Novel Ring Contraction Reaction for the Synthesis of Functionalized Tetrathiamacrocyclic Ligand Molecules

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Received July 9, 1997[⊗]

Chlorination of [14]aneS$_4$-ol (1,4,8,11-tetrathiatetradecan-6-ol) and *cis*/*trans*-[14]aneS$_4$-diol (*cis*/*trans*-1,4,8,11-tetrathiatetradecane-6,13-diol) yields the corresponding dichloro-substituted macrocycles [14]aneS$_4$-Cl (1,4,8,11-tetrathiatetradecane 6-chloride) and *cis*/*trans*-[14]aneS$_4$-Cl$_2$ (*cis*/*trans*-1,4,8,11-tetrathiatetradecane 6,13-dichloride) in good yield. Thiomethylation of the chlorides produces the ring-contracted pendent thioether macrocycles [13]aneS$_4$-CH$_2$SCH$_3$ (1,4,7,10-tetrathiatridecane-5-(methylthio)methane) and *cis*/*trans*-*anti*-[12]aneS$_4$-(CH$_2$SCH$_3$)$_2$ (1,4,7,10-tetrathiadodecane-5,11-bis((methylthio)methane)). The mechanism of the ring contraction reaction is discussed in terms of the reactivity of the monochlorinated macrocycle toward ring contraction and the stereochemistry of the chlorinated intermediates and the thiomethylated products, which are based on the X-ray crystal structure analyses of *trans*-[14]aneS$_4$-Cl$_2$ and *trans*-*anti*-[12]aneS$_4$-(CH$_2$SCH$_3$)$_2$.

Introduction

Polythiamacrocyclic molecules have attracted considerable attention as versatile ligands for soft metal ions.[1] Due to their lack of protonation behavior, thioether ligands are able to coordinate metal ions independent of the pH of the solution, i.e., even in highly acidic media. Therefore, polythiamacrocycles are potentially useful ligands for (selective) metal ion extractions. However, they generally have limited water solubility, and the fact that the exo-orientation of the sulfur donors requires a conformational rearrangement prior to coordination often leads to comparatively small complex stabilities. These factors limit the applicability of polythiamacrocycles as metal ion extractants. Both of these problems may be solved by introduction of appropriate, i.e., sterically demanding and/or polar or charged substituents into the backbone of the macrocycles.[2] Transition metal compounds of polythiamacrocyclic ligands have also been extensively studied because of their interesting spectroscopic and electrochemical behavior, and copper(II/I) couples have been of particular interest due to possible parallels with bioinorganic systems.[1,3] The limited complex stabilities and water solubilities have also complicated studies in this area.

Polythiamacrocycles have often been prepared by a $CsCO_3$-directed, usually high-yielding synthesis involving the alkylation of thiols.[1,4,5] However, substituted ligands are not generally available by this route. Consequently, only few functionalized polythiamacrocycles have been reported so far. These include species with 1,3-dithia-2-ol,[2] 1,3-dithia-2-one,[6a] and 1,3-dithia-2-methine[6b] fragments. In particular for small rings, i.e., 12- and 13-membered tetrathiamacrocycles and 9- or 10-membered trithiacycles, very few functionalized systems are known.

We now report a novel ring contraction reaction for the simple and regiospecific synthesis of mono- and symmetrically difunctionalized tetrathiamacrocycles, starting with the mono- or dichloro-substituted macrocycles that have one or two more ring atoms. The reaction has the potential for the synthesis of a variety of polythiamacrocycles with symmetrically arranged polar side chains.

Results and Discussion

Chlorination of [14]aneS$_4$-ol (1,4,8,11-tetrathiatetradecan-6-ol, **1**)[2] and *cis*/*trans*-[14]aneS$_4$-diol (*cis*/*trans*-1,4,8,11-tetrathiatetradecane-6,13-diol, **2**)[2] via the Appel reaction[7] yielded [14]aneS$_4$-Cl (1,4,8,11-tetrathiatetradecane 6-chloride, **3**) (93%) and *cis*/*trans*-[14]aneS$_4$-Cl$_2$, (*cis*/*trans*-1,4,8,11-tetrathiatetradecane 6,13-dichloride, **4**) (89%), respectively. Heating of the monochloride in DMF leads to a ring contraction, yielding the isomer [13]aneS$_4$-CH$_2$Cl (**5**) (94%) (Scheme 1). The pure trans isomer of **4** was obtained as X-ray quality crystals by fractional crystallization. Crystal data of **4** are assembled in Table 1, and Figure 1 shows an ORTEP[8] plot of the molecule.

Formation of the 13-membered ring via episulfonium ion (EPSI) intermediates (for the type of intermediate, see **6** in Scheme 3) during the Appel reaction can be excluded because of the stereospecificity of this reaction: pure *trans*-[14]aneS$_4$-diol (**2**) leads to pure *trans*-[14]aneS$_4$-Cl$_2$ (**4**). An increase in the reaction time of the chlorination of **1** (18 to 56 h) produces both isomers **3**

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⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1997.

(1) (a) Jones, T. E.; Sokol, L. S. W. L.; Rorabacher, D. B.; Glick, M. D. *J. Chem. Soc., Chem. Commun.* **1979**, 140. (b) Blake, A. J.; Gould, R. O.; Lavery, A. J.; Schroeder, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 274. (c) Gould, R. O.; Lavery, A. J.; Schroeder, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1492.

(2) (a) Pett, V. B.; Leggett, G. H.; Cooper, T. H.; Reed, P. R.; Situmeang, D.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.* **1988**, *27*, 2164. (b) Comba, P.; Fath, A.; Kühner, A.; Nuber, B. *J. Chem. Soc., Dalton Trans.* **1997**, 1889.

(3) Cooper, S. R. In *Crown Compounds, Toward Future Applications*; Cooper, S. R., Ed.; VCH: Weinheim, New York, 1992; p 285.

(4) (a) Buter, J.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 466. (b) Kellog, R. M. In *Crown Compounds, Toward Future Applications*; Cooper, S. R., Ed.; VCH: Weinheim, New York, 1992; p 261.

(5) Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4481.

(6) (a) Setzer, W. N.; Affshar, S.; Burns, N. L.; Ferrante, L. A.; Hester, A. M.; Meehan, E. J.; Grant, G. J.; Isaac, S. M.; Laudema, C. P.; Lewis, C. M.; VanDerveer, D. G. *Heteroatom. Chem.* **1991**, *1*, 375. (b) Buter, J.; Kellogg, R. M.; van Bolhuis, F. J. *J. Chem. Soc., Chem. Commun.* **1990**, 282.

(7) Appel, R. *Angew. Chem.* **1975**, *24*, 863.

(8) Johnson, C. K. ORTEP, A Thermal Elipsoid Plotting Program, Oak Ridge National Laboratories, Oak Ridge, TN, 1965.

S0022-3263(97)01246-2 CCC: $14.00

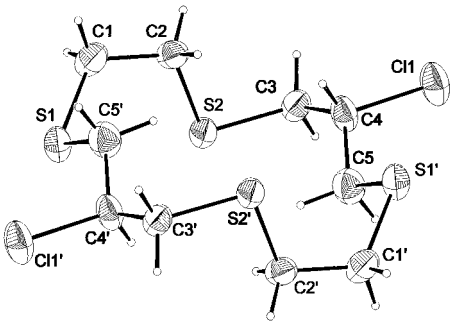


Figure 1. ORTEP[8] diagram of trans-[14]aneS_4-Cl_2 **4**.

Scheme 1

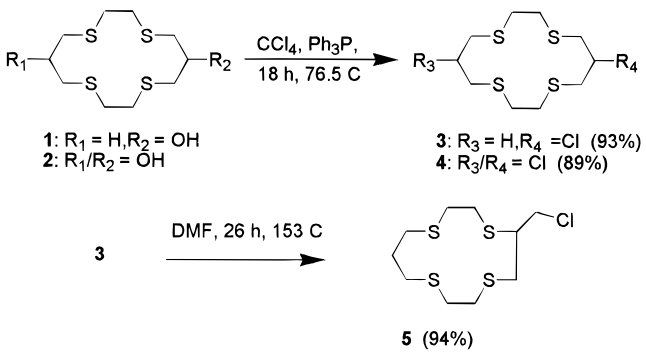


Table 1. Crystallographic Data for [14]aneS_4-Cl_2 (4) and [12]aneS_4-$(CH_2SCH_3)_2$ (7)[9]

formula	$C_{10}H_{18}S_4Cl_2$	$C_{12}H_{24}S_6$
M	337.40	360.68
cryst syst	monoclinic	monoclinic
space grp	$P2_{1/n}$	$P2_{1/n}$
a/Å	5.115(1)	9.213(5)
b/Å	13.777(6)	8.342(6)
c/Å	10.977(3)	11.406(6)
α/deg		
β/deg	97.34	92.49
γ/deg		
U/Å^3	767.2	876
Z	2	2
cryst size/mm	0.10 × 0.15 × 0.95	0.10 × 0.30 × 0.30
20 range/deg	3−52.5	3−52.5
D_e/g cm^{-1}	1.46	1.46
reflns measured	1797	2012
unique reflns	1084	707
F(000)	352	384
°μ/mm^{-1}	0.94	0.76
R′(F)[e]	0.056	0.087
R(F)[e]	0.062	0.100
no params	74	83
min, max peaks/e Å^{-3}	−0.46, 0.66	−0.48, 0.62

and **5** (Scheme 2). It follows that **5** is obtained via an EPSI **6** from already preformed **3** (Scheme 3). The formation of **6** is due to the neighboring group effect of a sulfur atom in β-position to the reaction center.[10] Only an endodentate sulfur atom is in a position to attack the chlorine-substituted carbon atom in a S_N2 mechanism.[11] This assumption is supported by the conversion of **4** with sodium thiomethylate to the doubly ring contracted *cis/trans*-[12]aneS_4-$(CH_2SCH_3)_2$ (**7**) (19%; Scheme 4): of the two possible regioisomers that could form, the exclusive

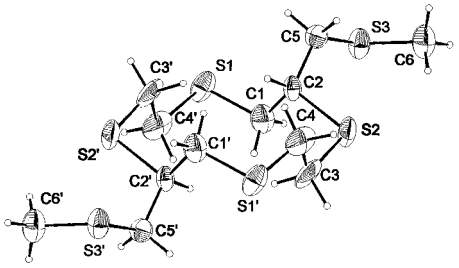
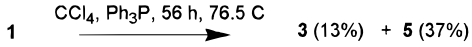
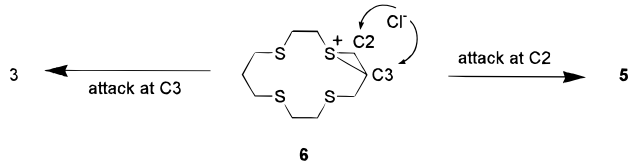


Figure 2. ORTEP[8] diagram of trans-anti-[12]aneS_4-$(CH_2SCH_3)_2$ **7**.

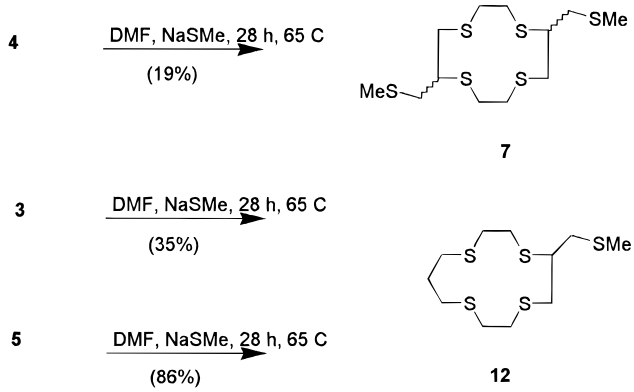
Scheme 2



Scheme 3



Scheme 4



formation of the one with the relative position of the two methylthio-substituted methylene bridges "anti" to each other was observed (Scheme 4). The orientation of the ring opening of the unsymmetrically substituted intermediate **6** depends on (a) steric factors[12,13] and (b) the polarity of the solvent.[14] The trans isomer of **7** was obtained by fractional crystallization, and the stereochemistry was assigned on the basis of an X-ray structural analysis. Crystal data of **7** are presented in Table 1, and an ORTEP[8] plot of **7** is given in Figure 2.

The nucleophilic attack of chloride at the least substituted (secondary) carbon atom (C2) is more likely than at the tertiary carbon atom (C3). This effect is strengthened by the electron-donating alkyl group attached to the sulfur atom in **6**. An electron withdrawing group would destabilize the positive charge at the sulfur atom of **6**, and the result would be an electron deficit at the highest substituted carbon atom (C3), leading to a smaller yield of the ring-contracted product **5**.

As important as the formation of **6** is the polarity of the reaction medium. By increasing the reaction time

(9) The *R* value of the doubly ring contracted macrocycle **7** is larger than we would prefer. However, we have not been able to isolate more suitable crystals, and the quality of the structural analysis allows an unambiguous assignment of the trans-anti configuration.

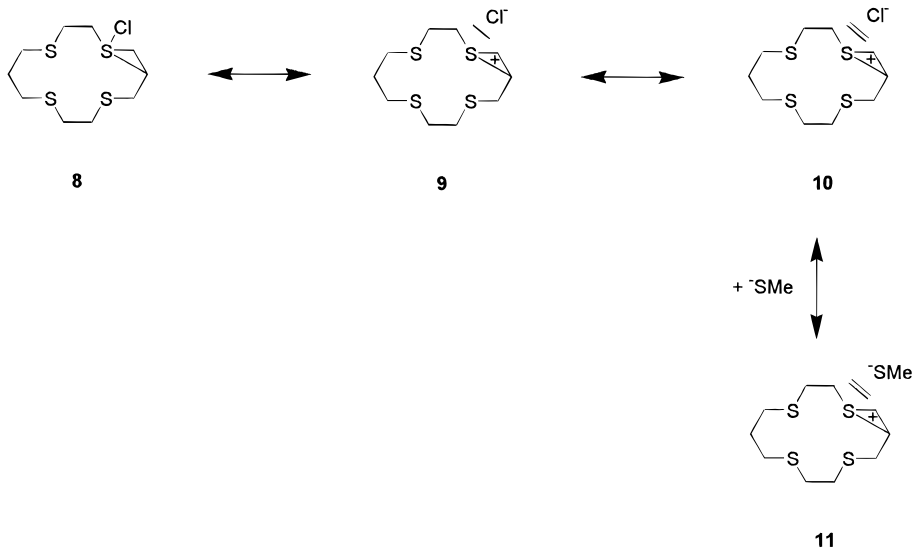
(10) Levroy, C.; Martin, M.; Bassery, C. *Bull. Soc. Chim. Fr.* **1974**, *3*, 590.

(11) Wolf, R. E.; Hartmann, J. R.; Storey, J. M. E.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1987**, *109*, 4328.

(12) Schmid, G. H.; Strukelj, M.; Dalipi, S. *Can. J. Chem.* **1987**, *65*, 1945.

(13) Mueller, W. H. *Angew. Chem.* **1969**, *13*, 475.

Scheme 5

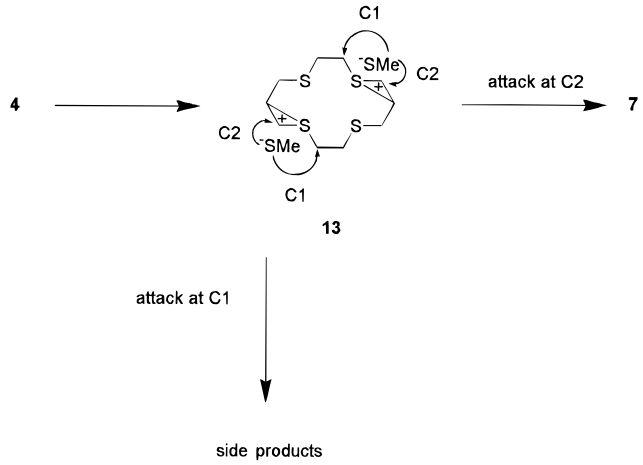


8 9 10 11

for the synthesis of **3** in CCl_4, a product mixture of **3** (12%) and **5** (37%) resulted. Heating of **3** in DMF produced pure **5** (94%). From the results discussed above, it emerges that an S−Cl bond (see **8** in Scheme 5) or a tight ion-pair (see **9** in Scheme 5) is involved in the conversion of intermediate **6** to the products.[12] In our case, the absence of the complete dissociation of the S−Cl bond prevents the complete formation of rearranged chloro compounds and leads to a mixture of products. The use of strongly polar solvents (e.g., DMF) may serve to stabilize solvent-separated ion pairs **10**, allowing for the net result of nucleophilic attack of the chloride ion, leading to the rearranged monochloride **5**. This consideration is just as important during the reaction of **3** and **4** with sodium thiomethylate in DMF to the corresponding rearranged and doubly rearranged (methylthio)-methyl-substituted [13]aneS_4-CH_2SCH_3 (**12**) (35%) and **7** (19%). With DMF, a shift from a tight to a solvent-separated polar ion pair (**9** → **10**) and the transformation of ion pair **10** to **11** may occur, due to anion exchange within the ion pairs.

The following facts support this assumption: (i) the reactions of **3** and **5** with sodium thiomethylate under the same reaction conditions yielded **12** in 35% and 86%, respectively (Scheme 5); (ii) if the substitution to **12** takes place after the rearrangement of **3** to **5**, the yield is higher than that for the direct conversion of **3** to **12**. The stronger nucleophile thiomethylate exchanges with chloride in the ion pair (**9** → **11**) and is now able to attack both secondary carbon atoms (this situation is shown in Scheme 6 for the conversion of **4** to **7**, where the two secondary carbon atoms are C1 and C2). Attack at C1 leads to side products and a decreasing yield of the rearranged product **12**. For the conversion of **4** to **7**, involving intermediate **13** (two EPSI in one macrocycle, see Scheme 6) the yield is considerably lower than for the conversion of **3** to **12** (19% and 35%, respectively). Here, the macrocyclic ring of intermediate **13** may break at two sides, leading to a decreasing yield of the rearranged product **7**, and this supports the mechanistic proposal of intramolecular ion exchange. We have not isolated and characterized the side products, but ^{1}H NMR spectra of product solutions indicated the presence of a number of different products with methylene groups, besides the starting material and ring-contracted product, and by GC−MS only the two expected macrocycles

Scheme 6



(**3** and **12** or **4** and **7**, respectively) were identified, suggesting that the side products are low molecular weight fragments.

Experimental Section

General Methods. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were measured on a Bruker AC 200 spectrometer in $CDCl_3$. Chemical shifts are reported in ppm (δ) downfield of Me_4Si as an internal reference (δ 0.0). Splitting patterns are abbreviated as follows: s, singlet, and m, multiplet. Mass spectra were measured on a Finnigan 8400 mass spectrometer. Elemental analyses were performed by the Microanalysis Facility of the Department of Chemistry, University of Heidelberg.

Materials. [14]aneS_4-ol (**1**) and [14]aneS_4-diol (**2**) were prepared by potassium ion template-enhanced condensation of ω,ω-dithiols with ω,ω-bis(chlorohydrins) in basic DMF.[2] CCl_4 was distilled from P_4O_{10}, and DMF was purified by distillation from CaH_2. All other compounds were purchased from Aldrich and used without further purification. All reactions were performed under nitrogen atmosphere.

Syntheses. [14]aneS_4-Cl (3). Triphenylphosphine (5.24 g, 20 mmol) was dissolved in 50 mL of CCl_4. Upon addition of **1** (2.84 g, 10 mmol), the solution was stirred and refluxed for 18 h. Then, additional triphenylphosphine (5.24 g, 20 mmol) was added, and the mixture was refluxed for an additional 14 h. After the solvent was vacuum evaporated, the brown residue was extracted for 8 h with 150 mL of diethyl ether in a Soxhlet extractor. The ether extract was first concentrated

and then flash chromatographed on a 5 × 30 cm silica gel column with diethyl ether, yielding three fractions. The second fraction (R_f ~0.8) yielded pure **3** as a colorless solid: 2.79 g, 93%; ^{13}C NMR ($CDCl_3$) δ 60.6, 39.3, 33.4, 32.1, 30.4, 30.1; MS (CI) *m/z* (rel intensity) 304 (M^{2+}, 49), 302 (M^+, 100), 267 (M − Cl, 6). Anal. Calcd for $C_{10}H_{19}S_4Cl$: C, 39.65; H, 6.32; S, 42.33. Found: C, 39.71; H, 6.42; S, 42.17.

[13]aneS$_4$-CH$_2$Cl 5. A solution of **3** (1.50 g, 49 mmol) in 50 mL of DMF was simply refluxed for 26 h and produced pure **4** as a white solid: 1.40 g, 94%; ^{1}H NMR ($CDCl_3$) δ 1.81−2.03 (m, 2H), 2.62−3.00 (m, 14H), 3.27 (m, 1H), 3.84−3.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 47.5, 46.6, 34.8, 32.4, 32.1, 31.8, 31.7, 30.3, 29.7, 29.3; MS (CI) *m/z* (relative intensity) 304 (M^{2+}, 45), 302 (M^+, 100), 267 (M − Cl), 12). Anal. Calcd for $C_{10}H_{19}S_4Cl$: C, 39.65; H, 6.32; S, 42.33. Found: C, 39.83; H, 6.36; S, 42.14.

[14]aneS$_4$-Cl$_2$ (4). The synthesis of this compound followed essentially the same procedure as that given for **3** above. Triphenylphosphine (1.5 g, 6 mmol) and a cis/trans mixture of **2** were dissolved in 30 mL of CCl_4 and held under steam bath temperature for 16 h. Then, more triphenylphosphine (1.5 g, 6 mmol) was added, and the reaction mixture was refluxed for an additional 26 h. The workup and chromatography used for **3** gave as a second fraction colorless crystals of **4**: 860 mg, 89.0%; ^{1}H NMR ($CDCl_3$) cis/trans δ 2.92−3.19 (m, 8H), 2.90 (d, 8H), 4.05−4.15 (m, 2H); ^{13}C NMR ($CDCl_3$) cis isomer, δ 59.9, 38.8, 32.8; trans isomer, δ 60.9, 39.5, 34.1; MS (CI) *m/z* (relative intensity) 338 (M^{2+}, 16), 336 (M^+, 18), 301 (M − Cl, 7). Anal. Calcd for $C_{10}H_{18}S_4Cl_2$: C, 35.60, H, 5.38, S, 38.01, Cl, 21.02. Found: C, 35.50, H, 5.32, S, 37.73, Cl, 20.81. The third fraction yielded pure *cis/trans*-[14]aneS$_4$-ClOH as white crystals: 30 mg, 3.1%; ^{1}H NMR ($CDCl_3$) cis/trans δ 2.60−3.25 (m, 18H), 3.80−4.02 (m, 1H), 4.05−4.22 (M, 1H); ^{13}C NMR ($CDCl_3$) cis isomer, δ 69.9, 60.6, 39.1, 38.8, 38.5, 37.9; trans isomer, δ 68.6, 60.1, 33.9, 33.4, 33.1, 32.5; MS (CI) *m/z* (relative intensity) 320 (M^{2+}, 56), 318 (M^+, 100), 301 (M − OH, 48), 383 (M − Cl, 66).

[13]aneS$_4$-CH$_2$SCH$_3$ (12). (a) To a solution of **5** (300 mg, 1 mmol) in 50 mL of DMF was added sodium methylthiolate (140 mg, 2 mmol), and the suspension was held for 38 h at 65 °C. After the reaction mixture was allowed to come to room temperature, salts were removed by vacuum filtration and DMF was removed on a rotary evaporator. The resulting white solid was dissolved in 40 mL of H_2O and extracted four times with 50 mL of diethyl ether. The combined ether fractions were dried with anhydrous Na_2SO_4, concentrated with a rotary evaporator, and purified by flash chromatography on a 5 × 30 cm silica gel column with diethyl ether as solvent. Removal of the solvent under reduced pressure gave **12** as a colorless oil: 270 mg, 86%; ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 2H), 2.13 (s, 3H), 2.66−3.03 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 46.3, 38.6, 38.3, 32.8, 32.0, 31.8, 31.5, 30.3, 29.7, 29.3, 16.8; MS (CI) *m/z* (relative intensity) 314 (M^+, 13), 267 (M − SCH_3, 51). Anal. Calcd for $C_{11}H_{22}S_5$: C, 42.05, H, 7.06, S, 51.03. Found: C, 42.27, H, 7.18, S, 50.55.

(b) As with the synthesis of **12** from **5** in part (a), the chloride **3** (300 mg, 1 mmol) was reacted with sodium methylthiolate (140 mg, 2 mmol) under the same conditions as that used above to afford **12**: 108 mg, 35%.

[12]aneS$_4$-(CH$_2$SCH$_3$)$_2$ (7). Sodium methylthiolate (205 mg, 1.2 mmol) was reacted with **4** (400 mg, 1.2 mmol) in DMF over a period of 12 h at 65 °C. After this time more sodium methylthiolate (205 mg, 2.8 mmol) was added, and the reaction mixture was held at 65 °C for an additional 16 h. The workup and chromatography followed that for **12** above to yield 80 mg (19%): ^{1}H NMR ($CDCl_3$) cis/trans, δ 2.15 (s, 6H), 2.79−3.24 (m, 18H); ^{13}C NMR ($CDCl_3$) cis isomer, δ 42.9, 38.8, 37.6, 33.7, 29.2, 17.2; trans isomer, δ 49.0, 38.6, 34.6, 33.4, 29.6, 17.0; MS (CI) *m/z* (relative intensity) 360 (M^+, 10), 313 (M − SCH_3, 22). Anal. Calcd for $C_{12}H_{26}S_6$: C, 39.96, H, 6.71, S, 53.33. Found: C, 39.68, H, 6.73, S, 53.06.

Crystal Structure Analyses. The atom numbering is given in Figures 1 and 2. The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Reflections were measured at room temperature on a Nicolet R3-diffractometer, employing graphite monochromated Mo Kα radiation (λ = 0.7107 Å); ω scan mode; data reduction and application of Lorentz and polarization absorption corrections were carried out. An empirical absorption correction was conducted. The structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically. The crystallographic data are assembled in Table 1.[14]

Acknowledgment. Financial support by the German Science Foundation (DFG) and the Fonds der Chemischen Industrie (FCI) is gratefully acknowledged.

Supporting Information Available: Crystallographic data for compounds **4** and **7** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971246Y

(14) Smit, W.; Zefirov, N. S.; Bodrikov, V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282.