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Steric Control of Oxidation Selectivity in Macrocyclic Phosphine Oxide-Dithioethers

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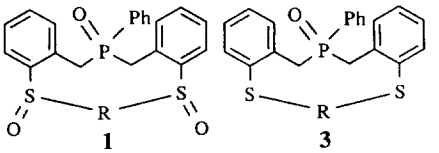
Abstract: Macrocyclic phosphine oxide-disulfoxides **1a** - **e** and **2a** - **e** were synthesized by oxidation of the corresponding dithioethers with *m*-CPBA. Four stereoisomers are possible, but a single stereoisomer was isolated as the major product in each case. This paper describes the structural characterization of several trioxides as well as studies designed to determine the origin of oxidation selectivity.

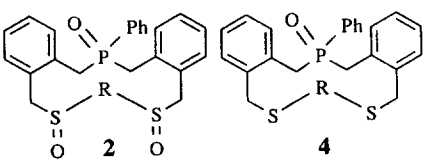
INTRODUCTION

Phosphine oxide and sulfoxide groups are attractive components for the design of artificial receptors, because of the strong local dipoles of these units. We have shown, for example, that macrocyclic phosphine oxide-disulfoxide **2e** can bind cations, anions, and cation-anion pairs.[1] Modification of **2e** generated a selective receptor for hexosammonium ions.[1c] There have been relatively few other reports of receptors containing multiple phosphine oxide and/or sulfoxide groups, however, perhaps because of difficulties associated with stereochemical control.[2] Here we present a detailed examination of the stereoselective formation of 10 macrocyclic phosphine oxide-disulfoxides, **1a** - **e** and **2a** - **e**.



1 **3**

a R= $-(CH_2)_3-$ **b** R= $-(CH_2)_4-$
c R= $-(CH_2)_5-$ **d** R= *m*-xylylene
e R= *o* -xylylene

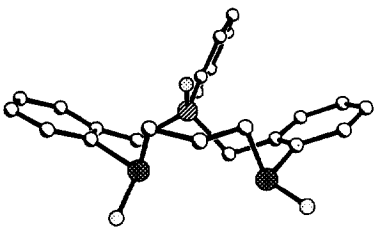


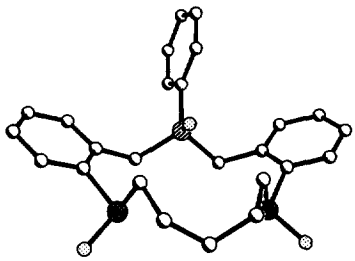
2 **4**

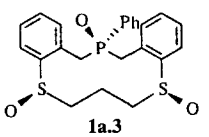
a R= $-(CH_2)_2-$ **b** R= $-(CH_2)_3-$
c R= $-(CH_2)_4-$ **d** R= *m*-xylylene
e R= *o* -xylylene

RESULTS AND DISCUSSION

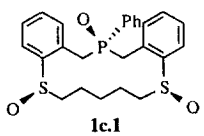
Phosphine oxide-dithioether macrocycles **3a** - **e** and **4a** - **e** were synthesized as described previously.[1b,1] Four stereoisomeric trioxides could result from oxidation of **3a** - **e** and **4a** - **e**, two meso compounds and a dl-pair of enantiomers. Reaction of these dithioethers with *m*-CPBA, however, provided one stereoisomer as the major product in each case. The ^{1}H NMR spectrum of each major product was symmetrical, suggesting that these were meso compounds. X-ray crystal structures were determined for six of these macrocycles, **1a.3**, **1c.1**, **1d.1**, **1e.1**, **2d.3** and **2e.3**, confirming meso stereochemistry in all cases (Figure 1). (The number after the period refers to the order of HPLC elution, as described below.)



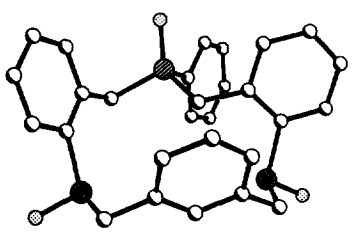


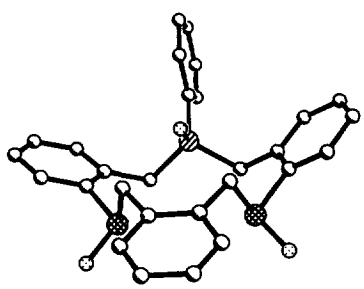


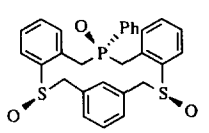
1a.3



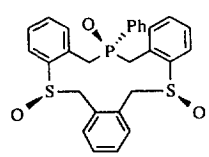
1c.1







1d.1



1e.1

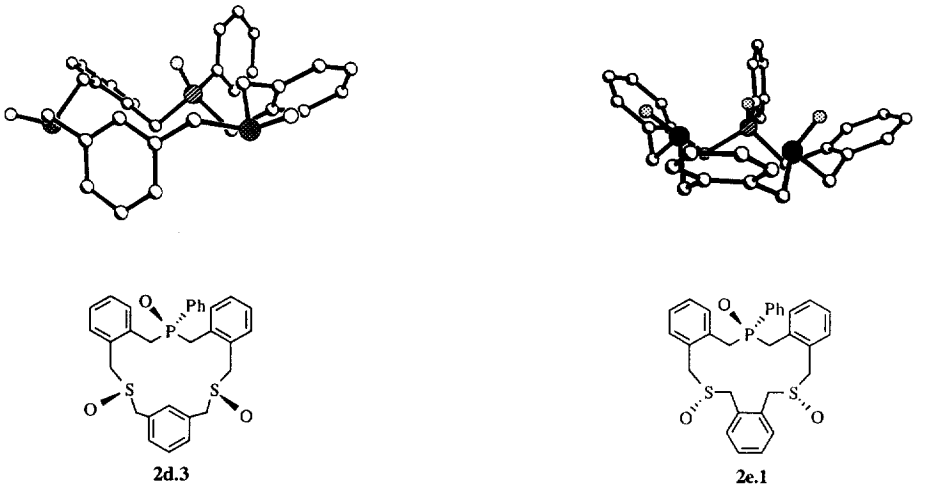


Figure 1. X-ray crystal structures of phosphine oxide-disulfoxides.

The stereoselectivity observed in the oxidation of dithioethers **3a** - **e** and **4a** - **e** suggested that approach of the oxidant to the sulfur atoms was constrained in some way. Additionally, the crystal structures of **1a.3**, **1c.1**, **1d.1**, and **1e.1** revealed a remarkable structural consistency: in each case an analogous meso stereoisomer was the major product. Thus, oxidation proceeded at the pro-S face of S1 and at the pro-R face of S2 (Figure 2). The conformational similarities observed among macrocycles **1a.3**, **1c.1**, **1d.1**, and **1e.1** suggested that the constraint affecting oxidant approach is similar for all dithioethers in family **3**.

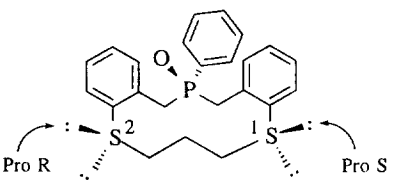
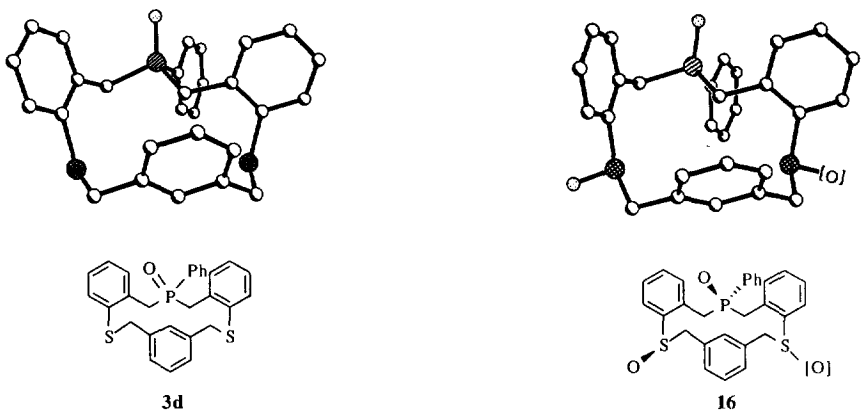


Figure 2. The pro-S and pro-R faces of sulfur atoms 1 and 2 of phosphine oxide-dithioether **3a**.

Two distinct (but not exclusive) explanations can be imagined for the oxidation selectivity observed with *m*-CPBA: a hydrogen bond directing effect, or a steric directing effect. A hydrogen bond directing effect would occur if hydrogen bond formation between the oxidant and the phosphine oxide resulted in preferential approach of the oxidant to one face of each sulfur atom. Stereoselective epoxidation of cyclic alkenes

containing a neighboring sulfoxide has previously been attributed to a hydrogen bond directing effect.[4] Alternatively, a steric directing effect would occur if the conformational preferences of the dithioether macrocycles hinder the accessibility of one face of each sulfur atom. It has been proposed that the conformational preferences of macrocyclic alkenes lead to stereoselective epoxidations.[5] Additionally, the oxidation of small ring thioethers with H_2O_2 and *m*-CPBA has been shown to proceed preferentially on the less sterically hindered side of the sulfur atom.[6]

If the oxidation of the dithioethers is controlled by steric directing effects, the macrocycles must display well defined conformational preferences in their dithioether and monothioether monosulfoxide forms. We were able to obtain crystal structures of dithioethers **3a**, **c**, **d** and **e**. Unfortunately, attempted crystallizations of dithioethers **4a** - **e** were unsuccessful, and we therefore focused our attention on the structures and reactivity of dithioethers **3a** - **e**.



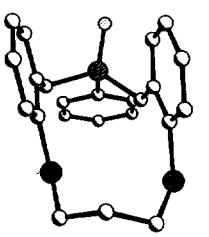
3d **16**

Figure 3. X-ray crystal structures of **3d** and **16**. Compare to crystal structure of **1d.1** shown in Figure 1.

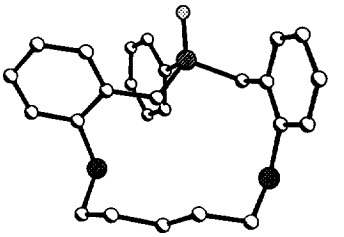
Comparison of the crystal structures for dithioether **3d**, monothioether monosulfoxide **16** (Figure 3; the notation [O] for structure **16** represents the presence of 8% disulfoxide **1d.1** in the crystal) and disulfoxide **1d.1** (Figure 1) suggests that there are indeed strong and analogous conformational preferences among these macrocycles. The macrocyclic backbone has a similar conformation in all three oxidation states, and these structures may serve as "snap shots" along the oxidation pathway. Oxidation appears to occur at the most exposed face of each sulfur atom of **3d**, i.e., the pro-S face of S1 and the pro-R face of S2, to yield the major trioxide stereoisomer **1d.1**.

The crystal structures of dithioethers **3a**, **3c** and **3e** also reveal that one face of each sulfur atom is buried in the center of the macrocycle (Figure 4). Oxidation of the exposed face of each sulfur atom, again the pro-S face of S1 and the pro-R face of S2, would yield the phosphine oxide-disulfoxide stereoisomers, **1a.3**, **1c.1**, and **1e.1** that are isolated as the major products after reaction of the thioethers with *m*-CPBA. While the solid state structures probably do not represent the only conformations available to these macrocycles, it seems likely that these conformations are important in solution. To the degree that the solid state conformations of

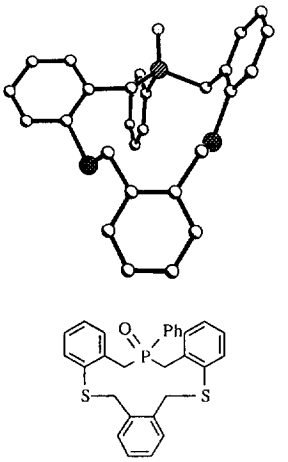
these macrocycles give us clues as to the dominant conformations in solution, the x-ray structures are consistent with the hypothesis that the oxidation preferences of dithioethers **3a** - **e** result from the conformational preferences of each macrocycle. The selectivities described here are also consistent with the solution and solid state behavior previously observed for dithioether **17**, which yields only the dl trioxide upon treatment with H_2O_2 in $AcOH/CH_2Cl_2$.[7]



3a

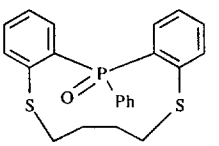


3c



3e

Figure 4. X-ray crystal structures of **3a**, **c** and **e**.



17

To test the influence of hydrogen bonding versus steric directing effects in solution, we examined the oxidation of dithioethers **3a** - **e** under a variety of conditions (Table 1). Initial oxidations were performed in methylene chloride with *m*-CPBA; under these conditions either hydrogen bond or steric directing effects may operate. Oxidation selectivity was also examined using *m*-CPBA in MeOH, and H_2O_2 in AcOH/CH_2Cl_2. The use of protic solvents was expected to diminish hydrogen bonding between oxidant and phosphine oxide, allowing us to probe for the influence of hydrogen bond-mediated directing effects.

	Ratio of Stereoisomers		
Dithioether	*m*-CPBA/CH_2Cl_2	*m*-CPBA/MeOH	H_2O_2
3a	21:2:77	21:4:75	22:2:76
3b	23:75:2	32:63:5	42:54:4
3c	85:15:<1	75:25:<1	77:21:2
3d	77:3:20	85:<1:15	92:<1:8
3e	100:<1:<1	98:2:<1	100:<1:<1

Table 1. Oxidation selectivity as determined by HPLC. Least:middle:most retained stereoisomer on xylose-silica eluting with 1 vol% (**3b**, **3d**), 2 vol% (**3e**), or 2.5 vol% (**3a**) MeOH in CH_2Cl_2, or on silica gel eluting with 3 vol% (**3c**) MeOH in CH_2Cl_2.

Previously, we had designed HPLC columns containing carbohydrates covalently linked to silica gel to aid in the screening of potential carbohydrate receptors.[1a,3] The columns were prepared by attaching the desired aldopentose to 5μ silica gel via an eight carbon linker, as shown for "xylose-silica" in Figure 5. The xylose-silica gel stationary phase efficiently separated the trioxide stereoisomers of **1a**, **b**, **d** and **e**, giving three well resolved peaks representing the two meso stereoisomers and the dl pair of enatiomers. The trioxide stereoisomers of **1c** were separable on an ordinary silica gel stationary phase.

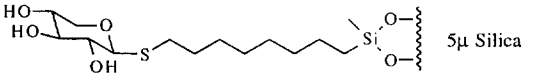


Figure 5. Chemical structure of xylose-silica.

The oxidation behavior of dithioethers **3a** - **e** is consistent with the operation of a steric directing effect. Reaction of **3a** with *m*-CPBA in CH_2Cl_2 gave a crude mixture of the least, middle and most polar phosphine oxide-disulfoxide stereoisomers (**1a.1**, **1a.2** and **1a.3**) in a ratio of 21:2:77. Oxidation of **3a** with *m*-CPBA in MeOH, or with H_2O_2 in AcOH/CH_2Cl_2, yielded the same three major products, in similar ratios (Table 1). These results suggest that oxidation of **3a** is controlled by the conformational preferences of the macrocycle, rather than by hydrogen bonding between the phosphine oxide and the oxidant.

The oxidation behavior of macrocycles **3b** - **e** was consistent with the conclusion that hydrogen bond directing effects are not dominant in this family of macrocycles. The trioxide stereoisomer ratio from dithioether **3e** does not show a strong dependence on the nature of the oxidizing solution, which is similar to the behavior of **3a**. The oxidation behavior of dithioethers **3b** - **d**, on the other hand, reveals a modest dependence on the presence or absence of hydrogen bonding solvents. Despite the small decrease in selectivity in protic vs. aprotic solvents, however, the oxidations of **3b** - **d** provided the same meso stereoisomer as the major product under all conditions, confirming that steric directing effects are dominant for these macrocycles.

Interpretation of the results in Table 1 depends upon assignment of observed HPLC peaks to different phosphine oxide-disulfoxide stereoisomers. That the same major products were observed by HPLC under different oxidation conditions was consistent with our structural assignment. Further evidence for these assignments was obtained from light-induced sulfoxide epimerization studies. It had previously been shown that optically active aryl sulfoxides may be photochemically epimerized.[8] Irradiation of **1a.3** in 10% MeOH in benzene resulted in a mixture of three major products by HPLC, which corresponded to the three products obtained upon oxidation, but in a ratio of 44:12:44 after complete photo-equilibration (Figure 6). The irradiation was repeated on a preparative scale, and the least polar material (**1a.1**) was isolated by semi-prep HPLC and shown to be a stereoisomer of **1a** by NMR, FTIR and MS. The ^{1}H and ^{13}C NMR data for **1a.1** show that the molecule is not symmetric suggesting that this compound is the dl pair of enantiomers. In a similar manner trioxide **1c.1** was irradiated to give the same three materials observed from the oxidation experiments but in a 32:49:19 ratio. The most polar stereoisomer (**1c.3**) was isolated after semi-prep HPLC, and the structure was confirmed by NMR, FTIR and MS. The NMR data shows that the molecule is not symmetric suggesting that this is the dl pair of enantiomers. Unfortunately, we were not able to perform irradiation experiments with **1d.1** and **1e.1** because these materials decomposed under the conditions of the experiment.[8a] A minor stereoisomer of **1b** was isolated in an alternative manner. Oxidation of **3b** with H_2O_2 gave a mixture of the three major products in a ratio of 42:54:4. The least polar material, **1b.1**, was isolated by chromatography and was shown to be a stereoisomer of **1b**.

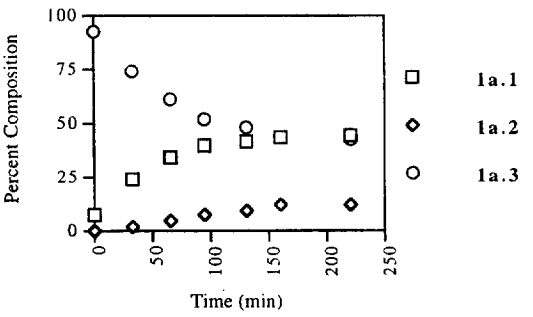


Figure 6 Stereoisomer composition as a function of irradiation time. Irradiation was performed as described in the experimental section.

Conclusion. We have described the stereoselective synthesis of 10 macrocyclic phosphine oxide-disulfoxides. Careful examination of the oxidation behavior of dithioether macrocycles **3a - e** suggests that selectivity results from steric directing effects. The conformations adopted by **3a**, **3c**, **3d**, **3e** and **16** in the solid state provide further support for the operation of a steric directing effect; one face of each sulfur atom is exposed, and oxidation of this face would lead to the meso stereoisomer isolated as the major oxidation product in each case. These findings suggest that macrocycles containing multiple phosphine oxide and /or sulfoxide groups in stereochemically defined arrays may be generally available.

EXPERIMENTAL SECTION

Instrumentation. NMR spectra were recorded on Bruker WP-200, WP-270, AM-300 and AM-500 spectrometers. Proton chemical shifts were referenced to internal tetramethylsilane (TMS), carbon shifts were referenced to the carbon resonance of solvent ($CDCl_3$ @ 77.0 ppm), and phosphorus shifts were referenced to neat phosphoric acid (@ 0.00 PPM). Infrared spectra were obtained on a Nicolet 740 spectrometer. High-resolution electron-impact mass spectra (HR-MS) were obtained on a Kratos MS-25 spectrometer. Fast atom bombardment (FAB) mass spectra were recorded on a VG Analytical ZAB-2F. Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Photochemical experiments were performed with a 450 watt medium intensity lamp using a pyrex filter. Semi-prep xylose silica columns were packed using an Alltech column packer in a manner analogous to that previously reported.[3b] HPLC was performed using a Shimadzu C-R5A integrator, SCL-6A controller, SPD-6A UV detector and LC-6A pump. X-ray crystallography was performed on Siemens R3m/V, P4 or P3f diffractometers. The crystal structures were solved using SHELXS-86 and refined using SHELXL-92.[9]

Oxidations. Specific examples are given for the oxidation of macrocycle **3a**, the other dithioethers were oxidized in a similar manner. *m-CPBA/CH_2Cl_2*: To thioether **3a** (0.016 g, 0.039 mmol) in CH_2Cl_2 (1.5 mL) at 0° C was added dropwise *m*-CPBA (0.015 g, 0.086 mmol) in CH_2Cl_2 (1.5 mL). The mixture was allowed to warm to room temp and oxidation was monitored by HPLC as described below. Reactions run on a preparative scale were warmed to room temp overnight and were treated as discussed below. *H_2O_2/AcOH*: To thioether **3a** (0.034 g, 0.083 mmol) in a 1:1 mixture of AcOH/CH_2Cl_2 (3 mL) at 0° C was added H_2O_2 (32% aqueous solution, 0.18 mmol). The mixture was allowed to warm to room temperature and oxidation was monitored by HPLC as described below. *m-CPBA/MeOH*: To thioether **3a** (0.019 g, 0.046 mmol) in MeOH (2 mL) at 0° C was added dropwise *m*-CPBA (0.018 g, 0.102 mmol) in MeOH (2 mL). The mixture was allowed to warm to room temperature and oxidation was monitored by HPLC as described below.

Photochemical Studies. Samples of each macrocycle were prepared in 10 vol% MeOH in benzene to give a final macrocycle concentration of 2 mM. Photolysis was continued until equilibrium had been reach as determined by HPLC.

HPLC. Chromatography was performed using a xylose-silica or an unmodified silica gel column eluting with a mobile phase consisting of MeOH in CH_2Cl_2 as described in Table 1. Samples from oxidation and irradiation experiments were prepared in the following manner: Oxidations with *m*-CPBA: 0.2 mL of the solution was removed and added to 3 mL $CHCl_3$. The chloroform solution was washed with 1 N NaOH (1 x 1 mL) and saturated sodium bicarbonate (1 x 1 mL), the chloroform was dried with $MgSO_4$ and filtered. 10 µl

of this material was injected onto the HPLC. Oxidations with H_2O_2: 0.2 mL of the solution was removed and solvents were removed on a vacuum rotovap. The residue was dissolved in 3 mL $CHCl_3$ and 10 μL of this material was injected onto the HPLC. Photolysis experiments: The lamp was shut off and 0.1 mL of the solution was removed and diluted to 1.5 mL with $CHCl_3$. 10 μL of the sample was injected onto the HPLC.

X-Ray Crystallography. X-ray suitable crystals of **3d**, **1a.3**, **2e.3**, and **16** were prepared by vapor diffusion of hexane into a $CHCl_3$ solution of each macrocycle. Crystals of **1e.1** were obtained by vapor diffusion of isooctane into a dichloroethane solution of the macrocycle. Macrocycles **3a**, **3c**, and **3e** gave x-ray quality crystals after slow evaporation of an EtOAc solution of each. **1d.1** and **2d.3** were crystallized by slow evaporation of each from a 1:1 mixture of MeOH:EtOAc and **1c.1** was obtained from a 1:1 mixture of $CHCl_3$:MeOH.

3,4;10,11-Bisbenzo-1-phenyl-1-phospha-5,9-dithiacyclododecane-1,5,9-trioxide (1a.3): Oxidation of **3a** (0.10 g, 0.00024 mol) with *m*-CPBA (0.092 g, 0.00054 mol) was performed as described above. $CHCl_3$ (40 mL) was added to the reaction mixture, and the $CHCl_3$ layer was washed with 3 mL 1 N NaOH. The $CHCl_3$ layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by SiO_2 chromatography eluting with 5% MeOH in chloroform to yield 0.087 g of a single meso stereoisomer of the desired product as a white solid (81%): mp: 258 °C (Decomposition, recryst. from MeOH/$CHCl_3$); ^1H ($CDCl_3$, 300 MHz) δ 8.00 (d, J = 7.7 Hz, 2H, Ar-*H*), 7.23-7.68 (m, 9H, Ar-*H*), 6.66 (d, J = 7.7 Hz, 2H, Ar-*H*), 4.37 (dd, $^2J_{HH}$ = 15.0 Hz, $^2J_{HP}$ = 15.0 Hz, 2H, PC*H*$_2$Ar), 3.82 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 12.1 Hz, 2H, SC*H*$_2$CH$_2$C*H*$_2$S), 3.56 (dd, $^2J_{HH}$ = 14.8 Hz, $^2J_{HP}$ = 6.9 Hz, 2H, PC*H*$_2$Ar), 3.20 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 5.6 Hz, 2H, SC*H*$_2$CH$_2$C*H*$_2$S), 3.00 (dt, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 12.2 Hz, 1H, SCH$_2$C*H*$_2$CH$_2$S), 2.46 (dt, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 6.1 Hz, 1H, SCH$_2$C*H*$_2$CH$_2$S); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 146.2, (d, J = 4.5 Hz), 132.5, 131.7, 131.3, 130.0-130.6 (m), 129.9, 129.8, 129.0, 128.9, 125.2, 60.5, 36.9 (d, J = 62.3 Hz), 19.5; ^{31}P NMR (2% $CDOD_3$/$CDCl_3$, 109.4 MHz) δ 34.5; FTIR (KBr) 2918, 2853, 2588, 2507, 1703, 1407, 1286, 1239, 1200, 1188, 1026, 996, 982, 819, 709 cm^{-1}; Anal. Calcd for $C_{23}H_{23}O_3PS_2$: C, 62.42; H, 5.24; Found: C, 62.10, H, 5.22; LRMS (FAB) *m/z* observed: 443.2, calculated for $C_{23}H_{24}O_3PS_2$: 443.1.

3,4;10,11-Bisbenzo-1-phenyl-1-phospha-5,9-dithiacyclododecane-1,5,9-trioxide (1a.1): Isolable quantities of the least polar stereoisomer of **1a** could be obtained by photochemical irradiation. Irradiation of a solution of 0.045 g **1a.3** in 50 mL 10 vol% MeOH in benzene, the solution was degassed by passing a stream of N_2 through the solution, for 1 h 40 min resulted in a solution containing the three stereoisomers in a ratio of 35:5:60. The least retained stereoisomer was obtained by SiO_2 chromatography eluting with 4% MeOH/$CHCl_3$ to give 0.01 g of the desired material. The mixture of the two more strongly retained isomers was again photolyzed in 10% MeOH/benzene for 2.5 h to yield an additional 0.016 g of the least polar stereoisomer. By HPLC the combined samples contained approximately 85 % of the least polar trioxide. The desired material was obtained as 0.015 g (33%) of a white solid after purification by semi-prep HPLC using a xylose silica column eluting with 2.5 % MeOH/CH_2Cl_2: ^1H ($CDCl_3$, 300 MHz) δ 7.73-7.87 (m, 3H, Ar-*H*), 7.54-7.65 (m, 4H, Ar-*H*), 7.18-7.44 (m, 6H, Ar-*H*), 4.46 (br s, 1H), 3.83 (dd, J = 15.3, 11.8 Hz, 1H), 3.62-3.75 (m, 3H), 3.38-3.49 (m, 1H), 3.35 (dd, J = 15.4, 12.6 Hz, 1H), 3.15 (dt, J = 14.0, 5.6 Hz, 1H), 2.44-2.61 (m, 1H, SCH$_2$C*H*$_2$), 2.23-2.35 (m, 1H, SCH$_2$C*H*$_2$); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 142.7 (d, J = 5.4 Hz), 126.9-132.9 (m), 125.0, 56.2, 33.8 (d, J = 61.0 Hz), 29.7, 18.4; ^{31}P NMR ($CDCl_3$, 121.4 MHz) δ 33.7; LRMS (FAB) *m/z* observed: 443.1, calculated for $C_{23}H_{24}O_3PS_2$: 443.1.

3,4;11,12-Bisbenzo-1-phenyl-1-phospha-5,10-dithiacyclotridecane-1,5,10-trioxide (1b.2): Oxidation of **3b** (0.10 g, 0.00024 mol) with *m*-CPBA (0.089 g, 0.00052 mol) was performed as described above. $CHCl_3$ (30 mL) was added to the reaction mixture, and the $CHCl_3$ layer was washed with 3 mL 1 N NaOH. The aqueous phase was washed with $CHCl_3$ (3x10 mL), and the combined $CHCl_3$ layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by SiO_2 chromatography (4% MeOH/$CHCl_3$) to give 0.055 g (51%) of the desired product, a meso stereoisomer by NMR, as a white solid: mp: 277 °C (Decomposition, recryst. from MeOH/$CHCl_3$); ^{1}H ($CDCl_3$, 300 MHz) δ 8.02 (d, J = 8.1 Hz, 2H, Ar-*H*), 7.60-7.74 (m, 5H, Ar-*H*), 7.41-7.48 (m, 2H, Ar-*H*), 7.17 (t, J = 7.7 Hz, 2H, Ar-*H*), 6.42 (d, J = 7.3 Hz, 2H, Ar-*H*), 4.08-4.15 (m, 2H, SCH_2CH$_2$), 4.00 (dd, $^2J_{HH}$ = 14.8 Hz, $^2J_{HP}$ = 14.8 Hz, 2H, ArCH_2P), 3.59 (dd, $^2J_{HH}$ = 14.6 Hz, $^2J_{HP}$ = 7.3 Hz, 2H, ArCH_2P), 2.78-2.87 (m, 2H, SCH_2CH$_2$), 2.53-2.70 (m, 2H, SCH$_2$CH_2), 2.04-2.22 (m, 2H, SCH$_2$CH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 144.6 (d, J = 3.8 Hz), 132.9 (d, J = 2.6 Hz), 130.8-131.3 (m), 128.3-129.3 (m), 125.2, 54.6, 35.0 (d, J = 62.3 Hz), 22.3; ^{31}P NMR (2% $CDOD_3$/$CDCl_3$, 109.4 MHz) δ 33.8; FTIR (KBr) 2930, 2920, 1470, 1442, 1227, 1196, 1188, 1154, 1059, 1033, 784, 752 cm^{-1}; Anal. Calcd for $C_{24}H_{25}O_3PS_2$: C, 63.14; H, 5.52; Found: C, 62.83; H, 5.46; LRMS (FAB) *m/z* observed: 457.1, calculated for $C_{24}H_{26}O_3PS_2$: 457.1.

3,4;11,12-Bisbenzo-1-phenyl-1-phospha-5,10-dithiacyclotridecane-1,5,10-trioxide (1b.1): It was shown by HPLC that oxidation of **3b** by H_2O_2 in 1:1 AcOH:CH_2Cl_2 gave a significant proportion of what was presumed to be the least polar stereoisomer on SiO_2. Thioether **3b** (0.100 g, 0.236 mmol) in 6 mL of a 1:1 mixture of AcOH:CH_2Cl_2 under N_2 at 0 °C was oxidized by the addition of 0.055 mL H_2O_2 (0.52 mmol). The reaction mixture was warmed to room temperature and was stirred for 24 h. The solvents were removed under vacuum and the crude products were purified by SiO_2 chromatography eluting with 3% MeOH/$CHCl_3$ to give 0.015 g (18%) of the least polar stereoisomer: mp: 210 °C (Decomposition, recryst. from $CHCl_3$/hexanes); ^{1}H ($CDCl_3$, 300 MHz) δ 7.92 (d, J = 7.8 Hz, 2H, Ar-*H*), 7.28-7.79 (m, 8H, Ar-*H*), 7.12 (t, J = 7.8 Hz, 2H, Ar-*H*), 6.32 (d, J = 7.8 Hz, 1H, Ar-*H*), 4.48 (br s, 1 H), 3.85 (br m, 2H), 3.66 (t, J = 14.2 Hz, 1H), 3.26 (br dd, J = 13.8, 6.4 Hz, 1H), 2.95 (br s, 1H), 2.75-2.80 (m, 1H), 2.43 (br m, 1H), 2.14-2.18 (m, 1H), 1.84-1.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 144.7, 141.6, 132.6, 132.5, 131.4, 131.0, 130.9, 130.8, 130.6, 129.4, 129.1, 129.0, 128.5, 128.0, 127.4, 125.2, 56.0, 51.5, 33.2, 21.6, 17.5; ^{31}P NMR ($CDCl_3$, 121.4 MHz) δ 34.9; FTIR (KBr) 2958, 2940, 2910, 1472, 1438, 1404, 1196, 1114, 1025, 1006, 768, 749 cm^{-1}; LRMS (FAB) *m/z* observed: 457.1, calculated for $C_{24}H_{26}O_3PS_2$: 457.1.

3,4;12,13-Bisbenzo-1-phenyl-1-phospha-5,11-dithiacyclotetradecane-1,5,11-trioxide (1c.1): Oxidation of **3c** (0.10 g, 0.00023 mol) with *m*-CPBA (0.086 g, 0.00050 mol) was performed as described above. CH_2Cl_2 (30 mL) was added to the reaction mixture, and the CH_2Cl_2 layer was washed with 4 mL 1 N NaOH. The aqueous phase was washed with CH_2Cl_2 (3x10 mL), and the combined CH_2Cl_2 layers were dried with $MgSO_4$, filtered and concentrated to an off white solid. The crude product was purified by SiO_2 (5% MeOH/$CHCl_3$) to give 0.080 g (75%) of the desired product, a meso stereoisomer by ^{1}H NMR, as a white solid: mp: 257 °C (Decomposition, recryst. from $CHCl_3$/hexanes); ^{1}H ($CDCl_3$ 200 MHz) δ 8.01 (d, J = 7.7 Hz, 2H, Ar-*H*), 7.53-7.69 (m, 5H, Ar-*H*), 7.40-7.46 (m, 2H, Ar-*H*), 7.17 (t, J = 7.7 Hz, 2H, Ar-*H*), 6.51 (d, J = 7.7 Hz, 2H, Ar-*H*), 4.11 (dd, $^2J_{HH}$ = 15.0 Hz, $^2J_{HP}$ = 15.0 Hz, 2H. ArCH_2P), 3.77-3.86 (m, 2H, SCH_2CH$_2$), 3.54 (dd, $^2J_{HH}$ = 14.6 Hz, $^2J_{HP}$ = 7.7 Hz, 2H, ArCH_2P), 2.92-2.99 (m, 2H, SCH_2CH$_2$), 2.14-2.30 (m, 3H, SCH$_2$CH_2CH_2CH_2CH$_2$S), 1.83-1.96 (m, 3H, SCH$_2$CH_2CH_2CH_2CH$_2$S); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ

144.4 (d, J = 5.1 Hz), 132.7, 131.0-131.3 (m), 130.0 (d, J = 8.9 Hz), 128.9-129.6 (m), 128.3, 125.6, 56.8, 34.5 (d, J = 62.3 Hz), 24.8, 22.5; ^{31}P NMR (2% $CDOD_3/CDCl_3$, 109.4 MHz) δ 34.6; FTIR (KBr) 2924, 2911, 2850, 1442, 1228, 1197, 1155, 1116, 1032, 1026, 830, 748 cm^{-1}; Anal. Calcd for $C_{25}H_{27}O_3PS_2$: C, 63.81; H, 5.78; Found: C, 63.50, H, 5.70; LRMS (FAB) *m/z* observed: 471.2, calculated for $C_{25}H_{28}O_3PS_2$: 471.1, observed: 455.2, calculated for M+1-O: 455.1.

3,4;12,13-Bisbenzo-1-phenyl-1-phospha-5,11-dithiacyclotetradecane-1,5,11-trioxide (1c.3): Photolysis of **1c.1** (0.15 g) in 10% MeOH/benzene (100 mL), the solution was degassed prior to photolysis by passing a stream of N_2 through the solution for 30 min, for 8 h gave a mixture of stereoisomers by HPLC. The least polar stereoisomer was isolated by semi-prep HPLC on xylose silica. The desired material was isolated as 0.009 g of a white solid: mp: 178 °C (Decomposition, recryst. from MeOH/benzene/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80-7.87 (m, 2H, Ar-*H*), 7.54-7.67 (m, 5H, Ar-*H*), 7.37 (t, J = 7.7 Hz, 2H, Ar-*H*), 7.26 (t, J = 7.1 Hz, 2H, Ar-*H*), 6.93 (d, J = 6.9 Hz, 2H, Ar-*H*), 4.30 (br s, 2H), 3.45-3.61 (m, 4H), 3.84-3.99 (m, 2H), 1.84-2.07 (m, 4H, SCH_2CH_2), 1.64-1.69 (m, 2H, $SCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 142.8, 132.5, 132.3, 132.0, 131.3, 131.2, 130.7, 130.4, 128.9 (d, J = 12.6 Hz), 127.9, 126.3, 54.7, 33.6, 29.7, 24.5, 19.8; ^{31}P NMR ($CDCl_3$, 109.4 MHz) δ 34.4; FTIR (KBr) 3055, 2937, 2932, 2906, 2857, 1475, 1438, 1202, 1114, 1063, 1025, 763, 759; LRMS (FAB) *m/z* observed: 470.9, calculated for $C_{25}H_{28}O_3PS_2$: 471.1.

3,4;7,9;12,13-Trisbenzo-1-phenyl-1-phospha-5,11-dithiacyclotetradecane-1,5,11-trioxide (1d.1): Oxidation of **3d** (0.11 g, 0.00023 mol) with *m*-CPBA (0.088 g, 0.00051 mol) was performed as described above. $CHCl_3$ (40 mL) was added to the reaction mixture, and the $CHCl_3$ layer was washed with 3 mL 1 N NaOH. The aqueous phase was washed with $CHCl_3$ (3x10 mL), and the combined $CHCl_3$ layers were dried with $MgSO_4$, filtered and concentrated to an off white solid. The crude product was purified by SiO_2 chromatography (5% MeOH/$CHCl_3$) to give 0.084 g (72%) of a meso stereoisomer of the desired product as a white solid: mp: 255 °C (Decomposition, recrystallized from MeOH/benzene/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, J = 7.7 Hz, 2H, Ar-*H*), 7.37-7.71 (m, 12H, Ar-*H*), 6.83 (t, J = 7.7 Hz, 1H, Ar-*H*), 6.39 (dd, J = 7.5 Hz, J=1.7 Hz, 2H, Ar-*H*), 4.11, 4.66 (AB_q, $^2J_{HH}$ = 11.9 Hz, 4H, SCH_2Ar), 2.47-2.67 (m, 4H, $ArCH_2P$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 139.3 (d, J = 6.4 Hz), 132.9, 132.0-132.7 (m), 130.7, 130.6, 129.9, 129.8, 129.4, 129.0, 128.8, 128.6 (d, J = 12.1 Hz), 124.7, 61.4, 30.4 (d, J = 64.2 Hz); ^{31}P NMR (2% $CDOD_3/CDCl_3$, 109.4 MHz) δ 32.5; FTIR (KBr) 2962, 2917, 2902, 1473, 1438, 1203, 1146, 1063, 1041, 840, 825, 760, 716 cm^{-1}; LRMS (FAB) *m/z* observed: 505.1, calculated for $C_{28}H_{26}O_3PS_2$: 505.1; observed: 489.1, calculated for M+1-O: 489.1.

3,4;7,8;11,12-Trisbenzo-1-phenyl-1-phospha-5,10-dithiacyclotridecane-1,5,10-trioxide (1e.1): Oxidation of **3e** (0.105 g, 0.00022 mol) with *m*-CPBA (0.084 g, 0.00049 mol) was performed as described above. $CHCl_3$ (40 mL) was added to the reaction mixture, and the $CHCl_3$ layer was washed with 3 mL 1 N NaOH. The aqueous phase was washed with $CHCl_3$ (3x10 mL), and the combined $CHCl_3$ layers were dried with $MgSO_4$, filtered and concentrated to an off white solid. The crude product was purified by SiO_2 chromatography (4% MeOH/$CHCl_3$) to give 0.097 g (87%) of a meso stereoisomer of the desired product as a white solid: mp: 272 °C (Decomposition); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J = 8.1 Hz, 2H, Ar-*H*), 7.45-7.71 (m, 11H, Ar-*H*), 7.21-7.26 (m, 2H, Ar-*H*), 6.56 (d, J = 7.7 Hz, 2H, Ar-*H*), 4.24 (t, J = 15.2 Hz, 2H,), 3.97, 5.34 (AB_q, $^2J_{HH}$ = 12.9 Hz, 4H, SCH_2Ar), 3.55 (dd, $^2J_{HH}$ = 14.6 Hz, $^2J_{HP}$ = 6.1 Hz, 2H, $ArCH_2P$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 145.7, 133.9, 132.8, 131.5, 131.2, 130.8 (d, J = 9.5 Hz), 130.3 (d, J = 10.2

Hz), 128.7-129.6 (m), 128.4, 125.9, 59.7, 35.8 (d, J = 62.3 Hz); ^{31}P NMR (2% $CDOD_3/CDCl_3$, 109.4 MHz) δ 33.7; FTIR (KBr) 3051, 2991, 2979, 2910, 1472, 1441, 1408, 1224, 1187, 1143, 1116, 849, 826 cm^{-1}; Anal. Calcd for $C_{28}H_{25}O_3PS_2$: C, 66.65; H, 4.92; Found: C, 67.00, H, 5.03; LRMS (FAB) *m/z* observed: 505.1, calculated for $C_{28}H_{26}O_3PS_2$: 505.1; observed: 489.1, calculated for M+1-O: 489.1.

2,3;11,12-Bisbenzo-1-phenyl-1-phospha-6,9-dithiacyclotridecane-1,6,9-trioxide (2a.3): 2,3;11,12-bisbenzo-1-phenyl-1-phospha-6,9-dithiacyclotridecane-1-oxide (**4a**) (0.14 g, 0.33 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to -78°C. *m*-chloroperbenzoic acid (0.125 g, 0.73 mmol) was added in CH_2Cl_2 (5 mL). The solution was allowed to slowly warm to ambient temperature and stir for 12 h. $CHCl_3$ (30 mL) was added, and the solution was washed with 1 N NaOH (2 x 40 mL) and saturated aqueous NaCl (40 mL), dried over $MgSO_4$ and concentrated to yield 0.133 g of a white solid. Two products were observed on HPLC, with a ratio 1:4.2 (silica, 6% MeOH in CH_2Cl_2), but only the more retained (major) product was recovered as 0.072 g (50% yield) of a white solid. The symmetry in the NMR spectra of the compound suggests that it is a meso diastereomer: mp: > 220°C (decomposed); ^{1}H NMR (5% CD_3OD in $CDCl_3$, 200 MHz) δ 7.77-7.66 (m, 2 H), 7.54-7.41 (m, 2 H), 7.38-7.23 (m, 9H), 4.41, 4.32 (ABq, $^2J_{HH}$ = 13.5 Hz, 2 H), 4.13 (s, 4H), 3.57-3.28 (m, 4 H); ^{13}C (5% CD_3OD in $CDCl_3$, 96 MHz) δ 132.3, 131.9, 131.5 (d, J = 6.3 Hz), 130.8 (d, J = 4.9 Hz), 130.1 (d, J = 9.6 Hz) 129.1-128.7 (m), 127.9, 57.2, 43.9, 35.7 (d, J = 64.6); ^{31}P NMR (5% CD_3OD in $CDCl_3$, 145 MHz) δ 37.6; FTIR (neat) 2939, 2912, 1662, 1636, 1437, 1178, 1035 cm^{-1}; LRMS (FAB) *m/z* observed: 457.1, calculated for $C_{24}H_{26}O_3PS_2$: 457.5.

2,3;12,13-Bisbenzo-1-phenyl-1-phospha-6,10-dithiacyclotetradecane-1,6,10- trioxide (2b.3): 2,3;12,13-Bisbenzo-1-phenyl-1-phospha-6,10-dithiacyclotetradecane-1-oxide (**4b**) (0.17 g, 0.39 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to -78°C. *m*-chloroperbenzoic acid (0.147 g, 0.85 mmol) was added in CH_2Cl_2 (5 mL). The solution was allowed to slowly warm to ambient temperature and stir for 12 h. $CHCl_3$ (30 mL) was added, and the solution was washed with 1 N NaOH (2 x 40 mL) and saturated aqueous NaCl (40 mL), dried over $MgSO_4$ and concentrated. After SiO_2 chromatography (6% MeOH in $CHCl_3$), 0.12 g of the major product (most retained stereoisomer) was recovered as a white solid (65% yield): mp: > 250°C (decomposed); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.73-7.63 (m, 2 H), 7.59-7.43 (m, 3 H), 7.36 (dd, J = 7.4, 1.8 Hz, 2 H), 7.28-7.09 (m, 4 H), 6.90 (dt, J = 7.4, 1.8 Hz, 2 H), 5.33 (t, J = 13.7 Hz, 2 H), 3.89 (d, J = 13.7 Hz, 2 H), 3.59 (t, J = 14.5 Hz, 2 H), 3.35 (dd, J = 14.5, 12.1 Hz, 2 H), 3.35-3.21 (m, 2 H), 3.15-3.01 (m, 2 H), 2.36-2.23 (m, 2 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 132.4-128.1 (m), 57.9, 51.9, 37.1 (d, J = 62.2 Hz), 16.9; ^{31}P NMR ($CDCl_3$, 109 MHz) δ 37.3; FTIR (neat) 3056, 2971, 2917, 1438, 1192, 1155, 1028, 835 cm^{-1}; LRMS (FAB) *m/z* observed: 471.2, calculated for $C_{25}H_{28}O_3PS_2$: 471.6.

2,3;13,14-Bisbenzo-1-phenyl-1-phospha-6,11-dithiacyclopentadecane-1,6,11-trioxide (2c.3): 2,3;13,14-Bisbenzo-1-phenyl-1-phospha-6,11-dithiacyclopentadecane-1-oxide (**4c**) (0.20 g, 0.44 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to -78°C. *m*-Chloroperbenzoic acid (0.17 g, 0.97 mmol) was added in CH_2Cl_2 (5 mL). The solution was allowed to slowly warm to ambient temperature and stir for 12 h. $CHCl_3$ (30 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ (2 x 40 mL), dried over $MgSO_4$ and concentrated. After SiO_2 chromatography (6% MeOH in $CHCl_3$), 0.11 g of the major product (most retained stereoisomer) was recovered as a white solid (52% yield). This stereoisomer appears to be a meso diastereomer due to the symmetry of its NMR spectrum: mp: > 240°C (decomposed); ^{1}H NMR (5% CD_3OD in $CDCl_3$, 200 MHz) δ 7.69-7.49 (m, 6 H), 7.33-7.29 (m, 1 H), 7.18 (bt, J = 7.4 Hz, 2

H), 7.05 (bt, J = 7.3 Hz, 2 H), 6.70 (bd, J = 7.4 Hz, 2 H), 5.33 (d, J = 13.6 Hz, 2 H), 3.89 (t, J = 15.4 Hz, 2 H), 3.73 (d, J = 13.6 Hz, 2 H), 3.52 (dd, J = 15.2, 8.4 Hz, 2 H), 3.21 (m, 4 H), 2.06 (m, 4 H); ^{13}C NMR (2% CH_3OH in $CDCl_3$, 90.6 MHz) δ 132.9, 132.5, 131.2-130.6 (m), 129.7 (d, J = 7.7 Hz), 128.8-128.5 (m), 127.7 (d, J = 2.2 Hz), 57.7, 53.7, 36.0 (d, J = 61.8 Hz), 31.1; ^{31}P NMR (2% CD_3OD in $CDCl_3$, 109 MHz) δ 36.1; FTIR (neat) 2943, 2921, 1489, 1193, 1036, 840 cm^{-1}; LRMS (FAB) *m/z* observed: 485.2, calculated for $C_{26}H_{30}O_3PS_2$: 485.6.

2,3;8,9;13,14-Trisbenzo-1-phenyl-1-phospha-6,11-dithiacyclopentadecane-1,6,11- trioxide (2d.3): 2,3;8,9;13,14-Trisbenzo-1-phenyl-1-phospha-6,11-dithiacyclopentadecane-1- oxide (**4d**) (1.27 g, 2.5 mmol) was dissolved in CH_2Cl_2 (100 mL), and the solution was cooled to -78°C. *m*-Chloroperbenzoic acid (0.96 g, 5.6 mmol) was added in CH_2Cl_2 (25 mL). The solution was allowed to slowly warm to ambient temperature and stir for 12 h. $CHCl_3$ (30 mL) was added, and the solution was washed with 1 N NaOH (150 mL), saturated aqueous $NaHCO_3$ (150 mL), dried over $MgSO_4$ and concentrated. After SiO_2 chromatography (5% MeOH in $CHCl_3$), 0.79 g of a mixture of meso diastereomers was recovered as a white solid (60% yield). HPLC analysis (SiO_2 6%, CH_3OH in CH_2Cl_2) showed a 1:2.6 ratio of diastereomers. The more strongly retained of these two meso diastereomers was isolated by precipitation from benzene:methanol (10:1) giving 0.48 g of a white solid (36%): mp: > 275°C (decomposed); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.62-7.35 (m, 11 H), 7.25-7.06 (m, 6 H), 4.51 (d, J = 13.4 Hz, 2 H), 4.23 (d, J = 13.3 Hz, 2 H), 4.25 (d, J = 13.3 Hz, 2 H), 3.89 (d, J = 13.0 Hz, 2 H), 3.61 (t, J = 14.6 Hz, 2 H), 3.32 (dd, J = 14.8, 11.7 Hz, 2 H); ^{13}C NMR (5% CD_3OD in $CDCl_3$, 90.6 MHz) δ 132.1-130.5 (m), 128.8-128.4 (m), 127.6, 56.4, 55.9, 35.4 (d, J = 63.0); ^{31}P NMR (5% CD_3OD in $CDCl_3$, 145 MHz) δ 36.7; FTIR (neat) 3027, 2930, 1493, 1438, 1339, 1198, 1160, 1021, 764 cm^{-1}; LRMS (FAB) *m/z* observed: 533.2, calculated for $C_{23}H_{24}O_3PS_2$: 533.6.

2,3;8,10;14,15-trisbenzo-1-phenyl-1-phospha-6,12-dithiacyclopentadecane-1,6,12- trioxide (2e.3): 2,3;8,10;14,15-Trisbenzo-1-phenyl-1-phospha-6,12-dithiacyclopentadecane-1-oxide (**4e**) (0.30 g, 0.59 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to -78°C. *m*-Chloroperbenzoic acid (0.22 g of 80% peracid, 1.30 mmol) was added. The solution was allowed to slowly warm to ambient temperature and stir for 12 h. $CHCl_3$ (30 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ (75 mL), dried over $MgSO_4$ and concentrated. After SiO_2 chromatography (6% MeOH in $CHCl_3$), 0.08 g of the major product (most retained stereoisomer) was recovered as a white solid (24% yield): mp: > 225°C (decomposed); ^{1}H NMR (2% CD_3OD in $CDCl_3$, 200 MHz) δ 7.71-7.04 (m, 13 H), 6.89 (d, J = 7.4 Hz, 2 H), 4.33, 4.21(ABq, J_{AB} = 12.9 Hz, 4 H), 4.27 (d, J = 13.5 Hz, 2 H), 3.62 (d, J = 13.5 Hz, 2 H), 3.04, 2.93 (ABq of ABX, J_{AB} = 14.8 Hz, J_{AX} = 9.7 Hz, J_{BX} = 14.8 Hz, 4 H); ^{13}C NMR (5% CD_3OD in $CDCl_3$, 90.6 MHz) δ 132.1-127.6 (m), 58.1, 54.5, 23.7 (d, J = 61.5); ^{31}P NMR (5% CD_3OD in $CDCl_3$, 145 MHz) δ 36.2; FTIR (neat) 3061, 2958, 2917, 1653, 1489, 1192, 1113, 1029 cm^{-1}; LRMS (FAB) *m/z* observed: 533.2, calculated for $C_{23}H_{24}O_3PS_2$: 533.6.

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