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Synthesis, Characterization, and Copper(II) Chelates of 1,11-Dithia-4,8-diazacyclotetradecane

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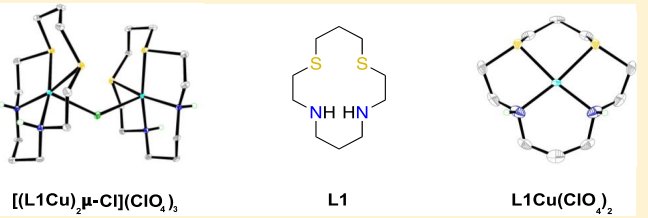
Supporting Information

ABSTRACT: Synthesis of 1,11-dithia-4,8-diazacyclotetradecane (**L1**), a constitutional isomer of the macrocyclic [14]aneN$_2$S$_2$ series, is accompanied with reaction and method optimization. Chelation of **L1** with copper(II) provided assessment of lattice packing, ring contortion, and evidence of conformational fluxionality in solution through two unique crystal structures: **L1Cu(ClO4)$_2$** and [**(L1Cu)$_2$μ-Cl**](**ClO$_4$**)$_3$. Multiple synthetic approaches are presented, supplemented with reaction methodology and reagent screening to access [14]aneN$_2$S$_2$ **L1**. Reductive alkylation of bis-tosyl-cystamine was integrated into the synthetic route, eliminating the use and isolation of volatile thiols and streamlining the synthetic scale-up. Late-stage cleavage of protecting sulfonamides was addressed using reductive N−S cleavage to furnish macrocyclic freebase **L1**.



INTRODUCTION

Mixed N, S-containing macrocyclic ligands continue to be of significant interest due to their metal chelate coordination and redox properties with d-block elements.[1] The property of the [14]aneN$_2$X$_2$ series (X = S or O) to chelate both hard and soft metals has been reported throughout the literature[2] with recently reporting as biological CO_2- and proton-reducing agents,[3] MRI contrast agents,[4] positron emission tomography imaging,[5] anticancer agents,[6] nitric oxide sensors,[7] and as a scaffold for cryptand formation.[8] Many copper(II) chelates within the [14]aneN$_2$S$_2$ series have been previously investigated by both Rorabacher and Siegfried with binding constants and comparisons to other mixed [14]ane systems including S$_4$ and N$_4$.[9] Practical pathways leading to the synthesis of [14]aneN$_2$S$_2$ **L2**[10] and **L3**[11] heteroconstitutional isomers (Figure 1) have been previously reported in moderate and reproducible yields.

Although the use and application of heteromacrocycle **L1** have been mentioned in the literature,[3,12] a descriptive synthetic strategy and characterization have been omitted including X-ray diffraction data for copper chelation. This prompted the design of a direct synthetic pathway to target macrocycle **L1**. Chelation of copper(II) in the presence of **L1** provided crystallographic information to compare against **L3**. The copper(I/II) chelates of macrocycle **L3** have been analyzed by Walker et al. providing binding constants with corresponding crystallographic structures assessing metal geometry and bond distances.[13]

The simple structural motifs of the macrocyclic isomers, **L1**−**L3**, can be synthetically deceptive due to the high variance of possible chemical manipulations. The tendency for macrocyclizations to produce complex reaction mixtures through kinetic oligomerization and polymerization provides an additional challenge for the synthetic optimization of these systems. Structural topology with respect to heteroatom placement was determined to dramatically influence a late-stage reductive N−S cleavage reaction and purification. Three synthetic strategies were implemented to afford [14]aneN$_2$S$_2$ **L1**, accompanied by reaction optimization and topological contrasts between constitutional macrocyclic isomer **L3**.

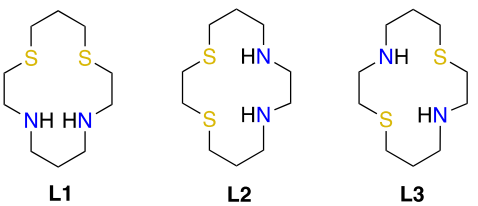


Figure 1. [14]aneN$_2$S$_2$ heteroconstitutional isomers.

DISCUSSION

The strategic pathway toward **L1** was initially assumed to be a simple four-step linear sequence, in which the macrocyclization of bis-acid chloride derived from bis-COOH **2** to the corresponding bis-lactam **1** would be the bottleneck reaction (Scheme 1). Reduction with borane followed by hydrolysis of the N−B bond would provide macrocycle **L1** efficiently with minimal chemical manipulations (Method 1). A second method was designed around macrocyclic sulfonamide **3**,

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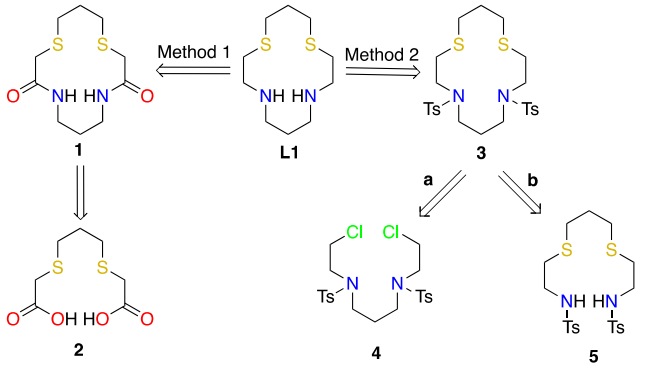
Scheme 1. Retrosynthetic Proposals toward the Synthesis of L1



which allowed two different modes for macrocyclization. The first mode (Method 2a) was envisioned to take advantage of sulfur's nucleophilicity for governing the macrocyclization of bis-chloride **4**. The second mode (Method 2b) of macrocyclization incorporating bis-sulfonamide **5** proved to be comparable in yield and was much more applicable to scale-up. Removal of sulfonamides (N−S cleavage) through known N−S cleavage reactions would provide pure **L1**. The use of different pathways to obtain heteromacrocycle **L1** provides multiple ways to construct analogs and design larger macrocycles. Overall yields of [14]aneN_2S_2 **L1** using methods 1, 2a, and 2b were 7, 48, and 52%, respectively.

The initial approach (Method 1) proceeded through a four-step sequence, in which the final borane reduction of bis-lactam **1** afforded macrocycle **L1**. Synthesis of bis-lactam **1** was synthesized through a tandem N-acylation−macrocyclization from a bis-acid chloride derived from carboxylic acid **2** (Scheme 2). Lactam **1** has been prepared previously by Bradshaw et al. through a tandem bis-alkylation of 1,3-propanedithiol and a symmetric α-chloroacetamide in a 31% yield; however, reduction to **L1** was not reported.[14]

Reaction optimization for the synthesis of bis-lactam **1** from bis-acid chloride **6** was implemented using high dilution, as well as the slow simultaneous addition of the electrophile and nucleophile from separate syringe pumps to provide a maximum yield of 37% (average yield ∼ 26%) (Table 1). This method of reactant addition during macrocyclizations has been implemented to thwart oligomerization and provide ample time for the intramolecular cyclization. The use of nonpolar and nonprotic solvents provided **1** in isolable quantities. Modulating the temperature during the course of the reaction provided no appreciable yield of lactam **1**; higher temperatures (>35 °C) provided oligomers, and at lower temperatures (<5 °C), bis-acid **2** was the major component, even after 72 h.

Table 1. Reaction Optimization of Bis-lactam 1

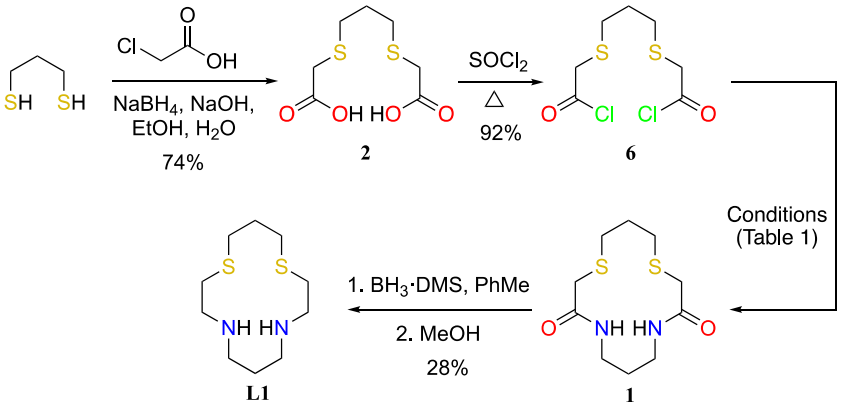
molarity (1,3-diaminopropane)	molarity 6	solvent	base	% yield
0.05	0.05	CH_2Cl_2	Cs_2CO_3	10
0.05	0.05	CH_2Cl_2	K_2CO_3	18
0.01	0.01	CH_2Cl_2	NEt_3	22
0.05	0.05	Et_2O	K_2CO_3	12
0.05	0.05	Et_2O	Cs_2CO_3	7
0.01	0.01	Et_2O	K_2CO_3	15
0.01	0.01	Et_2O	Cs_2CO_3	12
0.01	0.01	PhMe	K_2CO_3	17
0.05	0.05	PhMe	NEt_3	20
0.01	0.01	PhMe	NEt_3	37

Reduction of amides to their corresponding amines with borane dimethyl sulfide (BDS) has been previously performed with high yields during the preparation of macrocycle **L3**.[11] When lactam **1** was subjected to a BDS reduction, the majority of the mass was composed of byproducts following a difficult purification of macrocycle **L1**. Additionally, the cleavage of the nitrogen−boron adducts with methanol/triethanolamine contributed to low yields and long reaction times invoking a change in reaction conditions. Switching to LAH provided no further increase in the yield or purity of **L1**. With the last two synthetic steps being tedious and low yielding (see Scheme 2), an alternative route was established.

The second method was performed in four sequential steps starting from bis-sulfonamide **7**, providing a 48% overall yield of heteromacrocycle **L1**. Sulfonamide **7** was subjected to bis-hydroxyethylation through a KOH (20%)/ethylene carbonate melt affording the desired bis-hydroxyethyl sulfonamide **8a** along with monoalkylated sulfonamide **8b** and overalkylated ether **8c** (Scheme 3). This method was optimized (Table 2) through stoichiometric and temperature screening to obtain bis-hydroxyethyl sulfonamide **8a** in 89%. Crystal and structure refinement data are located in the Supporting Information for this manuscript.

Interestingly, the bis-hydroxyethylation resulted in a dramatic increase in the yield of hydroxyethyl sulfonamide **8a** between temperatures 100 and 115 °C (Table 2).

Scheme 2. Initial Synthetic Approach to the Synthesis of L1



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Scheme 3. Method 2a Synthetic Approach to L1. To Enhance Clarity of Thermal Ellipsoids, H Atoms on Carbon Have Been Omitted

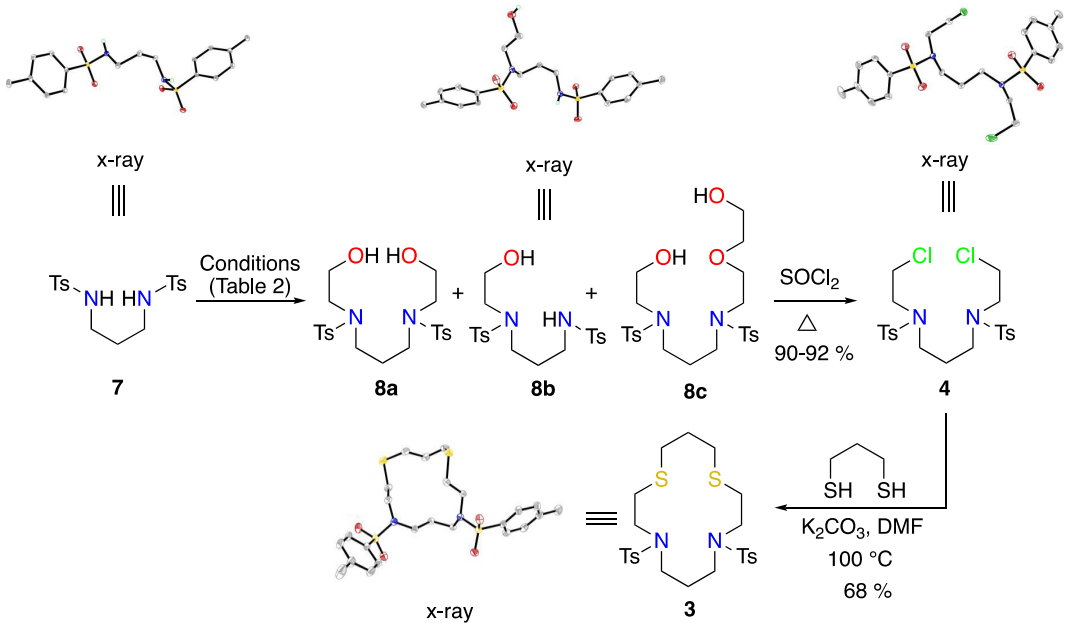


Table 2. Hydroxyethylation Reaction Optimization (4 h, 10 wt % KOH) Performed with 1 mmol of Bis-sulfonamide 7

ethylene carbonate (Eq)	temperature (°C)	% yield **8a**[a]	% yield **8b**[a]	% yield **8c**[a]
2	190	19	0	30
3	170	20	5	31
4	150	29	5	20
5	130	47	5	12
5	125	47	12	12
5	115	89	5	1
5	110	52	20	0

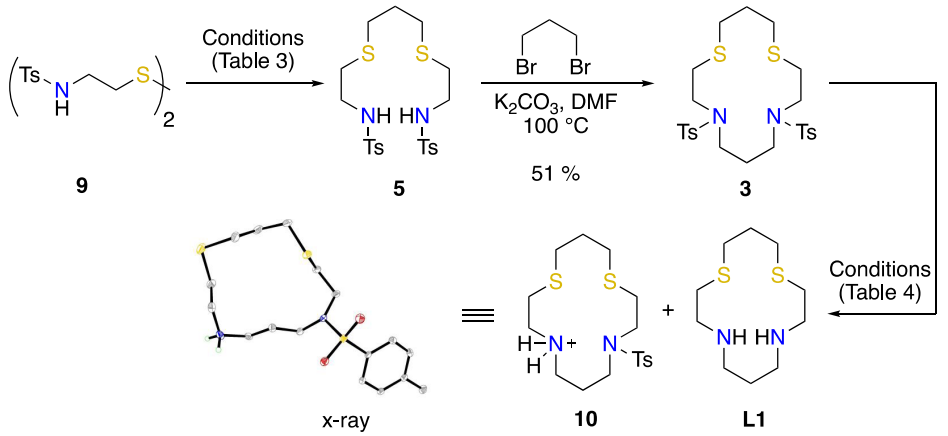
[a]Isolated yields.

Chromatographic separation of sulfonamides **8a**−**8c** was relatively tedious, used large amounts of the mobile phase, and appeared to have high retention to the stationary silica when using traditional ethyl acetate:hexane solutions. Purification using smaller quantities of mobile phase was remedied through the use of toluene:acetone, providing separation of **8a**−**8c**. The addition of potassium hydroxide above the catalytic 10% did not increase reaction rate or yield. The use of thionyl chloride provided bis-chloroethyl sulfonamide **4** in high yield (Scheme 3). This compound was crystallographically characterized, and the solution is available in the Supporting Information section.

The formation of macrocyclic sulfonamide **3** proceeded through nucleophilic addition followed by intramolecular macrocyclization. This was carried out using the modified dilution/addition conditions outlined by Dietrich and Lehn.[15] To increase reaction precision, reduce byproducts, and increase yields, dichloride **4** and propanedithiol were combined and added simultaneously to cesium carbonate in DMF at ∼95 °C to provide macrocycle **3** in a 68% yield. The use of cesium carbonate during macrocyclizations has shown to increase yields through a template effect,[16] serendipitously switching to potassium carbonate furnished macrocycle **3** in similar yields with a clean reaction profile observed in the crude ^{1}H NMR.

The use of cesium as a counter cation for template-driven macrocyclizations has been reported in the literature and is

Scheme 4. Cystamine-Based Synthesis of Macrocycle L1



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observed with oxygen-based heterocycles. When replacing the heteroatom to sulfur, this metal-template effect is diminished, presumably by the tendency for sulfide linkages to orient themselves in an exodentate fashion, directing lone pairs away from the center as shown with other metals.[17] The entropic reordering of sulfides is not energetically favorable and can cause metal ions to bridge the macrocycle instead of chelation within the cavity. Buter and Kellogg demonstrated that a high-yield cyclization of 1, ω-dithiols with 1, and ω-dihalides ruled out any template effect.[18] However, cesium carbonate did not surpass potassium carbonate in cyclization yields in DMF, suggesting that cesium is not critical in this case.

To eliminate the use of volatile thiols as reagents and provide a practical scale-up, Method 2b was pursued (Scheme 4). Starting from tosyl-cystamine (**9**), a triphenyl phosphine (TPP)-mediated reductive alkylation afforded acyclic bis-sulfide **5** in moderate yields. Separation of bis-sulfide **5** from triphenyl phosphine oxide (TPPO) byproduct proved difficult and often required two silica-based chromatographic separations. The use of ethanol and zinc chloride precipitated out ~90% of TPPO as $Zn(TPPO)_2Cl_2$ complex, allowing for effective purification and isolation (Table 3).[19]

Table 3. Reaction Conditions for the Formation of 5

conditions	yield of **5** (%)
(a) TPP, reflux (b) NaOH, 1,3-dibromopropane (c) $ZnCl_2$, EtOH	82
(a) TPP, reflux (b) K_2CO_3, 1,3-dibromopropane (c) $ZnCl_2$, EtOH	80
(a) DTT, K_2CO_3, reflux (b) K_2CO_3, 1,3-dibromopropane	81
(a) DTT, NaOH, reflux (b) NaOH, 1,3-dibromopropane	72
(a) PBu_3, reflux (b) NaOH, 1,3-dibromopropane	88
(a) PBu_3, reflux (b) K_2CO_3, 1,3-dibromopropane	79
(a) TCEP, NaOH, reflux (b) NaOH, 1,3-dibromopropane	91
(a) TCEP, NaOH, reflux (b) NaOH, 1,3-ditosylpropane	68

The major drawback was determined during scale-up using TPP, where ~10% of the TPPO is still present in solution causing contamination during chromatographic separation. Attempts to subject the solution with ~10% TPPO to more zinc chloride did not initially show any precipitation; however, after 72 h at 0 °C, small amounts of zinc−TPPO complex precipitated out allowing for acyclic bis-sulfide **5** purification. In an attempt to eliminate TPPO contamination and use an aqueous workup for purification, tosyl-cystamine (**9**) was subjected to dithiothreitol (DTT) as the reductant.

Issues regarding the use of DTT were observed during the alkylation with 1,3-dibromopropane. Both sodium thiolate molecules derived from DTT and tosyl-cystamine **9** have the potential to perform substitution, lowering the yield of **5**. Reducing the equivalents of DTT (1.3 equiv with respect to **9**), disulfide cleavage provided an increase in the yield of bis-sulfide **5** but was difficult to chromatographically separate from byproducts. Mixed S-alkylations were attributed to thiol−disulfide exchange between thiolate derived from tosyl-cystamine and the oxidized cyclic disulfide originated from DTT (Figure 2).[20]

Switching to tributyl phosphine (PBu_3) as the reductant provided **5** in an 88% yield with simple chromatographic separation (Table 3). Additionally, the disulfide cleavage with PBu_3 was completed within 25 min with no observable disulfide detected via TLC. The use of tris(carboxyethyl)-

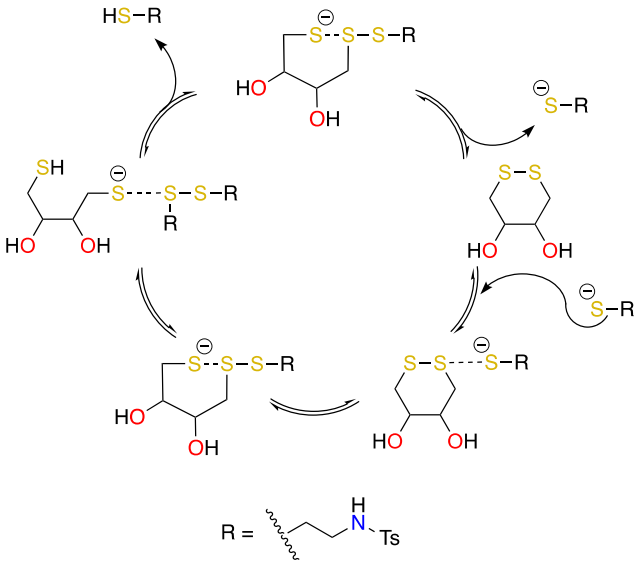

Figure 2. Proposed thiol−disulfide exchange modeled after posttranslational modification of cysteine by Gilbert.[20]

phosphine (TCEP) for reductive alkylation allowed for scale-up, simple aqueous workup, and elimination of column chromatography before macrocyclization. Acyclic, bis-sulfide **5** was subjected to macrocyclization conditions through substitution with the sulfonamide nitrogen atoms. Macrocycle **3** was obtained in a 51% yield through sulfonamide ring closure and then subjected to N−S cleavage conditions to obtain heteromacrocycle **L1**.

Reductive desulfonylation of sulfonamides to their corresponding free amines is reported throughout the literature, using a multitude of conditions ranging from sonication in methanol/magnesium to HBr/acetic acid.[21] Many conditions are either too harsh resulting in decomposition/low yields or no reaction with the starting material remaining intact (Table 4). Interestingly, heteromacrocycles **L1**, **L2**, and **L3** were

Table 4. Desulfonylation Conditions and Isolated Yields

conditions	yield of L1 (%)	yield of **10** (%)[a]	recovery of **3** (%)
Mg/methanol/sonication	2[b]	0	93
Na_2K/THF/23 °C	2[b]	0	90
K_2Na/THF/23 °C	0	0	89
NaK_2 stage I/THF/23 °C	0	0	91
HBr/HOAc/reflux	5−10	5−10	0
HBr/HOAc/23 °C	0	10	41
Na°/naphthalene/−50 °C	89	0	0
Red-Al/xylenes/reflux	38[b]	30	0
SmI_2/THF	0	0	95

[a]Yield determined through ^{1}H NMR.

isolated in optimal yields through differing detosylation conditions establishing a reagent bias with respect to heteroatom placement along the [14]aneN_2S_2 backbone. Most cleavage conditions attempted on macrocycle **3** failed to produce macrocycle **L1**. Red-Al (vitride) was the first reagent that provided **L1** in ~30% yield. A major limitation of this reduction was the presence of the mono-tosyl **10** (isolated

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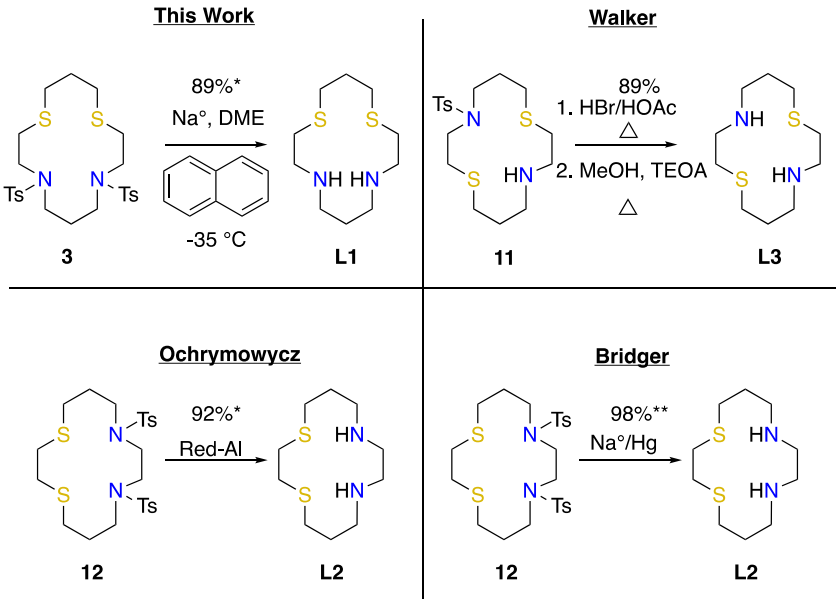

Figure 3. Detosylation reaction conditions of three heteroconstitutional isomers **3**, **11**, and **12**.

as the HCl salt) that was difficult to remove through chromatographic separation. The use of sodium naphthalenide to perform the N−S bond cleavage afforded [14]aneN_2S_2 **L1** cleanly over a 15 min period at −35 °C. Due to the freebase instability in the presence of oxygen and carbon dioxide, macrocyclic salt **L1-HCl** was initially made for storage purposes and maintained at −20 °C. The analysis of **L1-HCl** through ^{1}H and ^{13}C NMR provided frequency-resolved spectra, unlike the macrocyclic **L1** freebase that is composed of overlapping resonances.

For comparative desulfonylation conditions within the [14]aneN_2S_2 family, **L2** and **L3** were produced following the procedures outlined by Ochrymowycz et al.,[10] Bridger et al.,[22] and Walker et al.[11] (Figure 3). Two procedural modifications were performed for the synthesis of macrocycle **L2** following Bridger's method and are reported in the Experimental Section. This included a bis-Michael addition mediated through sonication affording bis-nitrile **13** (Supporting Information) along with a Red-Al detosylation on substrate **12**.

Switching desulfonylation conditions to refluxing Red-Al in xylenes afforded **L2** in near-quantitative yields and required no extensive purification, with the exception of acid/base workup. The analysis of [14]aneN_2S_2 **L2** through NMR spectroscopy proved troublesome as the resonances were overlapping, as seen with [14]aneN_2S_2 **L1**. The hydrogen chloride salt **L2-HCl** was used to provide frequency-resolved NMR spectra in deuterium oxide.

Heteroatom placement in the backbone of [14]aneN_2S_2 macrocycle systems imparts a significant role for the preference of reagents on the cleavage of the N−S system. Although many desulfonation conditions provided the freebase ligands (**L1**, **L2**, and **L3**), the isolated yields were negligible unless the appropriate conditions were applied. Topologic and heteroatom placements intrinsic to each sulfonamide with respect to the adjacent nitrogen and sulfur atoms could explain the variance in reagents with respect to isolated yield.

Due to the instability of **L1** freebase, the diprotonated species of **L1-HCl** was immediately formed and stored at ∼0 °C. Crystal structures of **L1-HCl** were obtained through the slow evaporation of methanol (Figure 4) with significant bond

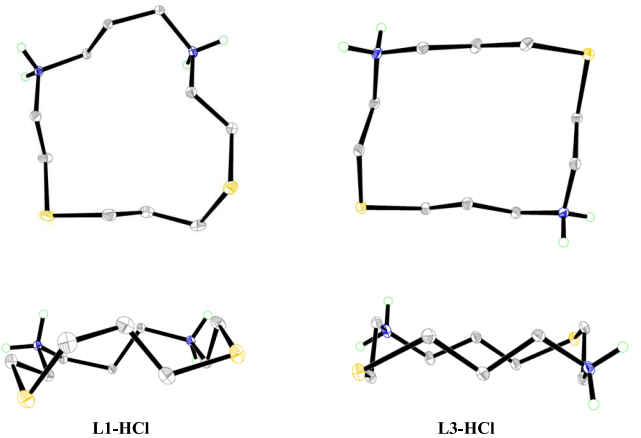

Figure 4. Thermal ellipsoid diagram of L1-HCl salt with 35% probability displacement ellipsoids. C−H hydrogen atoms are omitted for clarity. The trans-L3-HCl, previously reported, was used for comparison (CCDC 888496).[11]

lengths and bond angles shown in Table 5. Crystal and structure refinement data for **L1-HCl** are located in the Supporting Information. Compound **L2-HCl** failed to produce crystals, and the previously elucidated **L3-HCl** is shown for comparison. **L3-HCl** was reported to adopt a rectangular endodentate conformation with heteroatom placement at the four corners of the ring, resulting in the asymmetrical crown.[11] The bond length and bond angles of **L1-HCl** compared to those of **L3-HCl** are not statistically different; therefore, the structural conformations may be explained by the packing forces and crystal symmetry (see Supporting Information). Ligand **L1-HCl** was expected to adopt a preferred [3434] conformer (Dale notation)[23] similar to **L3-HCl**; however, the conformational assessment indicated a [3335] arrangement.

Crystallographic Data and Copper(II) Chelation. Crystallographic elucidation of **L1** with copper(II) is lacking. With access to the freebase, reaction with $Cu(ClO4)_2{\cdot}6H_2O$ in CH_3CN at ambient conditions with **L1** resulted in a deep purple color, which unlike the reported **L3** did not precipitate out. Slow evaporation at 4 °C produced two distinct unit cell

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Table 5. Selected Bond Angles and Bond Lengths for Ligands L1-HCl and L3-HCl

bond lengths, Å	L1-HCl	L3-HCl	bond angles, deg	L1-HCl	L3-HCl
S−C	1.8106(17), 1.8152(17), 1.8194(19), 1.8174(17)	1.807(2), 1.820(3), 1.807(2), 1.817(2)	C−S−C	101.87(8), 101.79(8)	102.5(12), 102.1(12)
N−C	1.4973(19), 1.5024(18), 1.5077(19), 1.4988(19)	1.501(3), 1.497(3), 1.491(3), 1.501(3)	C−N−C	115.09(12), 116.26(11)	117.2(19), 116.3(19)
			C−C−S	111.18(11), 112.04(11), 116.92(12), 114.29(12)	113.3(17), 114.4(17), 112.3(16), 114.9(17)
			C−C−C	112.80(12), 113.30(15)	110.0(2), 109.4(2)
			N−C−C	112.21(13), 111.25(12), 114.73(12), 109.78(12)	111.3(19), 112.8(2), 110.9(19), 112.2(19)

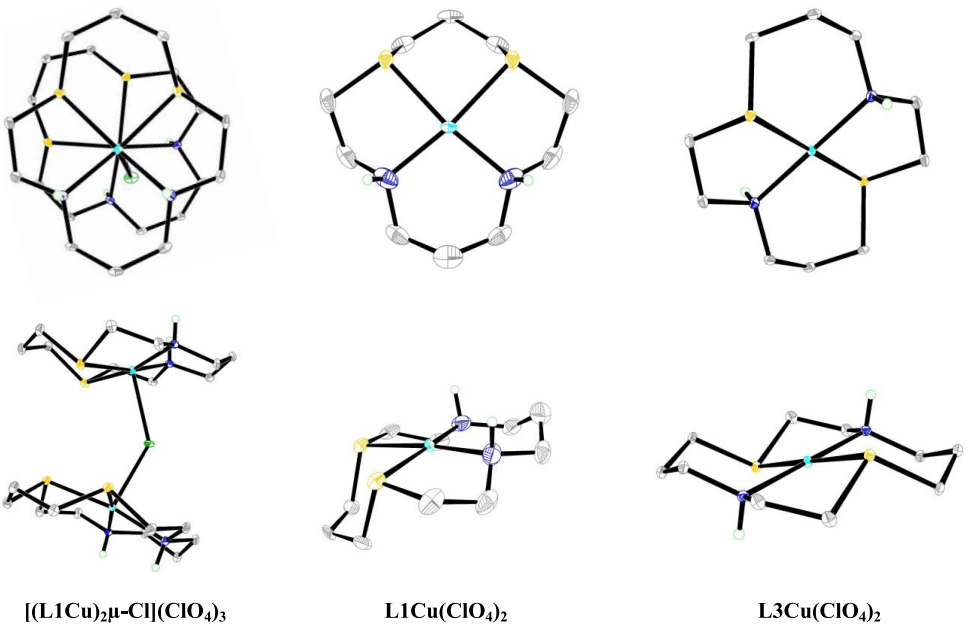

Figure 5. Thermal ellipsoid diagrams of two separate conformations of L1 copper complexes, $[(L1Cu)_2\mu\text{-}Cl](ClO_4)_3$, $L1Cu(ClO4)_2$, and previously reported $L3Cu(ClO4)_2$, (CCDC 905763)[11] at 35% probability displacement ellipsoids. All C−H hydrogen atoms are omitted for clarity, and $[(L1Cu)_2\mu\text{-}Cl](ClO_4)_3$ is shaded for comparison in the conformational structure to $L1Cu(ClO4)_2$.

Table 6. Selected Bond Angles and Bond Lengths for Copper Complexes

	$[(L1Cu)_2\mu\text{-}Cl](ClO_4)_3$	$L1Cu(ClO4)_2$	$L3Cu(ClO4)_2$
	Bond Lengths, Å		
S−C	1.822(3), 1.814(3), 1.824(3), 1.822(4), 1.822(3), 1.811(3), 1.818(3), 1.807(4)	1.816(17), 1.806(15)	1.816(2), 1.816(2)
N−C	1.468(4), 1.490(4), 1.488(4), 1.482(4), 1.486(4), 1.480(4), 1.486(4), 1.473(4)	1.44(2), 1.48(2)	1.492(2), 1.500(2)
N−Cu	2.025(3), 2.027(3), 2.028(3), 2.027(3)	2.008(15)	2.014(17)
S−Cu	2.3332(9), 2.3407(9), 2.3324(9), 2.3374(10)	2.315(4)	2.295(8)
	Bond Angles, deg		
C−S−C	102.94(16), 103.21(16), 102.22(16), 102.74(15)	102.6(8)	105.6(9)
C−N−C	110.5(3), 111.2(3), 111.3(3), 110.9(3)	112.6(15)	108.0(14)
C−C−S	112.4(2), 111.5(2), 106.1(2), 107.7(2), 112.4(2), 110.1(2), 106.4(2), 106.7(2)	109.1(12), 111.6(13)	105.6(13), 108.3(13)
C−C−C	116.0(3), 115.1(3), 115.3(3), 115.7(3)	116(2), 117.0(18)	115.1(16)
N−C−C	109.8(3), 111.4(3), 111.6(3), 109.3(3), 109.6(3), 112.6(3), 111.2(3), 109.9(3)	111.4(18), 112.2(15)	110.9(15), 114.9(16)
N−Cu−N	92.54(11), 91.77(11)	101.0(9)	180.0(22)
S−Cu−S	89.93(3), 90.71(3)	85.8(2)	179.9(11)
S−Cu−N	87.77(8), 168.85(8), 167.66(8), 87.40(8), 87.43(8), 168.35(8), 167.57(8), 87.58(8)	86.5(5), 171.6(5)	87.9(5), 92.0(5)

crystals suitable for X-ray diffraction (Figure 5) with crystal and refinement data, reported in the Supporting Information. All three systems exhibit planar coordination environments with respect to the metal center including comparable bond lengths and angles (Table 6).

Chelate $[(L1Cu)_2\mu\text{-}Cl](ClO_4)_3$ has S−Cu−N bond angles averaging 168° due to the bridging three-center, four-electron chloride atom compared to those of 172 and 180° for $L1Cu(ClO4)_2$ and $L3Cu(ClO4)_2$, respectively. More notably, $L1Cu(ClO4)_2$ differs from $[(L1Cu)_2\mu\text{-}Cl](ClO_4)_3$, in that the N−H bonds orientate opposite the sulfur lone-pair electrons. Both crystal packing and a bridging chloride atom induce changes in the ligand coordination, indicating that the binding

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conformation of **L1** is perhaps quite flexible and fluxional in solution.

Coordination of ligands **L1** and **L3** to copper(II) does, however, produce noteworthy structural changes. In both $[(\mathbf{L1Cu})_2\mu\text{-Cl}](ClO_4)_3$ and $\mathbf{L1Cu(ClO4)_2}$, the coordination of copper to both sulfur atoms exhibits a low strain chair conformation as compared to the torsion angles of cyclohexane[24] with the connecting five-membered chelate in a favorable equatorial position. However, in the case of $\mathbf{L1Cu(ClO4)_2}$, the coordination of copper to nitrogen induces a conformation similar to a distorted envelope.[24]

The copper(II)−thioether bonds are quite short (~2.3 Å) in both $[(\mathbf{L1Cu})_2\mu\text{-Cl}](ClO_4)_3$ and $\mathbf{L1Cu(ClO4)_2}$, suggesting that the bond orientation is overlapping with the magnetic orbital of copper(II).[25] Qualitative analysis depicted an observable difference with respect to the lone pairs on sulfur and the protons attached to the nitrogen atoms. As the lone pairs on sulfur are diffuse and flexible, $\mathbf{L1Cu(ClO4)_2}$ seemed to perform a pseudo-chair flip with respect to ligand−metal chelate $[(\mathbf{L1Cu})_2\mu\text{-Cl}](ClO_4)_3$, which will be further investigated.[26]

Ultraviolet−visible spectroscopy of $\mathbf{L1Cu(ClO4)_2}$ provided λ_{max} of 275, 335, and 535 nm in aqueous solution, comparable to the previously reported data.[12d] A slight blue shift was observed with $\mathbf{L1Cu(ClO4)_2}$ compared to that of $\mathbf{L3Cu(ClO4)_2}$ (295, 354, and 545 nm) due to heteroatom positioning (Supporting Information). The band at 535 nm corresponds to the (N) → Cu(II) ligand-to-metal charge transfer (LMCT), and the most intense absorption at 335 nm results from the (S) → Cu(II) LMCT.[9] Spectrochemical comparison with copper(II) chelates of [14]aneN$_4$ (cyclam), [14]aneS$_4$, and [14]aneN$_2$S$_2$ isomers (**L1** and **L3**) provided weaker ligand field bands associated with the sulfur-based systems, which corroborates the Kauffman et al. analysis of sulfide donation and configuration.[12d,27]

CONCLUSIONS

In summary, the synthetic methodology implemented for the synthesis of 1,11-dithia-4,8-diazacyclotetradecane (**L1**) has been completed and optimized. This is the first detailed synthesis of **L1** reported to date, which allows for a multitude of analogs to be tailored for select applications. This study provides a practical approach to macrocycles containing aza/thia heteroatoms and showcases the difference in reactivity associated with the [14]aneN$_2$S$_2$ heteroconstitutional isomers. A unique, efficient disulfide cleavage−alkylation mediated through TCEP was explored and optimized to attain disulfide **5**. This study expands upon the pioneering work performed by Lehn and Cram for inter/intratandem macrocyclizations, which implements high-dilution conditions and slow addition of reagents. For detosylation of the resulting sulfonamides, it was determined that some reagents were more amenable to individual constitutional isomers. Currently, computational assessments are underway to assess the fluxionality and conformational bias between macrocyclic chelates $\mathbf{L1Cu(ClO4)_2}$ and $[(\mathbf{L1Cu})_2\mu\text{-Cl}](ClO_4)_3$. The ligands also have the advantage of performing late-stage diversification, potentially leading to biologically compatible motifs used in imaging.

EXPERIMENTAL SECTION

All commercial reagents, unless otherwise stated, were used as received (Sigma-Aldrich, VWR, or Fischer Scientific Ltd.). Dichloromethane and acetonitrile were distilled from calcium hydride under nitrogen. Dimethylformamide was distilled from calcium hydride under vacuum and stored over 3 Å molecular sieves and degassed with argon using a gas dispersion frit. Reactions run at room temperature are in the range of 22−24 °C. ^{1}H and ^{13}C NMR were obtained on a Varian 400 spectrometer as solutions in $CDCl_3$ with and without TMS and referenced to the $CHCl_3$ residual protioisomer. For spectra taken in other NMR solvents, D_2O, and DMSO-d_6, the ^{1}H spectra were referenced to the solvent residual protioisomers, and ^{13}C spectra were referenced to the NMR solvent. Chemical shifts are expressed in parts per million values, and coupling constants (J) are reported in Hertz (Hz) and rounded to the nearest 0.5 Hz. The following abbreviations are used to indicate apparent multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplets; q, quartets; m, multiplet. Flash column chromatography on silica gel (60 Å, 230−400 mesh, low acidity, obtained from EMD Millipore Corporation) was performed using reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed on precoated aluminum-backed silica gel plates (EMD Millipore Corporation) and visualized with a UV lamp (254 nm) or an iodine/silica or potassium molybdic acid solution in ethanol or $KMnO_{4(aq)}$ or p-anisaldehyde$_{(EtOH)}$ or vanillin$_{(EtOH)}$.

PHYSICAL METHODS

For temperature control in tandem with the reaction, mixing an Ika RCT digital stir plate with a PT 10000.60 temperature probe was used. FTIR spectra were collected on a Jasco 4600 spectrophotometer running the Spectra Manager CFR, where samples were prepared as a neat oil or solid on a ZnSe window using attenuated total reflectance (ATR). Melting points were obtained on a MeltTemp melting point apparatus and are uncorrected.

High-resolution mass spectra (HRMS) were recorded on a time-of-flight JMS-T1000LC spectrometer with a DART ion source. ESI-MS spectra were acquired with a Bruker micrOTOF II, in the positive mode (parent ion plus H^+). ESI samples were prepared for analysis by dissolving samples to 10^{-4} M in acetonitrile and were directly infused into the mass spectrometer at a flow rate of 4 μL/min. The ESI was operated with a capillary offset of 4500 V and a skimmer potential of 48 V. The samples were calibrated using an internal standard.

X-ray intensity data were measured on a Bruker CCD-based diffractometer with a dual Cu/Mo ImuS microfocus optics (Cu Kα radiation, λ = 1.54178 Å, Mo Kα radiation, λ = 0.71073 Å). Crystals were mounted on a cryoloop using Paratone oil and placed under a steam of nitrogen at 100 K (Oxford Cryosystems). The detector was placed at a distance of 5.00 cm from the crystal. The data were corrected for absorption with the SADABS program. The structures were refined using the Bruker SHELXTL software package (version 6.1) and were solved using direct methods until the final anisotropic full-matrix, least-squares refinement of F2 converged.

UV and visible spectra in solution were run in 1 cm cells using a Perkin Elmer Lambda 365 UV−vis spectrometer at concentrations appropriate for measurements of absorption bands, and the data collection was obtained at ambient temperatures.

The Supporting Information (CCDC 1912553-1912560) contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1,11-Dithia-4,8-diazacyclotetradecane-3,9-dione (1). A 250 mL flame-dried three-neck round-bottom flask equipped with a magnetic stir bar, a nitrogen inlet, and three septa was charged with dry toluene (100 mL). A syringe was charged with 1,3-diaminopropane (0.14 mL, 1.60 mmol) and triethylamine (0.47 mL, 3.36 mmol) in toluene (40 mL), and a second syringe was charged with 2,2′-(propane-1,3-diylbis(sulfanediyl))diacetyl chloride (**6**) (0.428 g, 1.60 mmol) in toluene (40 mL); these two solutions were attached to individual syringe pumps and added to the vigorously stirring toluene at a rate of ~1 drop per 10 s simultaneously. After the addition of the reagents, the solution was allowed to stir for a 12 h period. This solution was then concentrated in vacuo and immediately subjected to column chromatography

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(EtOAc) to provide bis-lactam **1** in a 37% yield (155 mg, 0.592 mmol) as an amorphous white residue. R_f = 0.3 (EtOAc); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.07 (s, 1H), 3.48 (q, *J* = 5.8, 5.2 Hz, 2H), 3.25 (s, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.01−1.74 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 169.6, 39.7, 36.9, 32.3, 29.2, 28.9; IR ν_{max} 3315, 3300, 2923, 2857, 1730, 1638, 1529, 1451, 1054 cm^{-1}; HRMS (EI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{18}O_2N_2NaS_2$ 285.0702, found 285.0707.

2,2′-(Propane-1,3-diylbis(sulfanediyl))diacetic acid (2). A 50 mL flame-dried round-bottom flask equipped with a magnetic stir bar and a condenser was charged with 1,3-propanedithiol (1.00 mL, 9.96 mmol), ethanol (4.00 M, 2.49 mL), and sodium borohydride (0.0190 g, 0.498 mmol) in the indicated order. An aqueous potassium hydroxide solution (2.50 mL, 16 M, 39.8 mmol) was added slowly to the mixture (15 min). The addition of chloroacetic acid (1.88 g, 19.9 mmol) in ethanol (5.00 mL) was added dropwise over a period of 15 min, after which the solution was allowed to reflux for 12 h using a heating mantle. The reaction mixture was then concentrated in vacuo and dissolved in water (20 mL), and the impurities were washed out with diethyl ether (2 × 3 mL). The aqueous layer was acidified to pH ∼1 with concentrated sulfuric acid. The product was extracted with diethyl ether (3 × 20 mL). The combined ethereal layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residual oil was taken up in toluene (30 mL) and allowed to crystallize over a 12 h period at 0 °C. The bis-carboxylic acid was filtered off affording a white solid (1.653 g, 7.37 mmol) in a 74% yield. Mp = 69−70 °C; ^{1}H NMR (300 MHz, deuterium oxide) δ 3.45 (s, 3H), 2.80 (t, *J* = 7.2 Hz, 4H), 1.98 (p, *J* = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, deuterium oxide) δ 174.8, 33.3, 30.7, 27.6; IR ν_{max} 2922, 2672, 1707, 1419, 1288, 1205, 1141 cm^{-1}. HRMS (EI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_7H_{12}NaO_4S_2$ 247.0069, found 247.0062.

4,8-Ditosyl-1,11-dithia-4,8-diazacyclotetradecane (3). DMF was degassed with nitrogen for ∼20 min via gas dispersion frit prior to running the reaction, mitigating the possibility of disulfide formation.

Method A. A 100 mL three-neck round-bottom flask equipped with a septum, a nitrogen inlet, a condenser, and a magnetic stir bar was charged with anhydrous potassium carbonate (0.286 g, 2.07 mmol) and DMF (20 mL). A separate 25 mL pear flask was charged with DMF (10 mL), 1,3-propanedithiol (0.10 mL, 1.03 mmol), and bis-chloroethyl sulfonamide **6** (0.50 g, 0.985 mmol). This flask was fitted with an inlet line inserted through a septum from a fluid metering pump, and the terminal line was fitted into a septum attached to the three-neck round-bottom flask. The flask containing potassium carbonate and DMF was heated to 90−95 °C via a heating mantle, and the fluid metering pump was set to add the contents of the pear flask into the three-neck round-bottom flask at a rate of 1 drop/8 s. Once all of the contents from the pear flask were added, the reaction was stirred at 90−95 °C for 12 h. After which the reaction was cooled down to room temperature, the DMF was removed in vacuo, and the residue was subjected to column chromatography (19:1; PhMe/acetone) R_f = 0.4 (1:1 Hex/EtOAc) affording **3** (0.380 g, 0.670 mmol) in a 68% yield.

Method B. A 1 L two-neck round-bottom flask equipped with a septum, a nitrogen inlet, a condenser, and a magnetic stir bar was charged with anhydrous potassium carbonate (3.22 g, 23.31 mmol) and DMF (155 mL). A separate 250 mL two-neck pear flask was charged with DMF (78 mL), 1,3-dibromopropane (0.79 mL, 7.77 mmol), and *N*,*N*′-((propane-1,3-diylbis(sulfanediyl))bis(ethane-2,1-diyl))bis(4-methylbenzenesulfonamide) (**5**) (3.91 g, 7.77 mmol). This flask was fitted with an inlet line inserted through a septum from a fluid metering pump, and the terminal line was fitted into a septum attached to the 1 L two-neck round-bottom flask. The potassium carbonate and DMF were heated via a heating mantle to 100 °C, and the fluid metering pump was set to add the contents of the pear flask into the two-neck round-bottom flask at a rate of 1 drop/8 s. Once all of the contents from the pear flask were added, the reaction was stirred at 100 °C for 24 h. After which the reaction was cooled down to room temperature, the DMF was removed in vacuo, and the residue was subjected to column chromatography (19:1; PhMe/acetone) affording **3** (2.14 g, 3.96 mmol) in a 51% yield. Mp = 144−145 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.67 (d, *J* = 8.5 Hz, 4H), 7.32 (d, *J* = 8.5 Hz, 4H), 3.22 (q, *J* = 6.9 Hz, 8H), 2.81 (t, *J* = 7.4 Hz, 4H), 2.63 (t, *J* = 6.7 Hz, 4H), 2.43 (s, 6H), 2.05 (p, *J* = 7.4 Hz, 2H), 1.91 (p, *J* = 6.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 143.6, 135.3, 129.9, 127.2, 49.8, 48.5, 31.9, 29.7, 29.7, 21.5. IR ν_{max} 2924, 2857, 1337, 1157, 1089, 815, 721, 653 cm^{-1}. HRMS (APCI) *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{35}O_4N_2S_4$ 543.1474, found 543.1477.

***N*,*N*′-(Propane-1,3-diyl)bis(*N*-(2-chloroethyl)-4-methylbenzenesulfonamide) (4)[a].** A flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar, a condenser, and a calcium sulfate drying tube was charged with *N*,*N*′-(propane-1,3-diyl)bis(*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide) (**8**) (1.49 g, 3.20 mmol) and thionyl chloride (5 mL). The reaction was refluxed on a heating mantle for 12 h, at which time the reaction was cooled down to room temperature and toluene (10 mL) was added and removed in vacuo. The toluene (10 mL) washes were performed two additional times to azeotropically remove the excess thionyl chloride. The yellow oil was dissolved in minimal MTBE, and methanol or ethanol was added until a thick white precipitate was observed. This was heated to reflux and allowed to cool at −20 °C for 12 h to precipitate out the final bis-alkyl chloride **4** (0.428 g, 2.94 mmol) in a 92% yield as a white solid. Mp = 83−84 °C. R_f = 0.88 (EtOAc); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.66 (d, *J* = 8.1 Hz, 4H), 7.31 (d, *J* = 8.4 Hz, 4H), 3.62 (t, *J* = 7.0 Hz, 4H), 3.35 (t, *J* = 7.0 Hz, 4H), 3.17 (t, *J* = 7.3 Hz, 4H), 2.41 (s, 6H), 1.88 (p, *J* = 7.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 143.9, 135.6, 129.9, 127.2, 50.6, 47.7, 42.2, 28.7, 21.5. IR ν_{max} 2975, 2933, 2877, 1732, 1597, 1455, 1402, 1337, 1249, 1208, 1154, 1117, 1089, 913, 727 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{28}O_4N_2S_2NaCl_2$ 529.0760, found 529.0759.

***N*,*N*′-((Propane-1,3-diylbis(sulfanediyl))bis(ethane-2,1-diyl))bis(4-methylbenzenesulfonamide) (5).** *Method A.* A 250 mL round-bottom flask equipped with a magnetic stir bar, a nitrogen inlet, and a condenser was charged with THF/H_2O (5:1, 75 mL) and degassed with nitrogen via gas dispersion frit for 20 min. The addition of tosyl-cystamine (**9**) (7.60 g, 16.50 mmol) and triphenyl phosphine (5.20 g, 19.83 mmol) followed, and the reaction was refluxed for 12 h with a heating mantle. The solution was then cooled down to room temperature, and degassed 2 M NaOH (17.4 mL, 34.80 mmol) was added in one portion. The light pink solution was stirred at room temperature for 5 min, 1,3-dibromopropane (0.76 mL, 7.43 mmol) was added, and the solution was refluxed via a heating mantle for 12 h. The reaction mixture was diluted with EtOAc (50 mL) and 1 M HCl (40 mL), the aqueous layer was extracted with EtOAc (2 × 30 mL), and the organic layers were combined, dried with sodium sulfate, filtered, and concentrated in vacuo. The yellow residue was dissolved in ethanol (200 mL) and warmed to 40 °C followed by the addition of zinc chloride (11.24 g, 82.5 mmol) in ethanol (100 mL). The ethanolic solution was stirred at 40 °C for 0.5 h, then cooled down to room temperature, stirred for 3 h, and the cloudy solution was placed in a 0 °C fridge for 12 h. The white $Zn(TPPO)_2Cl_2$ was filtered, washed with cold ethanol (2 × 50 mL), the mother liquor concentrated, and subjected to column chromatography (3:1 → 2:1 → 1:1; Hex/EtOAc) affording **5** (3.44 g, 13.53 mmol) in an 82% yield as a clear oil.

Method B. A 250 mL round-bottom flask equipped with a magnetic stir bar, a nitrogen inlet, and a condenser was charged with THF/H_2O (5:1, 75 mL) and degassed with nitrogen via gas dispersion frit for 20 min. The addition of tosyl-cystamine (7.60 g, 16.50 mmol), potassium carbonate (6.84 g, 49.50 mmol), and dithiothreitol (DTT) (3.31 g, 21.45 mmol) followed, and the reaction was refluxed with a heating mantle until the disappearance of a starting material via TLC (∼1.5 h). The reaction was allowed to cool down to room temperature followed by the dropwise addition of 1,3-dibromopropane (1.85 mL, 18.15 mmol) over 15 min. The solution was refluxed with a heating mantle a final time for 12 h, cooled down to room temperature, and diluted with EtOAc (200 mL). The organic layer was washed with 1 M HCl (2 × 20 mL), water (20 mL), and brine (20 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was subjected to column chromatography (3:1 →

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2:1 → 1:1; Hex/EtOAc) to obtain **5** (6.72 g, 13.37 mmol) as a clear viscous oil in an 81% yield.

Method C. A 250 mL round-bottom flask equipped with a magnetic stir bar, a nitrogen inlet, and a condenser was charged with THF/H_2O (5:1, 75 mL) and degassed with nitrogen via gas dispersion frit for 20 min. The addition of tosyl-cystamine (7.60 g, 16.50 mmol) and tributyl phosphine (4.89 mL, 19.83 mmol) was followed, and the reaction was refluxed for 2 h via a heating mantle. The solution was then cooled down to room temperature, and degassed 2 M NaOH (17.4 mL, 34.80 mmol) was added in one portion. The solution was stirred at room temperature for 5 min, 1,3-dibromopropane (0.76 mL, 7.43 mmol) was added, and the solution was refluxed for 12 h via a heating mantle. The reaction mixture was diluted with EtOAc (150 mL), washed with 1 M HCl (2 × 20 mL), water (20 mL), and brine (15 mL), dried with sodium sulfate, filtered, concentrated in vacuo, and subjected to column chromatography (3:1 → 1:1, Hex/EtOAc). Compound **5** (7.30 g, 14.52 mmol) was obtained in an 88% yield as an opaque oil.

Method D. A 500 mL two-neck round-bottom flask equipped with a magnetic stir bar, a pressure-equalizing drop funnel, a condenser, and a nitrogen inlet was charged with THF/H_2O (5:1, 217 mL) and degassed with nitrogen via gas dispersion frit for 20 min. At which time, NaOH (0.95 g, 23.87 mmol) followed by TCEP·HCl (6.84 g, 23.87 mmol) was added, and the mixture was degassed with nitrogen via gas dispersion frit for 10 min. Tosyl-cystamine (10.0 g, 21.7 mmol) was added in one portion, and the solution was refluxed with a heating mantle until the disappearance of a starting material via TLC (~15 min). The solution was cooled down to room temperature, at which time, nitrogen-degassed 2 M NaOH (54 mL, 27.00 mmol) was added in one portion, and the pressure-equalizing drop funnel was charged with 1,3-dibromopropane in nitrogen-degassed THF (10 mL). The solution was stirred at room temperature for 5 min followed by the dropwise addition of 1,3-dibromopropane over 15 min and refluxed with a heating mantle for 12 h. The reaction mixture was diluted with EtOAc (300 mL), washed with 1 M HCl (2 × 30 mL), water (30 mL), and brine (20 mL), dried with sodium sulfate, filtered, concentrated in vacuo, and subjected to column chromatography (3:1 → 1:1, Hex/EtOAc) to afford compound **5** (9.82 g, 19.53 mmol) in a 90% yield as an opaque oil. R_f = 0.5 (Hex/EtOAc, 1:1). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.70 (d, J = 8.3 Hz, 4H), 7.25 (d, J = 8.2 Hz, 4H), 5.54−5.34 (m, 2H), 3.04 (t, J = 7.0 Hz, 4H), 2.52 (t, J = 6.8 Hz, 4H), 2.41 (t, J = 7.1 Hz, 8H), 2.36 (s, 6H), 1.65 (p, J = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 143.6, 136.8, 129.8, 127.0, 42.3, 31.6, 30.2, 28.9, 21.5. IR ν_{max} 3277, 2921, 2256, 1597, 1494, 1409, 1321, 1185, 1092, 1019, 813 cm^{-1}. HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{30}O_4N_2NaS_4$ 525.0981, found 525.0985.

2,2′-(Propane-1,3-diylbis(sulfanediyl))diacetyl Chloride (6). A 50 mL flame-dried round-bottom flask equipped with a magnetic stir bar, a condenser, and a calcium sulfate drying tube was charged with 2,2′-(propane-1,3-diylbis(sulfanediyl))diacetic acid (**2**) (0.400 g, 1.78 mmol), methylene chloride (17.8 mL), and thionyl chloride (0.320 mL, 1.78 mmol) in the indicated order. This mixture was refluxed with an external heating mantle for 12 h and then concentrated in vacuo. To the yellow oil, trituration from toluene (3 × 10 mL) afforded the final bis-acid chloride **6** (0.428 g, 1.64 mmol) in a 92% yield as a viscous light-yellow oil. ^{1}H NMR (300 MHz, chloroform-*d*) δ 3.71 (s, 1H), 2.78 (t, J = 7.1 Hz, 1H), 1.93 (p, J = 7.1 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, chloroform-*d*) δ 170.2, 45.2, 31.2, 27.8.

***N,N′*-(Propane-1,3-diyl)bis(4-methylbenzenesulfonamide) (7).** A 500 mL round-bottom flask equipped with a magnetic stir bar and a pressure-equalizing drop funnel was charged with water (80 mL) and potassium carbonate (13.82 g, 100.0 mmol) followed by 1,3-propanediamine (4.2 mL, 50.0 mmol). The pressure-equalizing drop funnel was charged with THF (85 mL) and *para*-toluenesulfonyl chloride (19.06 g,100.0 mmol) and was added over a 4.5 h period to the carbonate solution. Once added, the solution was stirred for 10 h at 23 °C and poured over water (40 mL) at 0 °C. The white solid was filtered, washed with ethanol (50.0 mL, 0 °C), and dried in vacuo to afford bis-sulfonamide **7** (18.17 g, 47.50 mmol) in a 95% yield. Mp = 145−148 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.73 (d, J = 8.3 Hz, 4H), 7.31 (d, J = 8.3 Hz, 4H), 4.83 (s, 2H), 3.02 (t, J = 6.1 Hz, 6H), 2.43 (s, 4H), 1.67 (p, J = 6.2 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 143.6, 136.8, 129.8, 127.0, 39.7, 29.9, 21.5. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{23}O_4N_2S_2$ 383.1094, found 383.1097.

***N,N′*-(Propane-1,3-diyl)bis(*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide) (8a).** *Method A.* A 25 mL round-bottom flask equipped with a condenser, a nitrogen inlet, and a magnetic stir bar was charged with *N,N′*-(propane-1,3-diyl)bis(4-methylbenzenesulfonamide) (**7**) (0.82 g, 2.14 mmol), potassium carbonate (0.65 g, 4.71 mmol), ethylene carbonate (0.75 g, 8.56 mmol), and DMF (0.5 M, 4.3 mL). This solution was maintained at 110−120 °C for 4 h in an oil bath controlled with a thermocouple and then cooled to 23 °C. The DMF was removed, and the yellow residue was taken up in ethyl acetate (50 mL) and washed with 0.5 M HCl (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo to afford a thick yellow oil. The residue was subjected to column chromatography (2:1, ethyl acetate/hexane) to afford **8a** (0.473 g, 1.01 mmol) as a clear viscous oil in a 47% yield.

Method B. A 50 mL round-bottom flask was charged with *N,N′*-(propane-1,3-diyl)bis(4-methylbenzenesulfonamide) (**7**) (5.00 g, 13.1 mmol), ethylene carbonate (2.88 g, 32.8 mmol), and potassium hydroxide (0.050 g, 0.891 mmol). The mixture was stirred for 4 h at 115 °C in an oil bath controlled with a thermocouple, at which time, the residue was cooled to 0 °C via an external ice bath and diluted with MilliQ water (10 mL). The solution was extracted with ethyl acetate (20 mL × 3), and the combined organic layers were washed with 1 M HCl (10 mL), water (10 mL), and brine (5 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The remaining residue was purified via flash chromatography (3:2 EtOAc/Hex) providing **8a** (5.47 g, 11.66 mmol) in an 89% yield as a clear oil. R_f = 0.40 (EtOAc); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.63 (d, J = 8.4 Hz, 4H), 7.25 (d, J = 8.1 Hz, 4H), 3.74−3.64 (m, 4H), 3.42−3.33 (m, 4H), 3.20−3.09 (m, 8H), 2.35 (s, 6H), 1.90 (p, J = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 143.6, 135.5, 129.8, 127.2, 61.4, 51.7, 47.9, 28.6, 21.5. IR ν_{max} 3524, 2927, 1597, 1455, 1331, 1155, 1088, 815, 728, 656 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{31}O_6N_2S_2$ 471.1618, found 471.1619.

***N*-(2-Hydroxyethyl)-4-methyl-*N*-(3-((4-methylphenyl)sulfonamido)propyl)benzenesulfonamide (8b).** A 50 mL round-bottom flask was charged with *N,N′*-(propane-1,3-diyl)bis(4-methylbenzenesulfonamide) (**7**) (5.00 g, 13.1 mmol), ethylene carbonate (2.88 g, 32.8 mmol), and potassium hydroxide (0.050 g, 0.891 mmol). The mixture was stirred for 2 h at 110 °C in an oil bath controlled with a thermocouple, at which time, the residue was cooled to 0 °C via an external ice bath and diluted with MilliQ water (10 mL). The solution was extracted with ethyl acetate (20 mL × 3), and the combined organic layers were washed with 1 M HCl (10 mL), water (10 mL), and brine (5 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The remaining residue was purified via flash chromatography (3:2 EtOAc/Hex) providing **8b** (2.18 g, 5.11 mmol) in a 39% yield as a clear oil. R_f = 0.50 (EtOAc); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.71 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.31−7.21 (m, 4H), 5.64 (t, J = 6.4 Hz, 1H), 3.68 (q, J = 5.3 Hz, 2H), 3.28−3.10 (m, 4H), 2.99 (q, J = 6.3 Hz, 2H), 2.83 (s, 1H), 2.39 (s, 3H), 2.38 (s, 3H), 1.77 (p, J = 6.5 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 143.8, 143.3, 136.9, 135.3, 129.9, 129.7, 127.2, 127.0, 61.5, 51.8, 47.5, 39.9, 28.9, 21.5. IR ν_{max} 3475, 3217, 2932, 2873, 1597, 1493, 1451, 1326, 1151, 1091, 741 cm^{-1}. HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{19}H_{26}O_5N_2NaS_2$ 449.1175, found 449.1176.

***N*-(2-(2-Hydroxyethoxy)ethyl)-*N*-(3-((*N*-(2-hydroxyethyl)-4-methylphenyl)sulfonamido)propyl)-4-methylbenzenesulfonamide (8c).** A 50 mL round-bottom flask was charged with *N,N′*-(propane-1,3-diyl)bis(4-methylbenzenesulfonamide) (**7**) (5.00 g, 13.1 mmol), ethylene carbonate (2.88 g, 32.8 mmol), and potassium hydroxide (0.050 g, 0.891 mmol). The mixture was stirred for 4 h at 190 °C in an oil bath controlled with a thermocouple, at which time,

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the brownish residue was cooled to 0 °C via an external ice bath and diluted with MilliQ water (10 mL). The solution was extracted with ethyl acetate (20 mL × 3), and the combined organic layers were washed with 1 M HCl (10 mL), water (10 mL), and brine (5 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The remaining residue was purified via flash chromatography (3:2, EtOAc/Hex) providing *N*-(2-(2-hydroxyethoxy)ethyl)-*N*-(3-((*N*-(2-hydroxyethyl)-4-methylphenyl)sulfonamido)propyl)-4-methylbenzenesulfonamide **8c** (3.57 g, 6.94 mmol) in a 53% yield as a clear oil. R_f = 0.35 (EtOAc); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.60 (dd, J = 8.3, 2.5 Hz, 4H), 7.38−7.05 (m, 4H), 3.72−3.63 (m, 2H), 3.63−3.58 (m, 2H), 3.52 (t, J = 5.4 Hz, 2H), 3.45−3.38 (m, 2H), 3.24 (t, J = 5.4 Hz, 2H), 3.16 (dd, J = 8.4, 6.4 Hz, 2H), 3.14−3.04 (m, 4H), 2.33 (s, 6H), 1.86 (p, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 143.5, 143.4, 136.2, 135.5, 129.8, 129.7, 127.2, 127.1, 72.4, 70.0, 61.4, 61.2, 51.5, 48.4, 48.0, 47.3, 28.2, 21.4. IR ν_{max} 3516, 3411, 2926, 2875, 1597, 1328, 1151, 1087, 727 cm^{-1}. HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{22}H_{30}O_8N_2NaS_2$ 537.1700, found 537.1699.

***N,N′*-Bis-(*p*-toluenesulfonyl)cystamine (9).** A 300 mL round-bottom flask equipped with a magnetic stir bar, a nitrogen inlet, and a pressure-equalizing addition funnel was charged with cystamine (10.0 g, 44.0 mmol), potassium carbonate (24.32 g, 176.0 mmol), and MilliQ water (70 mL). The addition funnel was charged with THF (75 mL) and *p*-toluenesulfonyl chloride (16.77 g, 88.0 mmol) and added dropwise over 2 h at room temperature. The mixture was vigorously stirred for 12 h, at which time, the THF was evaporated in vacuo, and the aqueous layer was diluted with 0.5 M HCl (50 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was washed with 3 M HCl (2 × 20 mL), water (2 × 20 mL), and saturated NaCl (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated, providing a white solid. The crude product was recrystallized from methanol to give *N,N′*-bis-(*para*-toluenesulfonyl)-cystamine (19.0 g, 39.6 mmol) in a 90% yield as a white solid. Consistency of spectral data is shown with the lit. data.[28] Melting point: 89−90 °C (lit. 77−78 °C)[1]; R_f = 0.10 (7:3, Hex/EtOAc); IR ν_{max} 3281, 2925, 2865, 1595, 1418, 1324, 1157, 1092, and 814, cm^{-1}; ^{1}H NMR (chloroform-*d*, 300 MHz): δ 7.77 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.96 (t, J = 6.4 Hz, 1H), 3.26 (q, J = 6.4 Hz, 2H), 2.73 (t, J = 6.4 Hz, 2H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (chloroform-*d*, 75 MHz): δ 21.7, 38.0, 41.8, 127.2, 130.0, 136.8, 143.8.

1,11-Dithia-4,8-diazacyclotetradecane (L1). A flame-dried 100 mL round-bottom flask equipped with a septum, a magnetic stir bar, and a nitrogen inlet was charged with small pieces of sodium metal (41.4 mg, 1.80 mmol), freshly distilled dimethoxy ethane (2 mL), and naphthalene (254.0 mg, 1.98 mmol). This mixture was stirred at room temperature under a nitrogen atmosphere for 2 h, affording a dark green solution. A second flame-dried round-bottom flask equipped with a septum, a magnetic stir bar, and a nitrogen inlet was charged with freshly distilled dimethoxy ethane (1 mL), and bis-sulfonamide **3** (100.0 mg, 0.180 mmol) was cooled to −30 °C via an external acetone/liquid nitrogen bath. The sodium naphthalenide solution was added dropwise using a gas-tight syringe to the round-bottom flask at −30 °C, until the solution maintained the dark green color for 5 min. The reaction was then allowed to warm to room temperature over 15 min and cooled to 0 °C via an external ice bath. At this time, water (1 mL) was added, which dissipated the green color immediately, and the solution was concentrated in vacuo. The residue was treated with 3 M HCl (10.0 mL, pH ∼ 1) and washed with ethyl acetate (4 × 5 mL). The aqueous layer was then basified using 6 M NaOH (5.00 mL, pH ∼ 11) at 0 °C, and the freebase was extracted with chloroform (5 × 5 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The orange oil was then subjected to a Dowex50W-X12 $(H^+)^b$ column (methanol wash, eluted with 6 M $NH_{3(MeOH)}$) to afford **L1** (36.70 mg, 0.157 mmol) as a clear oil in an 87% yield. ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.88−2.81 (m, 4H), 2.80−2.72 (m, 12H), 1.89 (p, J = 6.5 Hz, 2H), 1.82 (p, J = 5.8 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 46.9, 46.8, 32.4, 29.0, 28.3, 27.2. IR ν_{max} 3284, 2912, 2809, 1660, 1445, 1294, 1256, 1129, 742 cm^{-1}. HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{10}H_{23}N_2S_2$ 235.1297, found 235.1297.

1,11-Dithia-4,8-diazacyclotetradecane-4,8-diium Dichloride (L1-HCl). A 25 mL round-bottom flask was charged with 1 M $HCl_{(MeOH)}$ (3 mL), cooled to ∼0 °C via an external ice bath, and **L1** (36.70 mg, 0.157 mmol) in MeOH (1 mL) was added. The solution was warmed to room temperature and concentrated in vacuo affording 1,11-dithia-4,8-diazacyclotetradecane-4,8-diium dichloride (0.483 mg, 0.157 mmol) as a white residue in quantitative yield. ^{1}H NMR (400 MHz, deuterium oxide) δ 3.27 (t, J = 6.1 Hz, 4H), 3.23 (t, J = 7.3 Hz, 4H), 2.86 (t, J = 6.1 Hz, 4H), 2.73 (t, J = 6.4 Hz, 4H), 2.16 (p, J = 7.3 Hz, 2H), 1.86 (p, J = 6.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, deuterium oxide) δ 44.1, 42.5, 29.5, 27.5, 26.3, 20.5; HRMS (ESI) *m/z* [M−2HCl+H]$^+$ calcd for $C_{10}H_{23}N_2S_2$ 235.1279, found 235.1298.

1,11-Dithia-4,8-diazacyclotetradecane Copper II Perchlorate (L1Cu(ClO4)$_2$). A 25 mL round-bottom flask equipped with a magnetic stir bar, a nitrogen inlet, and rubber septa was charged with MeCN (5 mL) and **L1** (36.70 mg, 0.157 mmol) and cooled to ∼0 °C via an external ice bath; in copper(II) perchlorate, MeCN (2 mL) was added. The solution immediately turned a vibrant purple color and was stirred at room temperature for an additional 30 min, followed by concentration in vacuo. Chelate $\mathbf{L1Cu(ClO4)_2}$ was obtained as purple prisms in quantitative yields. $\mathbf{[(L1Cu)_2\mu\text{-}Cl](ClO_4)_3}$ was isolated using an identical procedure but as a separate sample. **Caution!** Perchlorate salts of metal complexes containing organic ligands as solids or in organic solvents are potentially explosive. Although no problems were encountered by us, cautious handling of only small amounts of these compounds should be the rule.

3,3′-(Ethane-1,2-diylbis(sulfanediyl))dipropanenitrile (13). A Pyrex test tube was charged with potassium carbonate (0.304 g, 2.20 mmol), 1,2-ethanedithiol (0.08 mL, 1.00 mmol), and acrylonitrile (0.28 mL, 4.40 mmol). This solution was placed in a sonication bath and sonicated for 30 min at 53 °C. After which, chloroform (5 mL) was added, potassium carbonate was filtered off, and the mother liquor was concentrated in vacuo to provide 0.197 g (98%) of 3,3′-(ethane-1,2-diylbis(sulfanediyl))dipropanenitrile as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 2H), 2.82 (t, J = 7.0 Hz, 2H), 2.65 (t, J = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 118.4, 32.2, 27.8, 19.1. IR ν_{max} 2938, 2917, 2239, 1417, 1279, 1213, 901, 739 cm^{-1}. HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_8H_{12}N_2NaS_2$ 223.0334, found 223.0335.

1,4-Dithia-8,11-diazacyclotetradecane Bis-hydrochloride (L2-HCl). A 25 mL round-bottom flask equipped with a condenser, a nitrogen inlet, and a magnetic stir bar was charged with 8,11-ditosyl-1,4-dithia-8,11-diazacyclotetradecane (12) (0.200 g, 0.368 mmol) and xylene (0.12 M, 3.1 mL). The solution was cooled to 0 °C, Red-Al (3.5 M (toluene), 1.7 mL) was added dropwise, and the mixture was refluxed with a heating mantle for 2 h and then cooled to 23 °C. The solution was cooled to 0 °C, 3 M sodium hydroxide (4 mL) was added dropwise, and the cloudy solution was extracted with chloroform (5 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a yellow residue. The crude product was treated with methanolic HCl (1 M, 10 mL), concentrated to ∼1 mL, and filtered. The filter cake was washed with cold methanol (1 mL) to provide L2-HCl (0.984 g, 0.320 mmol) as a white powder in an 87% yield. ^{1}H NMR (400 MHz, deuterium oxide) δ 4.65 (s, 4H), 3.51 (s, 4H), 3.28 (t, J = 7.3 Hz, 4H), 2.85 (s, 4H), 2.68 (t, J = 6.7 Hz, 4H), 1.98 (p, J = 6.9 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, deuterium oxide) δ 47.7, 42.9, 33.7, 30.5, 26.1. IR ν_{max} 3381, 2935, 1616, 1455, 1015, 805 cm^{-1}. HRMS (ESI) *m/z* [M−2HCl+H]$^+$ calcd for $C_{10}H_{23}N_2S_2$ 235.1297, found 235.1298.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01682.

^{1}H, ^{13}C, gCOSY, gHSQC, and gHMBC spectra, including X-ray crystallography, and HRMS (PDF)

X-ray crystallographic data for compound **7** (CIF)

X-ray crystallographic data for compound **8b** (CIF)

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X-ray crystallographic data for compound **4** (CIF)
X-ray crystallographic data for compound **3** (CIF)
X-ray crystallographic data for compound **10** (CIF)
X-ray crystallographic data for compound **L1-HCl** (CIF)
X-ray crystallographic data for compound [(**L1Cu**)$_2$$\mu$-**Cl**](**ClO**$_4$)$_3$ (CIF)
X-ray crystallographic data for compound **L1Cu(ClO4)**$_2$ (CIF)

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Notes

The authors declare no competing financial interest.

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ADDITIONAL NOTES

[a]Potential nitrogen mustard derivative, use safe laboratory practices when isolating the product.
[b]If ammonium salts are present after ion-exchange chromatography, dissolve the freebase in chloroform, filter, and concentrate in vacuo to provide **L1** free of salts.

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