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Synthesis and Structural Studies of Hydrophilic Mesocyclic Trithioethers

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ABSTRACT

The functionalized mesocyclic trithioethers, 1,4,7-trithiacyclodecane-9,9-dimethanol (10S3-diMeOH), 9-methyl-1,4,7-trithiacyclodecane-9-carboxylic acid (Me-10S3-acid), 1,4,7-trithiacycloundecane-9,10-diol (dihydroxy-11S3), 1,5,9-trithiacyclododecane-3,3-dimethanol (12S3-diMeOH), 3-methyl-1,5,9-trithiacyclododecane-3-carboxylic acid (Me-12S3-acid), and 1,5,9-trithiacyclotridecane-11,12-diol (dihydroxy-13S3), have been synthesized using the cesium dithiolate technique. The single-crystal X-ray structure has been determined for 3-methyl-1,5,9-trithiacyclododecane-3-carboxylic acid. The compound crystallizes in the monoclinic space group $P2_1/n$, with $a = 9.513(2)$ Å, $b = 5.706(1)$ Å, $c = 25.70(1)$ Å, $\beta = 96.50(1)°$, $Z = 4$, and $R = 0.075$. © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:123–128, 1998

Dedicated to Prof. William E. McEwen on the occasion of his seventy-fifth birthday and to celebrate his many contributions to the field of heteroatom chemistry.

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†Taken, in part, from the Master's thesis of S.-Y. Liou (University of Alabama in Huntsville, 1993).

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INTRODUCTION

There has been a great deal of interest in the preparation and coordination chemistry of crown thioethers in the past 15 years, and a number of review articles have appeared [1]. Medium-sized ring trithioethers can serve as facially coordinating tridentate ligands in complexing a number of transition-metal and heavy-metal ions as well as metals in zero or low oxidation states [1]. The complex stabilities, ligand field strengths of homologous members of this class depend on the size of the ring of the ligand as well as the size of the chelate ring [1].

The hydrophobic character of thioethers makes these compounds essentially insoluble in water. This disadvantage restricts the application when necessary to bind metal ions in aqueous media. In order to increase water solubility, some workers have resorted to combinations with crown ethers [2] or poly(ethylene glycol) [3]. In our program, we wished to design and synthesize crown thioethers appended with hydrophilic functional groups to allow their use as potential therapeutic chelators for remediation of heavy-metal poisoning (sensu Jones [4]). Functionalized crown thioethers [5] not only provide increased water solubility, but also allow for further

elaboration, attachment to solid substrates, etc. [6]. In addition to providing sites for synthetic elaboration and hydrophilicity, the steric effects of the appended functional groups may also help to raise the strain energy of exodentate conformations, thus favoring conformations of the free ligand with endodentate sulfurs [7]. In this article, we report the synthesis and complexation of the following functionalized mesocyclic trithioethers: 1,4,7-trithiacyclodecane-9,9-dimethanol (10S3-diMeOH), 9-methyl-1,4,7-trithiacyclodecane-9-carboxylic acid (Me-10S3-acid), 1,4,7-trithiacycloundecane-9,10-diol (dihydroxy-11S3), 1,5,9-trithiacyclododecane-3,3-dimethanol (12S3-diMeOH), 3-methyl-1,5,9-trithiacyclododecane-3-carboxylic acid (Me-12S3-acid), and 1,5,9-trithiacyclotridecane-11,12-diol (dihydroxy-13S3) (Figure 1). In addition, the X-ray crystal structure of Me-12S3-acid is presented.

RESULTS AND DISCUSSION

The syntheses of the functionalized mesocyclic trithioethers have been conveniently carried out using the cesium dithiolate technique [8] in yields ranging from 9% (12S3-diMeOH) to 33% (Me-10S3-acid) (Table 1). The synthesis involves reaction of equimolar amounts of a dithiol and a functionalized dihalide. The reactions are performed under high dilution conditions using dimethylformamide as solvent. Each cyclization requires two equivalents of base, except for the preparation of carboxylic acid derivatives, which need three equivalents of base. We have found that control of reaction temperatures at 60°C and a dry nitrogen atmosphere are crucial in maximizing the yields of these hydrophilic crown thioethers.

A single-crystal X-ray structural determination has been carried out for Me-12S3-acid (Table 2). The crystallographic coordinates are listed in Table 3, and selected bond lengths, bond angles, and torsion angles are presented in Table 4. The conformation adopted by the compound in the solid state is the same as that found for 12S3 [9] and hydroxy-12S3 [8c]. The compound adopts a [3333] conformation with the two substituents, the methyl group and the carboxylic acid moiety, occupying the "corner" position in order to minimize transannular steric repulsions (Figure 2).

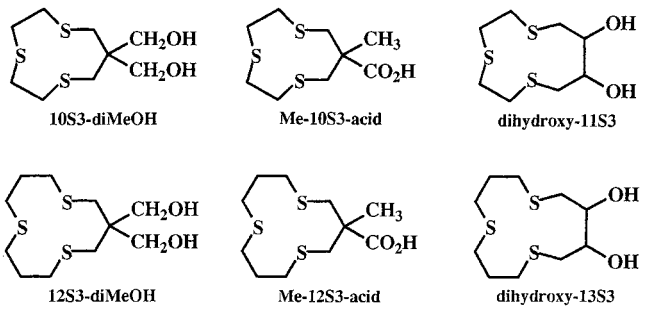

FIGURE 1 The hydrophilic mesocyclic trithioethers discussed in this article.

EXPERIMENTAL

Materials

The solvents tetrahydrofuran (THF), dimethylformamide (DMF), ethanol (EtOH), ethyl acetate (EtOAc), and hexanes (C_6H_{14}) were dried and distilled using common methods [10]. The reagents acetic anhydride (Ac_2O), lithium aluminum hydride (LAH), sodium, sodium hydride, cesium carbonate, anhydrous magnesium sulfate, silica gel (grade 60, 230–400 mesh), bis(2-mercaptoethyl) sulfide, 2,2-bis(bromomethyl)-1,3-propanediol, 3,3′-dichloropivalic acid, and 1,4-dibromo-2,3-butanediol were used as received from Aldrich Chemical Co. Bis(3-mercaptopropyl) sulfide was prepared as described in the literature [8c]. All heavy-metal salts were used as received from Alfa Inorganics.

Measurements

Melting points were determined using a Mel-Temp II device and are uncorrected. Infrared spectra were obtained using a Bio-Rad FTS-60 Fourier transform infrared spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on an IBM/Bruker AF 200 spectrometer. Mass spectra were obtained on a Hewlett-Packard HP-5988 mass spectrometer. Analyses were performed by Atlantic Microlab, Inc. (Atlanta, Georgia) or by Galbraith Laboratories, Inc. (Knoxville, Tennessee).

Preparation of 9,9-Bis(hydroxymethyl)-1,4,7-trithiacyclodecane (10S3-diMeOH)

A 1 L three-necked round-bottom flask, equipped with syringe-drive pump, magnetic stir bar, reflux condenser, oil bath, and a nitrogen inlet–outlet, was charged with freshly distilled DMF (500 mL) and cesium carbonate (7.17 g, 0.022 mol). Into one syringe was added a solution of bis(2-mercaptoethyl) sulfide (3.09 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. Into the other syringe was added a solution of 2,2-bis(bromomethyl)-1,3-propanediol (5.24 g, 0.020 mol) and sufficient anhydrous DMF to

TABLE 1 Preparation of Hydrophilic Mesocyclic Trithioethers

Mesocyclic Trithioether	*Dithiol*	*Dihalide*	*% Yield*
10S3-diMeOH	$S(CH_2CH_2SH)_2$	$(BrCH_2)_2C(CH_2OH)_2$	10.4%
Me-10S3-acid	$S(CH_2CH_2SH)_2$	$(ClCH_2)_2C(CH_3)CO_2H$	33.5%
Dihydroxy-11S3	$S(CH_2CH_2SH)_2$	$BrCH_2CHOHCHOHCH_2Br$	14.1%
12S3-diMeOH	$S(CH_2CH_2CH_2SH)_2$	$(BrCH_2)_2C(CH_2OH)_2$	9.2%
Me-12S3-acid	$S(CH_2CH_2CH_2SH)_2$	$(ClCH_2)_2C(CH_3)CO_2H$	10.8%
Dihydroxy-13S3	$S(CH_2CH_2CH_2SH)_2$	$BrCH_2CHOHCHOHCH_2Br$	11.4%

TABLE 2 Crystallographic Data for Me-12S3-acid

Molecular formula	$C_{11}H_{20}S_3O_2$
Molecular weight	280.45
Crystal system, space group	Orthorhombic, $P2_{1/n}$
Radiation, wavelength, Å	Mo$K\alpha$, 0.71073
Cell dimensions	
a, Å	9.513(2)
b, Å	5.706(1)
c, Å	25.70(1)
β, deg	96.50(1)
V, Å^3	1386.1(7)
Z	4
D_{calcd}, g cm^{-1}	1.344
Absorption coeff. cm^{-1}	4.988
No. refls. measd.	3377
No. obsd. refls.	1739
No. variables	206
R	0.075
R_w	0.076

TABLE 3 Final Atomic Parameters for Me-12S3-acid

Atom	*x*	*y*	*z*	*B* (Å^2)
S1	0.8659(2)	0.1218(3)	0.70313(6)	3.76(3)
C2	0.7592(6)	0.025(1)	0.6441(2)	3.1(1)
C3	0.7132(6)	0.2281(9)	0.6071(2)	2.5(1)
C4	0.8394(6)	0.354(1)	0.5872(2)	3.3(1)
S5	0.9364(2)	0.1649(3)	0.54693(6)	4.11(3)
C6	1.1055(7)	0.314(1)	0.5510(3)	4.7(2)
C7	1.2024(7)	0.253(1)	0.6002(3)	5.0(2)
C8	1.2512(7)	−0.005(1)	0.6015(3)	5.1(2)
S9	1.3380(2)	−0.1031(4)	0.66320(9)	5.82(5)
C10	1.1982(7)	−0.071(1)	0.7045(3)	4.4(2)
C11	1.0693(7)	−0.222(1)	0.6913(2)	3.6(1)
C12	0.9508(7)	−0.156(1)	0.7227(2)	4.0(1)
C13	0.6262(7)	0.410(1)	0.6334(2)	3.5(1)
C14	0.6211(6)	0.125(1)	0.5597(2)	2.8(1)
O1	0.6017(5)	−0.0817(7)	0.5519(2)	4.2(1)
O2	0.5645(5)	0.2872(8)	0.5275(2)	4.9(1)

dilute it to 25 mL. The two solutions were added simultaneously (1.5 mL/h) to the rapidly stirred and heated (held at ca. 60°C) DMF/Cs_2CO_3 mixture. Upon completion of the addition (18 h), the reaction mixture was stirred for an additional 24 hours and was allowed to cool to room temperature. The reaction mixture was filtered and the DMF was removed from the filtrate under vacuum (temperature <60°C) to give a yellow residual oil. The residue was chromatographed using medium-pressure liquid chromatographic techniques (MPLC) on a silica gel column (51 mm diameter × 45 cm length) with 20% EtOAc in hexanes to give 480 mg (10.4% yield) 10S3-diMeOH as a colorless crystalline solid: mp 157–158°C; IR (KBr) 3289 (s, b, O-H), 2942 (s), 2876, 1421 (s), 1192, 1033 (s), 724 cm^{-1}; ^{1}H NMR (CD_3NO_2/TMS) δ 4.35 (t, 2 H, -OH), 3.53 (s, 4 H, -CH_2OH), 2.81 (m, 8 H, -SCH_2CH_2S-), 2.69 (s, 4 H, -SCH_2C$(CH_2OH)_2$-); ^{13}C NMR (CD_3NO_2/TMS) δ 61.52 (-CH_2OH), 44.88 (*quat.* C), 33.93, 33.29, 31.26; mass spectrum (EI, 70 eV) *m*/*e* 254. The macrocyclic product, 20S6-tetraMeOH (320 mg, 3.1% yield), was also isolated from the MPLC of the reaction mixture (eluted out before 10S3-diMeOH). Anal. calcd for $C_9H_{18}S_3O_2$: C, 42.49; H, 7.13; S, 37.81. Found: C, 42.60; H, 7.12; S, 37.71.

Preparation of 9-Methyl-1,4,7-trithiacyclodecane-9-carboxylic Acid (*Me-10S3-acid*)

A 1 L three-necked round-bottom flask, equipped with syringe-drive pump, magnetic stir bar, reflux condenser, and a nitrogen inlet–outlet, was charged with freshly distilled DMF (500 mL) and cesium carbonate (20.2 g, 0.062 mol). Into one syringe was added a solution of bis(2-mercaptoethyl) sulfide (3.09 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. Into the other syringe was added a solution of 3,3′-dichloropivalic acid (3.42 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. The two solutions were added simultaneously (1.5 mL/h) to the rapidly stirred DMF/Cs_2CO_3 mixture at room temperature. Upon completion of the addition (18 h), the reaction mixture was stirred for an additional 48 hours. The reaction mixture was filtered and the DMF was removed from the filtrate under vacuum (temperature < 45°C) to give a yellow sticky liquid. The residue was dissolved in 50 mL 0.1 *M* NaOH and washed with diethyl ether (3 × 50 mL). The aqueous phase was neutralized with 0.1 *M* HCl

TABLE 4 Selected Geometrical Parameters for Me-12S3-acid

Selected Bond Lengths (Å)			
S1–C2	1.814(5)	S9–C10	1.802(7)
C2–C3	1.530(8)	C10–C11	1.508(9)
C3–C4	1.535(8)	C11–C12	1.506(9)
C4–S5	1.816(6)	C12–S1	1.824(7)
S5–C6	1.811(7)	C3–C13	1.532(8)
C6–C7	1.518(9)	C3–C14	1.537(7)
C7–C8	1.54(1)	C14–O1	1.206(7)
C8–S9	1.793(7)	C14–O2	1.316(7)
Selected Bond Angles (°)			
S1–C2–C3	112.4(4)	C11–C12–S1	113.9(4)
C2–C3–C4	112.5(4)	C12–S1–C2	98.8(3)
C3–C4–S5	112.4(4)	C2–C3–C13	111.8(4)
C4–S5–C6	101.3(3)	C2–C3–C14	107.4(4)
S5–C6–C7	113.1(5)	C4–C3–C13	108.2(5)
C6–C7–C8	112.9(6)	C4–C3–C14	108.1(4)
C7–C8–S9	115.0(5)	C13–C3–C14	108.8(4)
C8–S9–C10	101.1(3)	O1–C14–O2	122.7(5)
S9–C10–C11	116.4(5)	O1–C14–C3	124.6(5)
C10–C11–C12	112.1(5)	O2–C14–C3	112.6(5)
Selected Dihedral Angles (°)			
S1–C2–C3–C4	62.61 (0.51)	C12–S1–C2–C3	−159.81 (0.40)
C2–C3–C4–S5	64.39 (0.51)	S1–C2–C3–C13	−59.35 (0.53)
C3–C4–S5–C6	−159.24 (0.41)	S1–C2–C3–C14	−178.58 (0.35)
C4–S5–C6–C7	82.66 (0.55)	S5–C4–C5–C13	−171.65 (0.37)
S5–C6–C7–C8	66.71 (0.68)	S5–C4–C3–C14	−54.02 (0.52)
C6–C7–C8–S9	−168.86 (0.47)	C2–C3–C14–O1	−6.16 (0.72)
C7–C8–S9–C10	62.76 (0.56)	C2–C3–C14–O2	174.03 (0.45)
C8–S9–C10–C11	63.91 (0.56)	C4–C3–C14–O1	115.41 (0.59)
C9–C10–C11–C12	−171.34 (0.44)	C4–C3–C14–O2	−64.39 (0.58)
C10–C11–C12–S1	71.66 (0.59)	C13–C3–C14–O1	−127.31 (0.58)
C11–C12–S1–C2	76.96 (0.48)	C13–C3–C14–O2	52.88 (0.60)

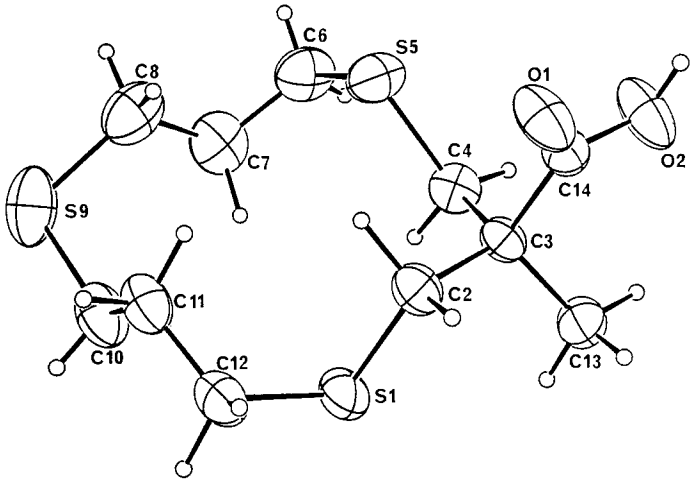

FIGURE 2 ORTEP perspective drawing of Me-12S3-acid.

and extracted with dichloromethane (3 × 100 mL). The dichloromethane extracts were combined, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum to give a brown solid that was purified by recrystallization (4×) from dichloromethane to give 1.69 g (33.5% yield) Me-10S3-acid as a colorless crystalline (needles) solid: mp 225–227°C; IR (KBr) 3057 (s, b, O–H), 2988 (s), 2929 (s), 1693 (s), 1424, 1372, 1217 (s), 940 (s), 837 cm^{-1}; ^1H NMR (CD_3NO_2/TMS) δ 12.68 (s, CO_2H), 3.35 (s, 4 H, -SCH_2C-(CH_3)(CO_2H)-), 2.86 (t, 4 H, -SCH_2CH_2S-), 2.73 (t, 4 H, -SCH_2CH_2S-), 1.28 (s, 3 H, -CH_3); ^{13}C NMR (CD_3NO_2/TMS) δ 194.36 (CO_2H), 47.50 (*quat.* C), 33.20 (-SCH_2CH_2S-), 31.13 (-SCH_2CH_2S-), 21.25 (-CH_3); mass spectrum (EI, 70 eV) *m/e* 252. Anal. calcd for $C_9H_{16}S_3O_2$: C, 42.82; H, 6.39; S, 38.11. Found: C, 42.86; H, 6.42; S, 38.10.

Preparation of 1,4,7-Trithiacycloundecane-9,10-diol (*dihydroxy-11S3*)

A 1 L three-necked round-bottom flask, equipped with syringe-drive pump, magnetic stir bar, reflux

condenser, oil bath, and a nitrogen inlet–outlet, was charged with freshly distilled DMF (500 mL) and cesium carbonate (7.17 g, 0.022 mol). Into one syringe was added a solution of bis(2-mercaptoethyl) sulfide (3.09 g, 0.020 mol) and sufficient anhydrous DMF to dilute to 25 mL. Into the other syringe was added a solution of 1,4-dibromo-2,3-butanediol (4.96 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. The two solutions were added simultaneously (1.5 mL/h) to the rapidly stirred and heated (held at ca. 60°C) DMF/Cs_2CO_3 mixture. Upon completion of the addition (18 h), the reaction mixture was stirred for an additional 24 hours and was allowed to cool to room temperature. The reaction mixture was filtered and the DMF was removed from the filtrate under vacuum (temperature <60°C) to give a pale yellow residual solid. The crude product was recrystallized from H_2O to give 640 mg (14.1% yield) dihydroxy-11S3 as a colorless microcrystalline solid: mp 178–180°C; IR (KBr) 3398 (s, b, O–H), 2899 (s), 1700, 1659, 1405 (s), 1263, 1092, 1037, 939, 879 cm^{-1}; ^1H NMR (CD_3NO_2/TMS) δ 4.07 (p, 2 H, -OH), 3.03 (m, 2 H, -SCH_2CH(OH)-), 2.95–2.60 (m, 12 H, -$SCH_2CH_2SCH_2$-); ^{13}C NMR (CD_3NO_2/TMS) δ 66.95 (-CHOH-), 31.59, 28.48, 28.01; mass spectrum (EI, 70 eV) *m/e* 240. Anal. calcd for $C_8H_{16}S_3O_2$: C, 39.97; H, 6.71; S, 40.01. Found: C, 39.96; H, 6.75; S, 39.94.

Preparation of 3,3-Bis(hydroxymethyl)-1,5,9-trithiacyclododecane (12S3-diMeOH)

A 1 L three-necked round-bottom flask, equipped with syringe-drive pump, magnetic stir bar, reflux condenser, oil bath, and a nitrogen inlet–outlet, was charged with freshly distilled DMF (500 mL) and cesium carbonate (7.17 g, 0.022 mol). Into one syringe was added a solution of bis(3-mercaptopropyl) sulfide (3.56 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. Into the other syringe was added a solution of 2,2-bis(bromomethyl)-1,3-propanediol (5.24 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. The two solutions were added simultaneously (1.5 mL/h) to the rapidly stirred and heated (held at ca. 60°C) DMF/Cs_2CO_3 mixture. Upon completion of the addition (18 h), the reaction mixture was stirred for an additional 24 hours and was allowed to cool to room temperature. The reaction mixture was filtered and the DMF was removed from the filtrate under vacuum (temperature <60°C) to give a yellow residual oil. The residue was chromatographed using medium-pressure liquid chromatographic techniques (MPLC) on a silica gel column (51 mm diameter × 45 cm length) with 30% EtOAc in hexanes to give 520 mg (9.2% yield) 10S3-diMeOH as a colorless crystalline solid: mp 170–172°C; IR (KBr) 3261 (s, b, O–H), 2915 (s), 2847, 1832 (s), 1803, 1419 (s), 1260, 1094 (s), 890, 771 cm^{-1}; ^1H NMR (CD_3NO_2/TMS) δ 3.46 (s, 4 H, -CH_2OH), 2.67 (s, 4 H, -$SCH_2C(CH_2OH)_2$-), 2.65–1.50 (m, 8 H, -$SCH_2CH_2CH_2S$-), 2.04 (br. s, OH), 1.88 (m, 4 H, -$SCH_2CH_2CH_2S$-); ^{13}C NMR (CD_3NO_2/TMS) δ 61.51 (-CH_2OH), 27.50 (*quat.* C), 26.83, 22.71, 22.23, 21.29; mass spectrum (EI, 70 eV) *m/e* 282. Anal. calcd for $C_{11}H_{22}S_3O_2$: C, 46.77; H, 7.85; S, 34.05. Found: C, 46.70; H, 7.89; S, 34.01.

Preparation of 3-Methyl-1,5,9-trithiacyclododecane-3-carboxylic acid (Me-12S3-acid)

A 1 L three-necked round-bottom flask, equipped with syringe-drive pump, magnetic stir bar, reflux condenser, and a nitrogen inlet–outlet, was charged with freshly distilled DMF (500 mL) and cesium carbonate (20.2 g, 0.062 mol). Into one syringe was added a solution of bis(3-mercaptopropyl) sulfide (3.56 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. Into the other syringe was added a solution of 3,3′-dichloropivalic acid (3.42 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. The two solutions were added simultaneously (1.5 mL/h) to the rapidly stirred DMF/Cs_2CO_3 mixture at room temperature. Upon completion of the addition (18 h), the reaction mixture was stirred for an additional 24 hours. The reaction mixture was filtered and the DMF was removed from the filtrate under vacuum (temperature <45°C) to give a yellow sticky liquid. The residue was dissolved in 50 mL of 0.1 *M* NaOH and washed with diethyl ether (3 × 50 mL). The aqueous phase was neutralized with 0.1 *M* HCl and extracted with dichloromethane (3 × 100 mL). The dichloromethane extracts were combined, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum to give a yellow solid that was purified by recrystallization (4×) from dichloromethane to give 605 mg (10.8% yield) Me-12S3-acid as a colorless microcrystalline solid: mp 181–183°C; IR (KBr) 3086 (s, b, O–H), 2955 (s), 2928 (s), 1686 (s), 1463, 1419, 1396, 1262, 1191 (s), 911 cm^{-1}; ^1H NMR (CD_3NO_2/TMS) δ 12.11 (s, CO_2H), 3.04 (s, 4 H, -$SCH_2C(CH_3)(CO_2H)$-), 2.72–2.59 (m, 8 H, -$SCH_2CH_2CH_2S$-), 1.96 (m, 4 H, -$SCH_2CH_2CH_2S$-), 1.35 (s, 3 H, -CH_3); ^{13}C NMR (CD_3NO_2/TMS) δ 179.91 (CO_2H), 35.94 (*quat.* C), 31.53, 26.92, 26.30, 24.25 -CH_3); mass spectrum (EI, 70 eV) *m/e* 280. Anal. calcd for $C_{11}H_{20}S_3O_2$: C, 47.11; H, 7.19; S, 34.29. Found: C, 47.09; H, 7.21; S, 34.23.

Preparation of 1,5,9-Trithiacyclotridecane-11,12-diol (dihydroxy-13S3)

A 1 L three-necked round-bottom flask, equipped with syringe-drive pump, magnetic stir bar, reflux

condenser, oil bath, and a nitrogen inlet–outlet, was charged with freshly distilled DMF (500 mL) and cesium carbonate (7.17 g, 0.022 mol). Into one syringe was added a solution of bis(3-mercaptopropyl) sulfide (3.56 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. Into the other syringe was added a solution of 1,4-dibromo-2,3-butanediol (4.96 g, 0.020 mol) and sufficient anhydrous DMF to dilute it to 25 mL. The two solutions were added simultaneously (1.5 mL/h) to the rapidly stirred and heated (held at ca. 60°C) DMF/Cs_2CO_3 mixture. Upon completion of the addition (18 h), the reaction mixture was stirred for an additional 24 hours and was allowed to cool to room temperature. The reaction mixture was filtered and the DMF was removed from the filtrate under vacuum (temperature <60°C) to give a brown residual solid. The residue was chromatographed using medium-pressure liquid chromatographic techniques (MPLC) on a silica gel column (51 mm diameter × 45 cm length) with 30% EtOAc in hexanes to give 610 mg (11.4% yield) dihydroxy-13S3 as a colorless crystalline solid: mp 149– 152°C; IR (KBr) 3261 (s, b, O–H), 2915 (s), 2847 (s), 1831 (s), 1803, 1419 (s), 1260, 1166, 1093, 1049 (s), 890, 770 cm^{-1}; ^1H NMR (CD_3NO_2/TMS) δ 4.11–3.80 (br, 2 H, -OH), 3.74 (m, 1 H, -SCH_2CH(OH)-), 3.60 (m, 1 H, -SCH_2CH(OH)-), 3.00–2.45 (m, 12 H, -SCH_2-) 1.83 (m, 4 H, -$SCH_2CH_2CH_2S$-); ^{13}C NMR (CD_3NO_2/TMS) δ66.47 (-CHOH-), 64.38 (-CHOH-), 31.83, 31.19, 30.43, 27.85, 25.92, 25.33, 24.56, 22.63; Mass spectrum (EI, 70 eV) *m/e* 268. Anal. calcd for $C_{10}H_{20}S_3O_2$: C, 44.74; H, 7.51; S, 35.83. Found: C, 44.81; H, 7.55; S, 35.74.

X-ray Single-Crystal Structure Study of Me-12S3-acid [11]

A clear colorless crystal suitable for X-ray diffraction was mounted on a CAD-4 diffractometer. The θ-2θ technique ($0° \leq 2\theta \leq 27.5°$) was used to collect the data of which those with $I \geq 3\sigma(I)$ were considered observed and were used in the calculations. The structure was solved by direct methods and refined by full-matrix least-squares techniques. The hydrogen atoms were added to the model in geometrically ideal positions and were not refined. Anisotropic refinement converged at $R = 0.0755$ and $R_w = 0.0762$.

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[11] Tables of atomic coordinates, thermal parameters, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre, United Kingdom, and are available upon request from the Director, CCDC, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation.