0 Hz (entry 4) *versus* an upfield shift of $H_{II(B)}$ of 5.5 (entry 1) and 6.0 Hz (entry 4) is especially notable. These observations are an evident sign of increasing rigidity of the six oxygen crown ether moiety as a result of potassium and sodium complexation.

The capability of accommodating potassium did not increase upon offering an extra four oxygen crown ether moiety (compound **9**, entry 2). Addition of potassium to biscrown **9** resulted in a 1 : 1 crown : salt complex. Final shifts of protons H_I–H_{III} were similar compared to monocrown **5** indicating complexation of potassium with the large crown ether moiety. Complexation with the small crown was not favored since small additional shifts of only 2.9 Hz were observed for protons H_{IV} and H_V. The equilibrium constant of 6.3 × 10^3 M for this 1 : 1 complex is in line with the constant of 5.9 × 10^3 M found for 1 : 1 complexation of **5** with potassium (entry 1). The situation changed significantly when the small crown ether moiety was enlarged with an ethoxy unit (biscrown **10**, entry 3). Compared to entry 2, shifts of protons H_{IV} and H_V increased by 4.9 and 10.3 Hz, respectively, upon addition of 5 equivalents of salt indicating that the small crown ether moiety now has reasonable capacity of binding potassium as well. The titration curves suggest initial formation of a 2 : 3 crown–salt complex. A complex comprising two biscrown compounds **10** which both accommodate one potassium ion in their large crown rings and sandwich a third between their small crown moieties is proposed here. The chemical shifts of protons H_I–H_{III} moved downfield up to addition of 2.5 equivalents of salt and remained constant beyond this point. However, shifts of protons H_{IV} and H_V moved downfield up to addition of 5 equivalents This observation suggests that complexation of potassium with the small crown ether ring is weaker than with the large one and that the 2 : 3 crown : salt complex slowly tended towards a 1 : 2 crown–salt complex.

A different picture was seen for addition of sodium to biscrowns **9** and **10** (entries 5 and 6). In both cases a 1 : 1 crown–salt complex was found with equilibrium constants (*K*) of 2.0 (**9**) and 1.1 × 10^3 M (**10**), respectively. The downfield shifts of protons H_I–H_{III} of **9** and **10** are of identical magnitude compared to monocrown **5** (entry 4). Moreover, the equilibrium constants found for **9** and **10** are of similar dimension compared to the value found for complexation of sodium with monocrown **5**. These findings indicate that sodium strongly favors complexation with the large, six oxygen containing, crown ether ring over the smaller four and five oxygen crown systems.

In all cases, potassium and sodium ions favor complexation with the large six oxygen crown ether ring of compounds **5**, **9**, and **10** as can be concluded from equal downfield shifts of protons H_I (~77 and 56 Hz), H_{II} (~68 and −5 Hz), and H_{III} (~10 Hz) in entries 1–3 and in entries 4–6 (H_I: ~60 and ~9 Hz; H_{II}: ~26 and −2 Hz; H_{III}: ~6.5 Hz) upon addition of 5 equivalents of salt. The increasing change in downfield shift of proton H_{IV} in entry series 1–3 (4.2 → 12.0 Hz) and 4–6 (2.7 → 9.9 Hz) and of proton H_V in entries

2 & 3 (2.9 → 13.1 Hz) and 5 & 6 (2.1 → 3.9 Hz) is in line with the increasing ability of cation accommodation at this side of the bisthioxanthylidene backbone going from crown ether **5** to **10**. In conclusion, sodium and potassium ions selectively bind to the large crown ether moiety of biscrown ether adduct **9** whereas sodium selectively complexes with the large crown ether ring of biscrown **10**.

Conclusions

Two new bisthioxanthylidene monocrown **5** and **6** and two new bisthioxanthylidene biscrown ethers **9** and **10** were synthesized. Biscrowns **9** and **10** both contain two crown ether moieties of different size of which one exhibits (*M*)- and the other exhibits (*P*)-helicity. Enantioresolution of monocrown ether compounds **7** and **8** and biscrowns **9** and **10** was achieved by chiral HPLC. UV and CD spectroscopy confirmed stability of enantiomers at ambient temperatures and absolute configurations were established. Potassium and sodium complexes with monocrown **5** and biscrowns **9** and **10** were observed. Favored crown : salt ratios and equilibrium constants were determined. It was found that sodium and potassium prefer complexation with the large six oxygen over the small four and five oxygen crown ether moieties of biscrowns **9** and **10**.

Experimental

^{1}H (200, 400 MHz) and ^{13}C (50 or 125 MHz) NMR spectra were recorded in $CDCl_3$ or DMSO-d_6. Chemical shifts are denoted in δ (ppm) referenced to the residual protic solvents. Column chromatography was performed on silica gel 60 PF_{254} under pressure. Procedures for synthesis of compounds **7**,[14] **8**,[14] **19**,[13,14] **21**.[6] Supplementary information contains atom numbering Schemes for compounds **5**, **6**, **24**, **25**, **28**, **29**, **32**, **33**, **9**, and **10**; X-ray analysis of **9**; chiroptical data of **7** and **8**; procedures for complexation experiments of compounds **5**, **9**, and **10**; ^{1}H and ^{13}C NMR-spectra of **5–10**.

4-(Phenylsulfanyl)isophthalic acid 12

Under nitrogen, 4-bromoisophthalic acid **11b** (8.00 g, 32.65 mmol), thiophenol **11a** (3.59 g, 32.64 mmol), Cu-bronze 100 mg (1.57 mmol), and K_2CO_3 (14.00 g, 101.27 mmol) were refluxed overnight in DMF (300 mL). After cooling, the mixture was filtered and the residue was dissolved in water (250 mL). The solution was carefully acidified with concentrated HCl (aq.) to pH < 1. The product precipitated and was collected on a glass filter. The product was thoroughly washed with water after which it was dried at 100 °C in air to yield pure **12** (8.43 g, 30.76 mmol, 94%) as a white powder. ^{1}H NMR (200 MHz, DMSO-d_6, 25 °C) δ 13.28 (br, 2H, OH), 8.45 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.54 (m, 5H), 6.76 (d, J = 8.5 Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6, 25 °C) δ 166.34, 165.98, 147.53, 135.13, 132.30, 131.82, 131.44, 130.10, 129.60, 127.74, 127.31, 126.77; HRMS calcd for $C_{14}H_{10}O_4S$: 274.0230; found: 274.0306.

9-Oxo-9*H*-thioxanthene-2-carboxylic acid 13

Under nitrogen, **12** (8.00 g, 29.20 mmol) was refluxed in dichloroethane (75 mL) and $SOCl_2$ (50 mL) until the evolution of HCl gas had ceased (approximately 2 h). The mixture was concentrated *in vacuo* and the residue was stripped twice with dichloroethane (50 mL). The residue was dissolved in dichloroethane (100 mL) and cooled to −5 °C after which $AlCl_3$ (15.0 g, 112.5 mmol) was added carefully. The resulting black mixture was stirred for 90 min at −5 °C. The reaction was quenched by careful addition of water (100 mL). The product was extracted with CH_2Cl_2 (twice 150 mL). The combined organic layers were thoroughly washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to yield pure **13** (6.82 g, 26.61 mmol, 91%) as a white powder. ^{1}H NMR (200 MHz, DMSO-d_6, 25 °C) δ 9.32 (d, J = 2.2 Hz, 1H, 1-H), 8.60 (d, J = 8.4 Hz, 1H, 4-H), 8.20 (dd, J = 8.4, 2.2 Hz, 1H, 3-H), 7.70–7.65 (m, 2H, 7-,8-H), 7.59–7.51 (m, 2H, 5-,6-H); ^{13}C NMR (50 MHz, DMSO-d_6, 25 °C) δ 172.44 (s), 161.21 (s), 138.72 (s), 129.58 (s), 127.82 (d), 126.86 (d), 126.09 (d), 124.73 (s), 123.81 (d), 122.85 (s), 122.62 (s), 121.14 (d), 120.64 (d), 119.94 (d).

Cyclohexyl 9-oxo-9*H*-thioxanthene-2-carboxylate 14

Substrate **13** (5.70 g, 22.27 mmol) was refluxed for 24 h in cyclohexanol (80 mL) and concentrated H_2SO_4 (0.75 mL). After cooling, a precipitate began to form. *n*-Hexane (80 mL) was added and the mixture was stirred for 5 min after which it was set aside for one night at −12 °C. A white precipitate was collected on a glass filter and the product was washed thoroughly with hot *n*-hexane to get rid of remaining cyclohexanol. Product **14** (5.84 g, 17.28 mmol, 78%) was obtained as a white powder. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 8.92 (s, 1H, 1-H), 8.31 (d, J = 7.7 Hz, 1H, 4-H), 7.96 (d, J = 7.7 Hz, 1H, 3-H), 7.39 (m, 3H, 5-,6-,7-H), 7.27 (dd, J = 6.6, 1.5 Hz, 1H, 5-H), 4.78 (m, 1H, $OCH(CH_2)_2$), 1.69–1.07 (m, 10H, *c*-hexyl); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 177.96 (s), 163.48 (s), 140.36 (s), 135.01 (s), 131.15 (d), 130.80 (d), 129.84 (d), 128.46 (d), 127.62 (s), 127.36 (s), 125.33 (d), 124.66 (d), 124.55 (d), 124.36 (s), 72.31 (d), 30.17 (t), 23.92 (t), 22.28 (t); HRMS calcd for $C_{20}H_{18}O_3S$: 338.0977; found: 338.0980.

9,9-Dichloro-9*H*-thioxanthene-2-carboxylic acid cyclohexyl ester 15 and *cis–trans*-cyclohexyl 9-{2-[(cyclohexyloxy)-carbonyl]-9*H*-thioxanthen-9-ylidene}-9*H*-thioxanthene-2-carboxylate 16

Under nitrogen, **14** (4.00 g, 11.83 mmol) was refluxed overnight in oxalyl dichloride (40 mL). After cooling, the excess of oxalyl dichloride was removed under reduced pressure. The residue (**15**) was dissolved in freshly distilled *p*-xylene (100 mL, from sodium). Activated Cu-bronze[11] (4.50 g, 70.82 mmol) was added and this mixture was refluxed overnight. After cooling, the mixture was filtered and the filtrate concentrated *in vacuo* to yield a brownish residue. Purification by column chromatography (SiO_2, CH_2Cl_2–*n*-hexane 1 : 1) yielded **16** (1.95 g, 3.03 mmol, 51%) as a light yellow powder. Product **16** was obtained in a *cis* : *trans* ratio of 1 : 1. A small fraction of **16** was purified by column chromatography (SiO_2, CH_2Cl_2–*n*-hexane 1 : 1) to separate the *cis* and *trans* isomer ($R_f = 0.28$ and $R_f = 0.37$). The two isomers were readily separated, however, no *cis* : *trans* assignment was performed. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) ($R_f = 0.28$) δ 7.81 (dd, J = 8.1, 1.7 Hz, 2H, 3-H), 7.60 (d, J = 8.1 Hz, 2H, 4-H), 7.54 (dd, J = 7.8, 1.5 Hz, 2H, 5-H), 7.42 (d, J = 1.7 Hz, 2H, 1-H), 7.17 (ddd, J = 7.8, 7.3, 1.5 Hz, 2H, 6-H), 6.93 (ddd, J = 7.8, 7.3, 1.2 Hz, 2H, 7-H), 6.84 (dd, J = 7.8, 1.2 Hz, 2H, 8-H), 4.81 (m, 2H, $OCH(CH_2)_2$), 1.72–0.84 (m, 20H, *c*-hexyl); ^{13}C NMR (50 MHz, CDCl$_3$, 25 °C) δ 163.46 (s), 139.62 (s), 133.66 (s), 133.32 (s), 133.32 (s), 131.93 (s), 129.14 (d), 128.43 (d), 126.93 (s), 126.42 (d), 125.68 (d), 125.59 (d), 125.39 (d), 71.26 (d), 29.86 (t), 29.71 (t), 23.94 (t), 21.86 (t); ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C) ($R_f = 0.37$) δ 7.83 (dd, $J = 8.0$, 1.7 Hz, 2H, 3-H), 7.59 (d, $J = 8.0$ Hz, 2H, 4-H), 7.52 (dd, $J = 7.8$, 1.5 Hz, 2H, 5-H), 7.50 (d, $J = 1.7$ Hz, 2H, 1-H), 7.14 (ddd, $J = 7.8$, 7.3, 1.5 Hz, 2H, 6-H), 6.91 (ddd, $J = 1.2$, 7.3, 7.8 Hz, 2H, 7-H), 6.78 (dd, $J = 7.8$, 1.2 Hz, 2H, 8-H), 4.86 (m, 2H, OC*H*(CH$_2$)$_2$), 1.73–1.27 (m, 20H, *c*-hexyl); ^{13}C NMR (50 MHz, CDCl$_3$, 25 °C) δ 163.63 (s), 139.67 (s), 133.84 (s), 133.35 (s), 133.20 (s), 131.94 (s), 129.42 (d), 128.10 (d), 126.96 (s), 126.25 (d), 125.79 (d), 125.55 (d), 125.46 (d), 124.66 (d), 71.12 (d), 29.81 (t), 29.66 (t), 23.95 (t), 21.68 (t).

***cis–trans*-{9-[2-(Hydroxymethyl)-9*H*-thioxanthen-9-ylidene]-9*H*-thioxanthen-2-yl}-methanol 17 and *cis–trans*-2-(chloromethyl)-9-[2-(chloromethyl)-9*H*-thioxanthen-9-ylidene]-9*H*-thioxanthene 18**

Under nitrogen, LiAlH$_4$ (0.60 g, 15.81 mmol) was suspended in diethyl ether (20 mL). Substrate **16** (1.50 g of *cis–trans* mixture, 2.33 mmol) was added and this mixture was stirred overnight at room temperature. To quench the reaction 2 M HCl (aq.) (20 mL) was added and the two layers were transferred to a separatory funnel. CH$_2$Cl$_2$ (100 mL) was added and the water and organic layer were separated. The water layer was extracted twice with CH$_2$Cl$_2$ (75 mL) and the combined organic layers were washed three times with 2 M HCl (aq.), dried (Na$_2$SO$_4$), and concentrated *in vacuo* to yield *cis–trans*-**17** as a yellow powder. The product was obtained as a *cis–trans* 1 : 1 mixture and the NMR data of one of the isomers are given here. ^{1}H NMR (200 MHz, DMSO-d_6, 25 °C) δ 7.65 (dd, $J = 7.7$, 1.1 Hz, 2H, 5-H), 7.60 (d, $J = 8.1$ Hz, 2H, 4-H), 7.27–7.18 (m, 4H, 3-,6-H), 6.98 (ddd, $J = 7.7$, 7.3, 1.1 Hz, 2H, 7-H), 6.69 (d, $J = 7.7$ Hz, 2H, 8-H), 6.63 (d, 2H, $J = 1.5$ Hz, 1-H), 5.00 (t, $J = 5.5$ Hz, 2H, OH), 4.14 (d, $J = 5.5$ Hz, 4H, PhC*H*$_2$OH). Without further purification **17** was added to pure SOCl$_2$ (15 mL). After 3 h of stirring at room temperature, water was added carefully to quench the reaction. The water layer was extracted twice with CH$_2$Cl$_2$ (50 mL) and the combined organic layers were washed twice with water (50 mL), dried (Na$_2$SO$_4$), and concentrated *in vacuo* to yield an orange residue. Purification by column chromatography (SiO$_2$, *n*-hexane–CH$_2$Cl$_2$ 1 : 1, $R_f = 0.65$) gave **18** (0.80 g, 1.64 mmol, 70%) as a *cis–trans* 1 : 1 mixture. NMR data of one of the isomers is given here. ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C) δ 7.52 (d, $J = 8.1$ Hz, 2H), 7.51 (d, $J = 8.1$ Hz, 2H), 7.14 (d, $J = 8.1$ Hz, 2H), 7.13 (dd, $J = 8.1$, 7.7 Hz, 2H), 6.92 (dd, $J = 7.7$, 7.7 Hz, 2H), 6.81–6.74 (m, 4H), 4.21 (AB, $J_{AB} = 11.7$ Hz, $\Delta\nu = 9.4$ Hz, 4H, PhCH$_2$Cl); ^{13}C NMR (50 MHz, CDCl$_3$, 25 °C) δ 134.47 (s), 134.16 (s), 133.91 (s), 133.82 (s), 133.76 (s), 131.87 (s), 128.55 (d), 128.3 (d), 125.98 (d), 125.68 (d), 125.61 (d), 125.49 (d), 124.43 (d), 44.27 (t); HRMS calcd for C$_{28}$H$_{18}$Cl$_2$S$_2$: 488.0227; found: 488.0213.

15,18,21,24,27,30-Hexaoxa-9,36-dithiaheptacyclo-[30.10.2.2^{10,13}.0^{2,11}.0^{3,8}.0^{35,43}.0^{37,42}]hexatetraconta-1,3,5,7,10(46),11,13(45),32,34,37,39,41,43-tridecaene 5

Under nitrogen, KO*t*Bu (276 mg, 2.46 mmol) was suspended in toluene (100 mL) and this mixture was heated to 90 °C. A solution of **18** (300 mg, 0.61 mmol) and pentaethylene glycol (146 mg, 0.61 mmol) in toluene (100 mL) was added very slowly (3 drops per min). After addition, the reaction mixture was stirred for 90 h at 90 °C. After cooling, the solvent was removed under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (15 mL) and 2 M HCl (aq.) (15 mL). After separation of the two layers the water layer was extracted with CH$_2$Cl$_2$ (15 mL) and the combined organic layers were washed with of 2 M HCl (aq.) (10 mL), dried (Na$_2$SO$_4$), and concentrated *in vacuo* to yield a brown residue. Purification by column chromatography (Al$_2$O$_3$, CH$_2$Cl$_2$–acetone 40 : 1 changing to CH$_2$Cl$_2$–acetone 8 : 1, $R_f = 0.60$ with CH$_2$Cl$_2$–acetone 40 : 1 as eluent) gave pure racemic **5** (58 mg, 8.9×10^{-2} mmol, 15%). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C) δ 7.51 (d, $J = 7.7$ Hz, 2H, 7-,38-H), 7.50 (d, $J = 8.1$ Hz, 2H, 34-,46-H), 7.15 (d, $J = 8.1$ Hz, 2H, 33-,45-H), 7.10 (dd, $J = 7.7$, 7.3 Hz, 2H, 6-,39-H), 6.89 (dd, $J = 7.7$, 7.3 Hz, 2H, 5-,40-H), 6.79 (d, $J = 7.7$ Hz, 2H, 4-,41-H), 6.73 (s, 2H, 12-,44-H), 4.23 (AB, $J_{AB} = 12.5$ Hz, $\Delta\nu = 19.4$ Hz, 4H, 14-,31-H), 3.70–3.58 (m, 12H, 19–26-H), 3.54 (AB part of ABXY system, apparent as ddd, $J = 22.7$, 10.3, 5.5 Hz, 4H, OCH$_2$, 17-,28-H), 3.31 (XY part of ABXY system, apparent as ddd, $J = 22.7$, 10.3, 5.5 Hz, 4H, OCH$_2$, 16-,29-H); ^{13}C NMR (50 MHz, CDCl$_3$, 25 °C) δ 134.98 (s), 134.49 (s), 134.33 (s), 134.12 (s), 133.25 (s), 132.03 (s), 128.20 (d), 127.32 (d), 125.66 (d), 125.63 (d), 125.23 (d), 124.64 (d), 124.22 (d), 70.86 (t), 69.45 (t), 69.35 (t), 69.27 (t), 69.15 (t), 67.80 (t); HRMS calcd for C$_{38}$H$_{38}$O$_6$S$_2$: 654.2110; found: 654.2124.

2-[2-(2-{2-[(9-Oxo-9*H*-thioxanthen-2-yl)oxy]ethoxy}-ethoxy)-ethoxy]-9*H*-thioxanthen-9-one 20

Under a nitrogen atmosphere, 2-hydroxy-9*H*-thioxanthen-9-one **19**[13,14] (2.55 g, 11.18 mmol), K$_2$CO$_3$ (1.82 g, 13.18 mmol), and triethylene glycol di-*p*-tosylate (2.41 g, 5.27 mmol) were suspended/dissolved in DMF (250 mL). This mixture was refluxed for 72 h and after cooling, the solvent was removed under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (150 mL) and 2 M HCl (aq.) (150 mL). After separation of the two layers the water layer was extracted with CH$_2$Cl$_2$ (50 mL). The combined organic layers were washed (twice with 2 M HCl (aq.)), dried Na$_2$SO$_4$, and concentrated *in vacuo* to yield a yellow residue. Purification by column chromatography (Al$_2$O$_3$ (5% water), CHCl$_3$–acetone 30 : 1) and subsequent recrystallization from CH$_2$Cl$_2$ yielded pure **20** (1.50 g, 2.63 mmol, 50%). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C) δ 8.55 (dd, $J = 8.4$, 1.1 Hz, 2H, 8-H), 7.99 (d, $J = 2.6$ Hz, 2H, 1-H), 7.56–7.48 (m, 4H), 7.43–7.38 (m, 4H), 7.23 (dd, $J = 8.8$, 2.6 Hz, 2H, 3-H), 4.22 (t, $J = 4.4$ Hz, 4H, CH$_2$C*H*$_2$OPh), 3.89 (t, $J = 4.4$ Hz, 4H, OC*H*$_2$CH$_2$OPh), 3.75 (s, 4H, C*H*$_2$OCH$_2$CH$_2$OPh); ^{13}C NMR (50 MHz, CDCl$_3$, 25 °C) δ 178.00 (s), 156.01 (s), 135.95 (s), 130.42 (d), 128.57 (s), 128.29 (d), 127.72 (s), 127.01 (s), 125.74 (d), 124.50 (d), 124.41 (d), 121.55 (d), 109.64 (d), 69.42 (t), 68.15 (t), 66.29 (t); HRMS calcd for C$_{32}$H$_{26}$O$_6$S$_2$: 570.1171; found: 570.1172.

14,17,20,23-Tetraoxa-9,28-dithiaheptacyclo-[22.10.2.2^{10,13}.0^{2,11}.0^{3,8}.0^{27,35}.0^{29,34}]octatriaconta-1,3,5,7,10(38),11,13(37),24,26,29,31,33,35-tridecaene 6

Under nitrogen, **20** (1.40 g, 2.46 mmol) was refluxed overnight in oxalyl dichloride (40 mL). After cooling, the excess of oxalyl dichloride was removed under reduced pressure and the residue was dissolved in freshly distilled *p*-xylene (300 mL, from sodium). Activated Cu-bronze[11] (3.50 g, 55.00 mmol) was added and this mixture was refluxed overnight. After cooling, the mixture was filtered and the filtrate was concentrated *in vacuo* to yield a brown residue. Purification by column chromatography (Al_2O_3 (3% water), CH_2Cl_2, $R_f = 0.58$) yielded pure racemic **6** (0.70 g, 1.30 mmol, 53%). ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 7.50 (d, $J = 7.7$ Hz, 2H, 7-,30-H), 7.42 (d, $J = 8.4$ Hz, 2H, 26-,38-H), 7.10 (dd, $J = 7.7$, 1.5 Hz, 2H, 6-,31-H), 6.87 (dd, $J = 7.7$, 1.5 Hz, 2H, 5-,32-H), 6.81 (dd, $J = 8.4$, 2.9 Hz, 2H, 25-,37-H), 6.76 (d, $J = 7.7$ Hz, 2H, 4-,33-H), 6.44 (d, $J = 2.9$ Hz, 2H, 12-,36-H), 3.95–3.88 (m, 2H, 15-,22-H), 3.80–3.59 (m, 10H, CH_2O, 15–22-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 155.75 (s), 155.75 (s), 135.37 (s), 134.43 (s), 134.43 (s), 132.15 (s), 128.45 (d), 126.62 (d), 125.47 (d), 125.22 (d), 124.14 (d), 114.00 (d), 113.68 (d), 69.64 (t), 68.16 (t), 66.78 (t); HRMS calcd for $C_{32}H_{26}O_4S_2$: 538.1272; found: 538.1260.

7-Hydroxy-9-oxo-9*H*-thioxanthene-2-carboxylic acid 22

Under nitrogen, 7-methoxy-9-oxo-9*H*-thioxanthene-2-carboxylic acid **21**[6] (16.00 g, 55.94 mmol) was suspended in CH_2Cl_2 (200 mL). The mixture was cooled to 0 °C and BBr_3 (25.0 mL, 0.26 mol) was added carefully. The reaction temperature was allowed to raise to room temperature and the mixture was stirred overnight. The mixture was cooled to 0 °C and ice was added carefully to quench the reaction. The suspension was filtered and the residue dissolved in 2.5 M NaOH (aq.) (600 mL) during 1 h of vigorous stirring. The resulting suspension was filtered and the filtrate was acidified to pH = 1 with concentrated HCl (aq.). The product precipitated as a yellow solid and after filtration the product was washed 4 times with hot water. The product was dried at 100 °C in air to yield **22** (11.20 g, 41.17 mmol, 74%) as a brown powder. ^1H NMR (200 MHz, DMSO-d_6, 25 °C) δ 10.20 (br, 1H, COOH), 8.96 (d, $J = 1.8$ Hz, 1H, 1-H), 8.14 (dd, $J = 8.4$, 1.8 Hz, 1H, 3-H), 7.91 (d, $J = 8.4$ Hz, 1H, 4-H), 7.83 (d, $J = 2.9$ Hz, 1H, 8-H), 7.71 (d, $J = 8.4$ Hz, 1H, 5-H), 7.27 (dd, $J = 8.4$, 2.9 Hz, 1H, 6-H), 3.50 (br, 1H, OH); ^{13}C NMR (50 MHz, DMSO-d_6, 25 °C) δ 178.50 (s), 166.72 (s), 157.19 (s), 141.86 (s), 132.04 (d), 130.59 (d), 129.70 (s), 128.69 (s), 128.23 (d), 127.63 (s), 127.11 (d), 125.70 (s), 123.16 (d), 113.64 (d); HRMS calcd for $C_{14}H_8O_4S$: 272.0143; found: 272.0157.

Cyclohexyl 7-hydroxy-9-oxo-9*H*-thioxanthene-2-carboxylate 23

Substrate **22** (11.00 g, 40.44 mmol) was suspended in cyclohexanol (100 mL). Concentrated H_2SO_4 (1 mL) was added and this mixture was refluxed overnight. After cooling, *n*-hexane (80 mL) was added and this mixture was stirred for 5 min at room temperature and then allowed to stand overnight at −12 °C. The orange precipitate was collected on a glass filter and thoroughly washed with hot *n*-hexane to get rid of cyclohexanol. After drying, pure **23** (11.78 g, 33.28 mmol, 82%) was obtained as a yellow powder. ^1H NMR (200 MHz, DMSO-d_6, 25 °C) δ 10.22 (br, 1H, OH), 8.93 (d, $J = 1.8$ Hz, 1H, 1-H), 8.13 (dd, $J = 8.6$, 1.8 Hz, 1H, 3-H), 7.91 (d, $J = 8.6$ Hz, 1H, 4-H), 7.82 (d, $J = 2.9$ Hz, 1H, 8-H), 7.70 (d, $J = 8.8$ Hz, 1H, 5-H), 7.26 (dd, $J = 8.8$, 2.9 Hz, 1H, 6-H), 4.98–4.92 (m, 1H, OC*H*(CH_2)$_2$), 1.87–1.32 (m, 10H, CH_2, *c*-hexyl); ^{13}C NMR (50 MHz, DMSO-d_6, 25 °C) δ 178.34 (s), 164.36 (s), 157.16 (s), 142.17 (s), 131.64 (d), 130.26 (d), 129.66 (s), 128.28 (d), 127.95 (s), 127.59 (s), 127.21 (d), 125.69 (s), 123.13 (d), 113.57 (d), 73.23 (d), 31.21 (t), 25.08 (t), 23.34 (t); HRMS calcd for $C_{20}H_{18}O_4S$: 354.0926; found: 354.0945.

Cyclohexyl 7-(2-{2-[2-({7-[(cyclohexyloxy)carbonyl]-9-oxo-9*H*-thioxanthen-2-yl}oxy)-ethoxy]-ethoxy}ethoxy)-9-oxo-9*H*-thioxanthene-2-carboxylate 24

Under nitrogen, **23** (6.40 g, 18.07 mmol), Cs_2CO_3 (8.60 g, 26.39 mmol), and triethylene glycol di-*p*-tosylate (3.30 g, 7.20 mmol) were dissolved/suspended in DMF (250 mL). This mixture was stirred at 65 °C for 80 h. After cooling, the solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (150 mL). The organic layer was washed with 2 M HCl (aq.) (2 × 100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield a brown residue. Purification by column chromatography (Al_2O_3 (4.5% water), CH_2Cl_2–acetone 40 : 1, $R_f = 0.72$) yielded **24** (3.74 g, 4.55 mmol, 63%) as a yellow powder. ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 9.09 (d, $J = 1.7$ Hz, 2H, 1-H), 8.07 (dd, $J = 8.6$, 1.7 Hz, 2H, 3-H), 7.88 (d, $J = 2.7$ Hz, 2H, 8-H), 7.44 (d, $J = 8.6$ Hz, 2H, 4-H), 7.31 (d, $J = 9.0$ Hz, 2H, 5-H), 7.17 (dd, $J = 9.0$, 2.7 Hz, 2H, 6-H), 5.06–4.97 (m, 2H, OC*H*(CH_2)$_2$), 4.18 (t, $J = 3.9$ Hz, 4H, CH_2C*H*$_2$OPh), 3.88 (t, $J = 3.9$ Hz, 4H, OC*H*$_2$$CH_2$OPh), 3.76 (s, 4H, C*H*$_2OCH_2CH_2$OPh), 1.98–1.35 (m, 20H, CH_2, *c*-hexyl); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 178.71 (s), 164.84 (s), 157.66 (s), 141.79 (s), 131.64 (d), 131.11 (d), 129.70 (s), 128.51 (s), 128.13 (s), 127.80 (s), 127.09 (d), 125.87 (d), 122.95 (d), 111.03 (d), 73.47 (d), 70.69 (t), 69.37 (t), 67.53 (t), 31.39 (t), 25.16 (t), 23.49 (t); HRMS calcd for $C_{46}H_{46}O_{10}S_2$: 822.2532; found: 822.2535.

Cyclohexyl 7-[2-(2-{2-[2-({7-[(cyclohexyloxy)carbonyl]-9-oxo-9*H*-thioxanthen-2-yl}oxy)-ethoxy]-ethoxy}ethoxy)ethoxy]-9-oxo-9*H*-thioxanthene-2-carboxylate 25

See procedure for **24**. **23** (6.40 g, 18.07 mmol), Cs_2CO_3 (10.00 g, 30.69 mmol), and tetraethylene glycol di-*p*-tosylate (3.65 g, 7.27 mmol) yielded **25** (4.29 g, 4.95 mmol, 68%) as a yellow powder after purification by column chromatography (Al_2O_3 (4.5% water), CH_2Cl_2–acetone 20 : 1). ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 9.15 (d, $J = 1.8$ Hz, 2H, 1-H), 8.13 (dd, $J = 8.4$, 1.8 Hz, 2H, 3-H), 7.96 (d, $J = 2.9$ Hz, 2H, 8-H), 7.52 (d, $J = 8.4$ Hz, 2H, 4-H), 7.40 (d, $J = 8.6$ Hz, 2H, 5-H), 7.24 (dd, $J = 8.6$, 2.9 Hz, 2H, 6-H), 5.06–4.97 (m, 2H, OC*H*(CH_2)$_2$), 4.20 (t, $J = 4.4$ Hz, 4H, CH_2C*H*$_2$OPh), 3.87 (t, $J = 4.4$ Hz, 4H, OC*H*$_2$$CH_2$OPh), 3.72–3.67 (m, 8H, OC*H*$_2$C*H*$_2$OCH_2CH_2OPh), 2.12–1.32 (m, 20H, CH_2, *c*-hexyl); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 178.82 (s), 164.85 (s), 157.76 (s), 141.81 (s), 131.71 (d), 131.18 (d), 129.82 (s), 128.60 (s), 128.18 (s), 127.91 (s), 127.15 (d), 125.92 (d), 123.03 (d), 111.12 (d), 73.47 (d), 70.63 (t), 70.52 (t), 69.32 (t), 67.64 (t), 31.39 (t), 25.16 (t), 23.48 (t); HRMS calcd for $C_{48}H_{50}O_{11}S_2$: 866.2794; found: 866.2795.

Dicyclohexyl 14,17,20,23-tetraoxa-9,28-dithiaheptacyclo-[$22.10.2.2^{10,13}.0^{2,11}.0^{3,8}.0^{27,35}.0^{29,34}$]octa-triaconta-1,3,5,7,10(38),11,13(37),24,26,29,31,33,35-tridecaene-5,32-dicarboxylate 28

Under nitrogen, **24** (3.00 g, 3.65 mmol) was refluxed in oxalyl dichloride (70 mL) for 24 h. The excess of oxalyl dichloride was removed under reduced pressure and the brown residue (crude *gem*-dichloride **26**) was dissolved in freshly distilled *p*-xylene (500 mL, from sodium). Activated Cu-bronze[11] (4.50 g, 70.82 mmol) was added and this mixture was refluxed overnight. After cooling, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to yield a brown residue. Purification by column chromatography (silica gel, CH_2Cl_2–*n*-hexane–acetone 60 : 15 : 2, R_f = 0.38) gave pure **28** (1.72 g, 2.18 mmol, 60%) as a yellowish powder. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 7.76 (dd, J = 8.0, 1.5 Hz, 2H, 6-,31-H), 7.55 (d, J = 8.0 Hz, 2H, 7-,30-H), 7.39 (d, J = 8.8 Hz, 2H, 26-,38-H), 7.36 (d, J = 1.5 Hz, 2H, 4-,33-H), 6.82 (dd, J = 8.8, 2.6 Hz, 2H, 25-,37-H), 6.43 (d, J = 2.6 Hz, 2H, 12-,36-H), 4.82–4.74 (m, 2H, OC*H*(CH_2)$_2$), 3.93–3.88 (m, 2H, OCH_2, 15-,22-H), 3.74–3.55 (m, 10H, OCH_2, 15-,22-H), 1.68–1.32 (m, 20H, CH_2, *c*-hexyl); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 164.81 (s), 157.41 (s), 141.39 (s), 135.88 (s), 134.65 (s), 133.34 (s), 130.70 (d), 128.15 (s), 127.97 (d), 127.77 (d), 126.62 (d), 125.87 (s), 115.41 (d), 115.41 (d), 72.46 (d), 70.98 (t), 69.45 (t), 68.07 (t), 31.08 (t), 30.94 (t), 25.20 (t), 23.04 (t); HRMS calcd for $C_{46}H_{46}O_8S_2$: 790.2634; found: 790.2620.

Dicyclohexyl 14,17,20,23,26-pentaoxa-9,31-dithiaheptacyclo-[25.10.2.2^{10,13}.0^{2,11}.0^{3,8}.0^{30,38}.0^{32,37}]hentetraconta-1,3,5,7,10(41),11,13(40),27,29,32,34,36,38-tridecaene-5,35-dicarboxylate 29

See procedure for **28**. Oxalyl dichloride (70 mL), **25** (3.50 g, 4.04 mmol), *p*-xylene (650 mL, from sodium), and activated Cu-bronze[11] (6.50 g, 102.14 mmol) gave pure **29** (2.40 g, 2.88 mmol, 71%) as a yellowish powder after purification by column chromatography (silica gel, CH_2Cl_2–acetone 30 : 1, R_f = 0.33); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 7.77 (dd, J = 8.0, 1.8 Hz, 2H, 6-,34-H), 7.56 (d, J = 8.4 Hz, 2H, 29-,41-H), 7.37 (d, J = 8.0 Hz, 2H, 7-,33-H), 7.36 (d, J = 1.8 Hz, 2H, 4-,36-H), 6.82 (dd, J = 8.4, 2.6 Hz, 2H, 28-,40-H), 6.40 (d, J = 2.6 Hz, 2H, 12-,39-H), 4.84–4.74 (m, 2H, OC*H*(CH_2)$_2$), 3.81–3.47 (m, 16H, CH_2O, 15-,25-H), 1.68–1.32 (m, 20H, CH_2, *c*-hexyl); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 164.80 (s), 157.36 (s), 141.32 (s), 135.84 (s), 134.48 (s), 133.32 (s), 130.56 (d), 128.19 (s), 127.98 (d), 127.78 (d), 126.64 (d), 126.03 (s), 116.25 (d), 114.63 (d), 72.48 (d), 70.71 (t), 70.63 (t), 68.98 (t), 67.97 (t), 31.07 (t), 30.93 (t), 25.18 (t), 23.04 (t); HRMS calcd for $C_{48}H_{50}O_9S_2$: 834.2896; found: 834.2869.

[32-(Hydroxymethyl)-14,17,20,23-tetraoxa-9,28-dithiaheptacyclo-[22.10.2.2^{10,13}.0^{2,11}.0^{3,8}.0^{27,35}.0^{29,34}]octatriaconta-1,3,5,7,10(38),11,13(37),24,26,29,31,33,35-tridecaen-5-yl]methanol 30

Under nitrogen, $LiAlH_4$ (0.40 g, 10.54 mmol) was suspended in diethyl ether (100 mL). Substrate **28** (2.50 g, 3.16 mmol) was added and this suspension was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (150 mL) and 2 M HCl (aq.) (100 mL). After separation of the two layers the water layer was extracted once with CH_2Cl_2 (50 mL) and the combined organic layers were washed (2 M HCl (aq.) (100 mL)), dried (Na_2SO_4), and concentrated *in vacuo* to yield a yellow residue. The residue was washed with *n*-hexane to remove cyclohexanol. Pure **30** (1.80 g, 3.01 mmol, 95%) was obtained as a yellow powder. ^{1}H NMR (200 MHz, DMSO-d_6, 25 °C) δ 7.53 (d, J = 2.6 Hz, 2H, 7-,30-H), 7.51 (d, J = 2.6 Hz, 2H, 6-,31-H), 7.15 (d, J = 8.4 Hz, 2H, 26-,38-H), 6.88 (dd, J = 8.4, 2.6 Hz, 2H, 25-,37-H), 6.52 (s, 2H, 4-,33-H), 6.26 (d, J = 2.6 Hz, 2H, 12-,36-H), 4.91 (t, J = 5.1 Hz, 2H, OH), 4.07 (d, J = 5.1 Hz, 4H, PhC*H*$_2$OH), 4.03–3.98 (m, 2H, OCH_2, 15-,22-H), 3.60–3.48 (m, 10H, OCH_2, 15-,22-H); Due to low solubility no ^{13}C NMR was recorded. HRMS calcd for $C_{34}H_{30}O_6S_2$: 598.1483; found: 598.1472.

[35-(Hydroxymethyl)-14,17,20,23,26-pentaoxa-9,31-dithiaheptacyclo[25.10.2.2^{10,13}.0^{2,11}.0^{3,8}.0^{30,38}.0^{32,37}]hentetraconta-1,3,5,7,10(41),11,13(40),27,29,32,34,36,38-tridecaen-5-yl]-methanol 31

See procedure for **30**. $LiAlH_4$ (0.45 g, 11.86 mmol) and **29** (2.40 g, 2.88 mmol) yielded pure **31** (1.70 g, 2.65 mmol, 92%) as a yellow powder. ^{1}H NMR (200 MHz, DMSO-d_6, 25 °C) δ 7.59 (d, J = 2.6 Hz, 2H, 29-,41-H), 7.57 (d, J = 2.6 Hz, 2H, 28-,40-H), 7.20 (d, J = 8.4 Hz, 2H, 7-,33-H), 6.95 (dd, J = 8.4, 2.6 Hz, 2H, 6-,34-H), 6.60 (s, 2H, 12-,39-H), 6.28 (d, J = 2.6 Hz, 2H, 4-,36-H), 4.97 (t, J = 5.1 Hz, 2H, OH), 4.10 (d, J = 5.1 Hz, 4H, PhC*H*$_2$OH), 3.96–3.80 (m, 2H, OCH_2, 15-,25-H), 3.65–3.40 (m, 14H, OCH_2, 15-,25-H); ^{13}C NMR (50 MHz, DMSO-d_6, 25 °C) δ 154.33 (s), 137.57 (s), 133.73 (s), 131.93 (s), 130.54 (s), 130.41 (s), 125.64 (d), 125.01 (d), 124.07 (d), 123.52 (s), 122.87 (d), 113.08 (d), 111.87 (d), 67.54 (t), 67.49 (t), 65.79 (t), 65.16 (t), 59.72 (t); HRMS calcd for $C_{36}H_{34}O_7S_2$: 642.1746; found: 642.1748.

5,32-Bis(chloromethyl)-14,17,20,23-tetraoxa-9,28-dithiaheptacyclo[22.10.2.2^{10,13}.0^{2,11}.0^{3,8}.0^{27,35}.0^{29,34}]octatriaconta-1,3,5,7,10(38),11,13(37),24,26,29,31,33,35-tridecaene 32

Under nitrogen, **30** (1.48 g, 2.47 mmol) was added in one portion to pure $SOCl_2$ (15 mL). The deep red solution was stirred for 3 h at room temperature. Water was added carefully to quench the reaction and subsequently CH_2Cl_2 (50 mL) was added. The water layer and organic layer were separated and the water layer was once extracted with CH_2Cl_2 (15 mL). The combined organic layers were washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield pure **32** (1.33 g, 2.10 mmol, 85%) as a yellow powder. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 7.50 (d, J = 8.0 Hz, 2H, 7-,30-H), 7.41 (d, J = 8.6 Hz, 2H, 26-,38-H), 7.13 (dd, J = 8.0, 1.8 Hz, 2H, 6-,31-H), 6.82 (dd, J = 8.6, 2.9 Hz, 2H, 25-,37-H), 6.69 (d, J = 1.8 Hz, 2H, 4-,33-H), 6.42 (d, J = 2.9 Hz, 2H, 12-,36-H), 4.20 (AB, J_{AB} = 11.5 Hz, $\Delta\nu$ = 7.4 Hz, 4H, $PhCH_2Cl$), 3.95–3.89 (m, 2H, OCH_2, 15-,22-H), 3.79–3.58 (m, 10H, OCH_2, 15-,22-H);^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 157.28 (s), 136.19 (s), 135.45 (s), 135.10 (s), 133.31 (s), 130.06 (d), 128.01 (d), 127.22 (d), 127.09 (d), 126.40 (s), 115.36 (d), 115.24 (t), 70.99 (t), 69.46 (t), 68.09 (t), 45.56 (t); HRMS calcd for $C_{34}H_{28}O_4S_2Cl_2$: 634.0806; found: 634.0804.

5,35-Bis(chloromethyl)-14,17,20,23,26-pentaoxa-9,31-dithiaheptacyclo[25.10.2.2^{10,13}.0^{2,11}.0^{3,8}.0^{30,38}.0^{32,37}]hentetraconta-1,3,5,7,10(41),11,13(40),27,29,32,34,36,38-tridecaene 33

See procedure for **32**. $SOCl_2$ (15 mL) and **31** (1.52 g, 2.37 mmol) yielded pure **33** (1.44 g, 2.12 mmol, 89%) as a yellow powder. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 7.50 (d, J = 8.0 Hz, 2H, 7-,33-H), 7.41 (d, J = 8.8 Hz, 2H, 29-,41-H), 7.13 (dd, J = 8.0, 1.8 Hz, 2H, 6-,34-H), 6.82 (dd, J = 8.8, 2.6 Hz, 2H, 28-,40-H), 6.71 (d, J = 1.8 Hz, 2H, 4-,36-H), 6.39 (d, J = 2.6 Hz, 2H, 12-,39-H), 4.21 (AB, J_{AB} = 11.4 Hz, $\Delta\nu$ = 11.4 Hz, 4H, $PhCH_2Cl$), 3.83–3.49 (m, 16H, OCH_2, 15-,25-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 157.23 (s), 136.14 (s), 136.14 (s), 135.31 (s), 135.11 (s), 133.28 (s), 129.94 (d), 128.03 (d), 127.26 (d), 127.09 (d), 126.53 (s), 116.04

(d), 114.63 (d), 70.74 (t), 70.64 (t), 69.01 (t), 68.00 (t), 45.53 (t); HRMS calcd for $C_{34}H_{28}O_4S_2Cl_2$: 678.1068; found: 678.1076.

8,11,14,17,30,33,36,39,42,45-Decaoxa-52,54-dithiaoctacyclo-[45.3.1.1^{3,7}.1^{4,50}.1^{18,22}.1^{21,25}.1^{24,28}.0^{2,23}]hexapentaconta-1(51),2(23),3(56),4,6,18,20,22(55),24(53),25,27,47,49-tridecaene 9

Under nitrogen, KO*t*Bu (274 mg, 2.44 mmol) was suspended in toluene (80 mL). The mixture was heated to 90 °C. At a very slow rate (3 drops per min) a solution of **32** (384 mg, 0.61 mmol) and pentaethylene glycol (144 mg, 0.60 mmol) in toluene (160 mL) was added. After addition, the mixture was stirred for another 60 h at 90 °C. After cooling, the solvent was removed to yield an orange residue which was dissolved in CH_2Cl_2 (40 mL). The organic layer was washed (4 × 25 mL 1 M HCl (aq.)), dried (Na_2SO_4), and concentrated *in vacuo.* The residue was purified by column chromatography (Al_2O_3, (3% water), CH_2Cl_2–acetone 20 : 1, $R_f = 0.30$) to yield pure racemic **9** (139 mg, 0.17 mmol, 28%) as an orange solid. λ_{max} (*n*-hexane–*i*-propanol 9 : 1)/nm 214 (ε/dm^3 mol^{-1} cm^{-1} 68400), 236 (33500), 271 (17100), 368 (7400); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.47 (d, J = 8.1 Hz, 2H, 26-,49-H), 7.40 (d, J = 8.8 Hz, 2H, 5-,20-H), 7.13 (dd, J = 8.1, 1.1 Hz, 2H, 27-,48-H), 6.79 (dd, J = 8.8, 2.6 Hz, 2H, 6-,19-H), 6.69 (d, J = 1.1 Hz, 2H, 51-,53-H), 6.41 (d, J = 2.6 Hz, 2H, 55-,56-H), 4.20 (AB, J_{AB} = 12.8 Hz, $\Delta\nu$ = 22.2 Hz, 4H, $PhCH_2O$, 29-,46-H), 3.90 (ddd, J = 11.6, 5.2, 2.1 Hz, 2H, OCH_2, 9-,16-H), 3.77–3.57 (m, 22H, OCH_2, 9–16-H, 34–41-H), 3.54 (AB part of ABXY system, 2 × ddd, J = 10.6, 6.0, 4.1 Hz, 4H, OCH_2, 32-,43-H), 3.27 (XY part of ABXY system, 2 × ddd, J = 10.6, 6.0, 4.1 Hz, 4H, OCH_2, 31-,44-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 157.29 (s), 136.80 (s), 136.45 (s), 136.04 (s), 135.20 (s), 133.70 (s), 129.03 (d), 128.23 (d), 127.11 (d), 127.01 (s), 126.27 (d), 115.42 (d), 115.17 (d), 72.41 (t), 71.21 (t), 71.05 (t), 70.94 (t), 70.86 (t), 70.73 (t), 69.71 (t), 69.29 (t), 68.30 (t); HRMS calcd for $C_{44}H_{48}O_{10}S_2$: 800.2688; found: 800.2696. Chiral HPLC analysis; Daicel OD column, *n*-hexane–*i*-propanol 9 : 1, retention times: 13 (*P*) and 19 min (*M*).

8,11,14,17,20,33,36,39,42,45,48-Undecaoxa-55,57-dithiaoctacyclo[48.3.1.1^{3,7}.1^{4,53}.1^{21,25}.1^{24,28}.1^{27,31}.0^{2,26}]nonapentaconta-1(54),2(26),3(59),4,6,21,23,25(58),27(56),28,30,50,52-tridecaene 10

See procedure for **9**. Substrate **33** (1.44 g, 2.12 mmol), pentaethylene glycol (0.51 g, 2.52 mmol), KO*t*Bu (0.95 g, 8.47 mmol), and toluene (150 mL) yielded pure racemic **10** (0.61 g, 0.72 mmol, 34%) as an orange solid after purification by column chromatography (Al_2O_3, (5% water), starting with CH_2Cl_2–acetone 20 : 1 (R_f = 0.10) changing to CH_2Cl_2–acetone 10 : 1) λ_{max} (*n*-hexane)/nm 236 (ε/dm^3 mol^{-1} cm^{-1} 36000), 271 (15700), 364 (6800); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.45 (d, J = 7.7 Hz, 2H, 29-,52-H), 7.37 (d, J = 8.4 Hz, 2H, 5-,23-H), 7.11 (dd, J = 7.7, 1.5 Hz, 2H, 30-,51-H), 6.76 (dd, J = 8.4, 2.6 Hz, 2H, 6-,22-H), 6.67 (d, J = 1.5 Hz, 2H, 54-,56-H), 6.35 (d, J = 2.6 Hz, 2H, 58-,59-H), 4.18 (AB, J_{AB} = 12.6 Hz, $\Delta\nu$ = 20.4 Hz, 4H, $PhCH_2O$, 32-,49-H), 3.78 ddd, J = 10.4, 5.1, 2.9 Hz, 2H, OCH_2, 9-,19-H), 3.75–3.60 (m, 26H, OCH_2, 9–19-H, 44 – 37-H), 3.55 (AB part of ABXY system, 2 × ddd, J = 10.6, 6.0, 4.1 Hz, 4H, OCH_2, 35-,46-H), 3.28 (XY part of ABXY system, 2 × ddd, J = 10.6, 6.0, 4.1 Hz, 4H, OCH_2, 34-,47-H); ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ 157.14 (s), 136.65 (s), 136.36 (s), 135.66 (s), 134.95 (s), 133.49 (s), 128.61 (d), 127.90 (d), 127.02 (s), 126.81 (d), 125.96 (d), 115.70 (d), 114.79 (d), 72.21 (t), 70.82 (t), 70.82 (t), 70.76 (t), 70.76 (t), 70.68 (t), 70.52 (t), 69.25 (t), 69.25 (t), 68.13 (t); HRMS calcd for $C_{46}H_{52}O_{12}S_2$: 844.2950; found: 844.2948. Chiral HPLC analysis; Daicel AD column, *n*-hexane–*i*-propanol–chloroform 8 : 1 : 1, retention times: 15 (*P*) and 23 min (*M*).

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