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Identification, synthesis, and conformation of novel tri- and tetrathiacycloalkanes from marine bacteria

Paul Sobik^(†), Joerg Grunenberg^(†), Katalin Böröczky^(‡), Hartmut Laatsch^(||), Irene Wagner-Döbler^(§),
Stefan Schulz^(†,*)

[†] Institut für Organische Chemie, Technische Universität Braunschweig, Germany.

[‡] Current address:

^{||} Institut für Organische und Biomolekulare Chemie, Universität Göttingen, Germany.

[§] Helmholtz-Zentrum für Infektionsforschung, Abteilung für Zellbiologie, Germany.

E-Mail address of the corresponding author: Stefan.Schulz@tu-bs.de

Table of Contents Graphic:

Abstract: 80-200 Wörter

Introduction:

Marine microbial metabolites are currently intensively studied because of their often interesting pharmaceutical and agrochemical properties. Most of the research is focused on compounds of medium polarity, while apolar and volatile compounds have received less attention. In a research program aimed at the diversity of secondary metabolites from North Sea bacteria we developed a gas-chromatographic dereplication and strain selection method for fast identification of strains containing unknown apolar metabolites (Böröczky, K.; Laatsch, H.; Wagner-Döbler, I.; Stritzke, K.; Schulz, S. *Chem. Biodiversity* **2006**, *3*, 622-634). Two *Cytophaga* strains (BIO137 and BIO138), isolated from biofilms from the North Sea, were thus identified as potentially promising strains. The unknown compounds proved to be small sulfur containing compounds. Volatile sulfur compounds play an important role in the global

cycle of sulfur, including acidic rain, cloud formation, and in climate regulation.¹²⁵ Furthermore, they contribute to the aroma of fermented foods.¹³⁰ Nevertheless, the known volatile sulfur compounds from bacteria are limited. (S. Schulz, J. Dickschat, Nat. Prod. Rep. 2006, in press) In the present article we describe the identification, synthesis, and conformational analysis of new dithia-, trithia-, and tetrathiacycloalkanes produced by the *Cytophaga* bacteria.

Results and Discussion

Identification. In general, the unknown compounds were identified by GC-MS analysis and interpretation of their mass spectra. To verify these proposals, compounds were synthesized and compared to the natural compounds. Thus, the GC-MS analysis of the *Cytophaga* strains BIO 137 and BIO 138 revealed the presence of five small peaks containing sulfur (Figure 1), identifiable by the suspicious $M^+ + 2$ isotope peak in their mass spectra. These compounds **A-E** showed gas chromatographic retention indices of 1175, 1472, 1516, 1727, and 1748, respectively. The molecular formula was determined by GC-HRMS analysis, resulting in $C_4H_8S_3$ for **A**, $C_8H_{16}S_3$ for **B** and **C**, and $C_8H_{16}S_4$ for **D** and **E**, each with one double bond equivalent.

FIGURE 1. Gas chromatogram of *Cytophaga* strain BIO137 from the North Sea.

Mass spectroscopical data of several cyclic polysulfides have been published,¹⁻¹¹ giving hints to the preferred mass spectrometric fragmentation of the unknown compounds. These data allowed us to make structural proposals for the compounds **A-E**. The mass spectrum of compound **A** contained characteristic

ions m/z 96 [S_3] $^+$, 55 [C_4H_7] $^+$, and 87 [$\text{C}_4\text{H}_7\text{S}$] $^+$, pointing to a sulfur triad, four connected carbon atoms, and a monocyclic structure (Figure S1). The presence of a small ion m/z 106 [$\text{M}-\text{CH}_2\text{S}$] $^+$ suggested a $-\text{CH}_2-\text{S}-$ fragment in the structure, while the prominent ion m/z 87 [$\text{C}_4\text{H}_7\text{S}$] $^+$ pointed to a $-\text{CH}(\text{CH}_3)_2-\text{S}-$ or $-\text{CH}(\text{C}_2\text{H}_5)-\text{S}-$ substructure. The latter one seemed to be less likely because no evidence for an ethyl group could be found in the mass spectrum. Furthermore, the published spectra of 3,5-dimethyl-1,2,4-trithiolane⁵ and 3-ethyl-1,2,4-trithiolane⁸ showed distinct differences, supporting the view of a sulfur triad. Therefore we proposed compound **A** to be 4,4-dimethyl-1,2,3-trithiolane (**1**), which was proved by synthesis (see below). The two isomeric compounds **B** and **C** obviously contained an additional C_4H_8 group compared to **1**, but no sulfur triad (Figure 2). Both C_4H_8 units were not connected directly, but via a S-atom. This can be deduced by m/z 143 [$\text{C}_8\text{H}_{15}\text{S}$] $^+$ and the absence of any CH containing fragment with more than four C-atoms. The C_4H_8 units are most likely again arranged in a dimethylethyl fashion, because in cyclic oligosulfides with longer alkyl side chains like 3,5-dipropyl- or diisopropyl-1,2,4-trithiolane^{7,8,11} no strong [$\text{M}-\text{C}_4\text{H}_8$] $^+$ ion (m/z 152) is formed. Instead, the intense [$\text{M}^+-\text{S}_2\text{H}$] $^+$ fragment at m/z 143 prevails. Furthermore, the complete lack of [$\text{M}-\text{C}_n\text{H}_{2n+1}$] $^+$ ions indicates the absence of longer alkyl side-chains. The mass spectra of **B** and **C** were thus consistent with the structural proposals 4,4,6,6-tetramethyl-1,2,5-trithiepane (**2**), 3,3,7,7-tetramethyl-1,2,5-trithiepane (**3**), and 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**). Mieloszynski¹ has published tabulated mass spectra of **2** and **3** isolated from undefined "mélanges industriels", showing the same ions as in our trithiepane mass spectra, but in markedly different abundances. The reported ^1H NMR data of **2** were similar to ours obtained from a synthetic sample, while that of **3** differed.¹

The mass spectra of compounds **D** and **E** contain the same fragments as **B** and **C** (except m/z 106), but obviously these compounds carry an additional S-atom, visible by the increase of 32 amu of the M^+ ion. Again, no S_3 fragment is observed, pointing to two disulfide bridges in the compounds. Therefore, 3,3,7,7-tetramethyl-1,2,5,6-tetrathiocane (**5**) and 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**) were proposed as target structures. The mass spectrum of **6** matches the literature data for compound **5** by Mieloszynski, who suggested this structure but did not report NMR data.¹ A table of the GC-HRMS-data

for the postulated structures **A-E** as well as mass spectra of compounds **1-2** and **5-8** are available in the supporting information.

CHART 1: Naturally occurring compounds from the bacterial *Cytophaga* strains BIO-137 and BIO-138. (Kann man die Strukturen so ausrichten, dass genau eine unter der anderen steht oder gibb das die vorgeschriebene Spaltenbreite nicht her?)

Synthesis. Synthetic reference material was then needed to prove the proposed structures, assign the potential isomers, and to obtain material for biotests. A first attempt to their synthesis was the nucleophilic thiolate ring opening of episulfides. 2,2-Dimethyloxirane (**9**) was transformed with KSCN into 2,2-dimethylthiirane (**10**).¹² Then NaSH was added to **10** assuming that the SH⁻ nucleophile could attack the episulfide from the least hindered side, forming an thiolate anion which in turn should open another thiirane molecule, forming target compound **3** after a spontaneous oxidative ring-closing coupling of two sulfur atoms. Compound **3** was isolated in 11% yield after extended chromatographic purification because of formation of many oligomeric side products. The isomeric thiepane **4** was also formed during the reaction and isolated in pure form; its formation can be rationalized by transfer of a proton from the primary to the tertiary sulfur position prior to the attack of the second thiirane molecule.

Scheme 1. Synthesis of 3,3,7,7-tetramethyl-1,2,5-trithiepane (3) and 3,3,6,6-tetramethyl-1,2,5-trithiepane (4).

Compounds **3** and **4** were distinguished by their high temperature NMR spectra. While **3** showed only one signal for the two methylene units, the spectrum of compound **4** was more complex due to the missing symmetry plane. Interestingly, both compounds showed identical gas chromatographic retention times on an apolar BPX-5 phase. Careful analysis of the slight differences in the mass spectra of the synthetic products and compound **B** (RI: 1472) proved that **B** is actually a 3:2 mixture of **3** and **4** (**Figure 2**).

Figure 2. Mass spectrum of the peak B of the natural extract, composed of a 3:2 mixture of the two coeluting sulfides 3 and 4.

Because the above synthesis gave no access to the other compounds, an alternative strategy was used to synthesize the isomeric trithiepane **2** (Scheme 2).

Scheme 2. Synthesis of 4,4,6,6-tetramethyl-1,2,5-trithiepane (2) and 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (6).

The major product of the addition of sulfur monochloride and isobutene is 2-chloro-1-(2-chloro-2-methylpropyl)disulfany-2-methylpropane (**11**).¹³ The following reaction with NaSH, which included the substitution of chloride, followed by a ring-closing reaction, led to **2** and **6**. By use of one equivalent NaSH trithiepane **2** was isolated, while tetrathiocane **6** was formed using two equivalents. These compounds were always accompanied by the trithiolane **1**, which showed identical GC and MS data as compound **A**. Unfortunately, its isolation failed, presumably because of the instability of trithiolanes.¹⁴ The crude 4,4-dimethyl-1,2,3-trithiolane (**1**) was then used in the synthesis in compound **5** (Scheme 3).

Scheme 3. Synthesis of 3,3,7,7-tetramethyl-1,2,5,6-tetrathiocane (5)

LAH reduction of **1** furnished the dithiol **8**, which was oxidatively coupled with NaOH and iodine,¹⁵ leading to 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**). This reaction sequence additionally proved the structure of **1**. Besides **6**, the compounds **1**, **4**, **7** and 6,6-dimethyl-(1,2,3,4,5)-pentathiepane were formed as byproducts during the oxidative coupling. These results suggested that the dithiol **8** might be involved in the biosynthesis of the sulfur cycles. Careful analysis of the MS data revealed its presence in traces in the natural extracts. During a slow oxidation process (with air in an open flask for three weeks) all of the compounds **1-7** were formed from **8**. The trithiepanes and tetrathiocanes are formed in an excess of their open ring forms. We also tried to synthesize 4,4-dimethyl-1,2,3-trithiolane by the addition of sulfur to isobutene, in analogy to experiments by Bartlett and Ghosh with norbornene.¹⁶ Small amounts of **1** were formed, but major components of the inseparable mixture were 5,5-dimethyl-1,2,3,4-tetrathiane (**7**) and also 6,6-dimethyl-1,2,3,4,5-pentathiepane. Compound **7** proved to be identical to an additional trace component of the natural extract.

NMR experiments

The synthesized compounds **2-6** showed interesting NMR spectra, pointing to considerable flexibility of the ring system. Some ^1H NMR spectra at room temperature are shown in **Figures 3** and **4**.

Figure 3. ^1H NMR spectra of the trithiepanes **2-4** at room temperature.

The spectrum of 4,4,6,6-tetramethyl-1,2,5-trithiepane (**2**) showed only one signal for the four methyl and for the two methylene groups, in opposite to the spectrum of 3,3,7,7-tetramethyl-1,2,5-trithiepane (**3**) in which two types of methyl groups can be differentiated. The protons of the methylene groups are also split into two doublets of an AB spin system. The spectrum of 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**) showed only broad signals, pointing to a point of coalescence near this temperature. Obviously the flexibility of the trithiepanes at room temperature increases from **2** to **4** and further to **3**. In case of the tetrathiocanes, similar spectra showed that **5**, again having a coalescence point near room temperature, is more flexible than **6** (Figure 4).

Figure 4. ^1H NMR spectra of the tetrathiocanes **5** and **6** at room temperature.

We then performed temperature-dependent NMR-experiments to get more insight into the conformations of the thiepanes. As an example, the spectra for **4** are shown in Figure 5. At low

temperature a preferred conformation exist which allows the observation of for different methyl groups and four different methylene-hydrogen atoms. In contrast, at high temperature only one signal for the two different methylene groups and the two types of methyl groups were observed.

Figure 5. A: Experimental ¹H NMR of 3,3,6,6-tetramethyl-1,2,5-trithiepane (4) at different temperatures; B: Simulated (DFT) spectra for the three calculated low energy conformations chair (upper trace), twist-boat (middle trace), and twist-chair (lower trace). (Skala für B?)

Theoretical calculations

In order to further analyze the conformational complexity and the dynamic properties due to rapid ring interconversion (lit. Hendrickson) in the thiepanes and thiocanes, we performed a series of DFT (density functional theory) gas phase calculations. The resulting optimized conformations were further used as a starting point for GIAO (gauche independent atomic orbitals, lit) simulations of the corresponding NMR data in order to characterize the dominating conformers. All calculations were done using the B3LYP (lit.) hybrid density functional in combination with a polarized triple (ζ?) zeta basis set (6-311+G(d,p)). The procedure will be shown for 3,3,6,6-tetramethyl-1,2,5-trithiepane (4) as an example. In a first step, an extensive force field (MMFF, lit.) scan of the energy surface was performed. Then all minima were re-optimized using the B3LYP functional. In the third phase, the energies and geometries of all transition

states connecting the minima were localized and finally the NMR spectra for all energy minima were computed. **Figure 6** shows the two conformers with the lowest energy, detected by this procedure.

Figure 6. Interconversion of the twist-chair global minima for 3,3,6,6-tetramethyl-1,2,5-trithiepane (4).

The interconversion of both low energy twist chair conformation occurs via several chair, twist-boat and chair conformations (**Figure 7**). Starting from the twist-chair minimum I (left) the next twist-boat minimum (6.12 kcal/mol) is reached via a boat transition state and separated by a barrier of 11.37 kcal/mol (back reaction: 5.71 kcal/mol), while the next transition structure (boat) is again 10.13 kcal/mol higher in energy (back reaction: 13.47 kcal/mol) leading to another minimum (chair), which is only 2.12 kcal/mol higher in energy compared to the twist-chair minimum I. Another transition state (6.12 kcal/mol; back reaction: 11.73 kcal/mol) – this time best described as twist boat – has to be climbed before finally the twist-chair II minimum is reached,. That means that the overall interconversion of the twist-chair conformations I and II occurs via two local minima. The activation barrier of the rate determining step in the gas phase is predicted to be around 13.5 kcal/mol. In order to find out if our theoretical findings hold also true for the condensed phase, we compared the simulated gas phase ^1H NMR spectra for all characterized minima with the experimental low temperature NMR spectrum of structure **4** in CD_2Cl_2 (**Figure 5**). The calculated spectra showed the relative positions of the methyl and methylene H atoms, omitting splitting due to coupling. The twist-chair conformation compares very well to the experimental spectrum, while the other two spectra showed marked differences. The experimental data supported the theoretical calculations and showed that in solution the twist-chair conformer is preferred, too. (andere Strukturen in Supporting?)

Figure 7. Conformational complexity of 3,3,6,6-tetramethyl-1,2,5-trithiepane (4). All stationary points were characterized at the B3LYP/6-311G(d,p) level of theory. (Strukturdaten wie Winkel etc. irgendwie angeben? Supporting information?)

The rate constant k_c for the interconversion of the twist-chair I conformers was calculated according to formula **I** from the experimental ^1H NMR-data. Therefore the difference in the frequency of two non-coupling signals from the ^1H NMR was measured ($\Delta\nu$). In conjunction with the temperature of coalescence (in Kelvin) the free activation enthalpy ΔG^{**} for this process was calculated (**formula II**).¹⁷

$$k_c = \frac{\pi\Delta\nu}{\sqrt{2}} = 2.22\Delta\nu \quad (\text{I}) \qquad \Delta G^{**} = 4.58T_c \left(10.32 + \log \frac{T_c}{k_c} \right) \text{ cal mol}^{-1} \quad (\text{II})$$

The value of 13.88 kcal/mol is in good agreement with the theoretical result (13.5 kcal/mol), pointing to a good agreement of theory and experiment.

Based on the given procedure, the favoured conformation of the trithiepanes **2** and **3** as well as the tetrathiocanes **5** and **6** were calculated.

Also the rate constants, temperatures of coalescence and the free activation enthalpies for all interconversion processes were calculated from the given formulas (**Table 1**).

Table 1. Rate constants, temperatures of coalescence and the free activation enthalpies for the interconversion processes of substance 2-6.

Products	$\Delta\nu$ [Hz]	k_c [1/s]	T_c [K]	ΔG^{**} [kcal/mol]
(2)	9,35	20,75	196	10,14
(3)	77,37	171,76	380	18,56
(4)	82,61	183,39	288	13,87
(5)	91,71	203,59	293	14,06
(6)	46,09	102,31	- ^a	-

^a The NMR could only run to a maximum Temperature of 373 K.

The free activation enthalpy for the interconversion processes of 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**) was theoretically calculated to about 21 kcal/mol. That would match a coalescence temperature of round about 420 K, which could not be measured on the given NMR equipment. All NMR data and MS spectra are available in the supporting information.

Conclusion:

In the extracts of two *Cytophaga* strains from the North Sea the new thiacycloalkanes 4,4-dimethyl-1,2,3-trithiolane (**1**), 4,4,6,6-tetramethyl-1,2,5-trithiepane (**2**), 3,3,7,7-tetramethyl-1,2,5-trithiepane (**3**),

3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**), 3,3,7,7-tetramethyl-1,2,5,6-tetrathiocane (**5**), and 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**), and 5,5-dimethyl-1,2,3,4-tetrathiane (**7**) as well as the dithiol methyl-1,2-propanedithiol (**8**) were identified and their structures proven by synthesis. The cyclic compounds exhibit melting points between 34°C and 106°C have a characteristic smell resembling diesel-fuel. This smell can also be recognized in the extracts. The dithiol **8** has a penetrative, 'breathtaking' smell, obviously blocking the odor receptors for some time. Its smell is not recognizable in the extracts, most likely because of the low concentration in the extracts. (Stefan, Biosynthese diskutieren)

In this research we were able to show the preferred conformations of the Oligosulfides **2-6**. In case of the trithiepanes, **3** has the most stable conformation showing a 'chair' arrangement. So does **2** which is the most flexible molecule of all three. The 'twist-chair' conformation of **4** which is described in detail is the most interesting arrangement, but surprisingly not the less stable one. A nearly similar 'twist' conformation is given by the tetrathiocane **6** which coalescence temperature should be round about 420 K. So its got an even more stable conformation than **5** with its given 'chair' arrangement.

The only structure which is known yet, but not as a nature product, is **4** found by Bhatti and Goethals as a degradation product of poly(thio-1,1-dimethylethylene)¹⁸ and was characterized by MS data. Other Ground structures like 1,2,5,6-tetrathiocane or 1,2,5-trithiepane are also known Paul:mehr Lit heraussuchen und angeben???. Trithiolane was recently found by Rushdi and Simoneit who did reactions with CS₂ and oxalic acid solutions in stainless steel vessels at high temperature and pressure¹⁹.

Methods and Materials: (Reihenfolge in Autorenanweisungen beachten!)

GC-MS analyses (EI, 70 eV) were performed using a GC 6890, coupled to a MSD 5973 (Hewlett-Packard). A BPX-5 (25m x 0.25mm x 0.25 µm, SGE) capillary column with He as the carrier gas was used with a constant flow rate of 1 ml/min. The initial oven temperature was 50°C, held for 2 minutes, followed by heating with 3°C/min to 320°C. NMR spectra were recorded with a Bruker AM-400 instrument with tetramethylsilane an internal standard. TLC analyses were performed on pre-coated silica gel sheets (Polygram® SIL G/UV₂₅₄, Macherey-Nagel). For visualization 8 % molybdato-phosphoric acid in ethanol

was used. Column chromatography was performed using silica gel (silica gel 60, corn size 0.069-0.200 mm, Merck). IR-data were obtained using a Bruker Tensor 27 with diamond-ATR-technique.

Biological material: Irene strain isolation. Referenz-Angabe reicht.

Calculations: All calculations were done using the program packages Gaussian03 (lit) and Macromodel 7. (Jörg: mehr Angaben!)

Synthesis of 2,2-dimethylthiirane (10): In a solution of 70 mmol KSCN in 7 ml H₂O was added 70 mmol 2,2-dimethyloxirane (**9**). The solution was stirred at room temperature over night. The solid KOCN was separated by filtration and washed with diethyl ether. The aqueous layer was separated from the organic and extracted several times with diethyl ether. The combined organic layers were dried with MgSO₄ and filtered. The product was purified by distillation (bp. 84-86°C, 55 mmol, 79 % yield). ¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.62 (s, 6H), 2.40 (s, 2H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 28.5, 35.4, 42.4.

Synthesis of 3,3,7,7-tetramethyl-1,2,5-trithiepane (3) and 3,3,6,6-tetramethyl-1,2,5-trithiepane (4):
In a tree necked round bottom flask 7 äq. NaSH · × H₂O (385 mmol, 21.56g) was dissolved in 200 ml MeOH and 10 mol% (relating to the Thiirane) triethylamine was added. That followed 55 mmol 2,2-dimethylthiirane was dropped in a time period of 30 min. The solution was stirred at room temperature. After 2 days the solution was hydrolysed and extracted with diethyl ether. After drying over MgSO₄ and following filtration the solvent was removed in reduced pressure. The remained liquid was purified by LC. Pentane is used as solvent. 3,3,7,7-tetramethyl-1,2,5-trithiepane (**3**) (1.2 g, 5.8 mmol, 11%, R_f = 0.15). Mp.: 46 ± 0.5°C. ¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.27 (s, 6H), 1.47 (s, 6H), 2.81 (dd, *J* = 2.3, 17.2 Hz, 4H). ¹³C-NMR (100 MHz, CDCl₃): δ [ppm] 27.0, 28.2, 50.2, 52.4. IR [cm⁻¹]: 2952, 1443, 1360, 1139, 1093. Anal. Calcd for C₈H₁₆S₃: C, 46.11 %; H, 7.74 %; S, 46.16 %. Found: C, 45.86 %; H, 7.34 %; S, 45.91 %. 3,3,6,6-tetramethyl-1,2,5-trithiepane (**7**) (0.9 g, 4.3 mmol, 8 %, R_f = 0.12). Mp.: 34 ± 0.5°C. ¹H

NMR (400 MHz, CDCl_3): δ [ppm] 1.33 (s_B , 12H), 2.55 (s_B , 1H), 2.92 (s, 2H), 3.15 (s_B , 1H). ^{13}C -NMR (100 MHz, CDCl_3): δ [ppm] 25.9, 27.1, 29.9, 30.9, 41.5, 45.6, 55.6, 57.7. IR [cm^{-1}]: 2957, 1441, 1375, 1137, 1093.

Synthesis of 2-chlor-1-(2-chlor-2-methylpropyldisulfanyl)-2-methylpropane (11): In a round bottom flask, cooled with liquid nitrogen 5.6 g (0.1 mol) isobutene was condensed and then dissolved in dichloromethane at -40°C . 0.5 äq. (67.5 g) of S_2Cl_2 was added and stirred for 60 min. at -40°C followed by 2h of stirring at room temperature. The solvent and the excess of S_2Cl_2 were separated by distillation. The remained liquid was purified by LC. Pentane is used as solvent. (52 mmol, 12.8 g, 52 %, $R_f = 0.2$). ^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.67 (s, 12H), 2.28 (s, 4H). ^{13}C -NMR (100 MHz, CDCl_3): δ [ppm] 31.3, 56.7, 69.0.

Synthesis of 4,4,6,6-tetramethyl-1,2,5-trithiepane (2): The synthesized 2-chlor-1-(2-chlor-2-methylpropyldisulfanyl)-2-methylpropane (0.5 g, 2 mmol) was dissolved in 10 ml MeOH and 2 mmol $\text{NaSH} \cdot x \text{H}_2\text{O}$ (0.11 g) is added portion wise. The solution was stirred at room temperature over night and was extracted with diethyl ether. After drying over MgSO_4 and following filtration the solvent was removed in reduced pressure. The remained liquid was purified by LC. A mixture of pentane and diethyl ether 200:1 was used as the solvent (0.42 mmol, 0.1 g, 21%, $R_f = 0.1$). ^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.43 (s, 12H), 3.16 (s, 4H). ^{13}C -NMR (100 MHz, CDCl_3): δ [ppm] 31.1, 52.7, 57.4. IR [cm^{-1}]: 2959, 2921, 1457, 1409, 1377, 1362, 1101.

Synthesis of 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (6): In 10 ml MeOH 4 mmol $\text{NaSH} \cdot x \text{H}_2\text{O}$ (0.22 g) was dissolved and 2 mmol 2-chlor-1-(2-chlor-2-methylpropyldisulfanyl)-2-methylpropane (0.5 g) was added. The solution was stirred at room temperature over night and was extracted with Diethyl ether. After drying over MgSO_4 and following filtration the solvent was removed in reduced pressure. The remained liquid is purified by LC. Pentane was used as solvent (0.5 mmol, 0.12 g, 25%, $R_f = 0.15$). Mp.:

71 $\pm$ 0.5°C. ^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.23 (s, 6H), 1.34 (s, 6H), 3.06 (d, J = 15.2 Hz, 2H), 3.70 (d, J = 15.2 Hz, 2H). ^{13}C -NMR (100 MHz, CDCl_3): δ [ppm] 25.2, 32.2, 51.1, 53.9. IR [cm^{-1}]: 2953, 2896, 1377, 1358, 1090. Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{S}_4$: C, 39.96 %; H, 6.71 %; S, 53.34 %. Found: C, 40.04 %; H, 6.55 %; S, 53.32 %.

Synthesis of 2-methyl-1,2-propanedithiol (8): The crude 4,4-dimethyl-1,2,3-trithiolane (1.5 g), co-product in the reactions of 4,4,6,6-tetramethyl-1,2,5-trithiepane and 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane, was added to a well excess of LiAlH_4 (2 g, 52 mmol) in abs. diethyl ether. The solution was boiled at 45°C for 3 h and hydrolyzed in the following. Conc. HCl was added till the solid dissolves and the aqueous layer was extracted several times with diethyl ether. The combined organic layers were dried with MgSO_4 , filtered and the solvent removed. The crude product was finally purified by distillation getting 0,7 g of (8) (40-41°C, 38 mm Hg). ^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.43 (s, 6H), 1.61 (t, J = 8.8 Hz, 1H), 2.02 (s, 1H), 2.75 (d, J = 8.8 Hz, 2H). ^{13}C -NMR (100 MHz, CDCl_3): δ [ppm] 30.25, 41.21, 45.12.

Synthesis of 3,3,7,7-tetramethyl-1,2,5,6-tetrathiocane (5): To a mixture of 10 mmol NaOH (0.4 g) and 10 mg (0,06 mmol) of KI, dissolved in 10 ml H_2O and cooled in an ice-bath to 0°C 5 mmol 2-methyl-1,2-propanedithiol (0.6 g) was added drop wise and the solution was stirred for 30 min. Then I_2 (1.27 g) was added portion wise till a light red color persist. The solution was extracted with dichloromethane. After drying over MgSO_4 and followed filtration the solvent was removed in reduced pressure. The remained liquid was purified by LC. Pentane was used as solvent (1.1 mmol, 0.26 g, 23%, R_f = 0.1). Mp.: 106 $\pm$ 0.5°C. ^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.35 (s_B , 12H), 3.17 (s_B , 2H). ^{13}C -NMR (100 MHz, CDCl_3): δ [ppm] 56.3. IR [cm^{-1}]: 2953, 1450, 1363, 1134, 1091, 548.

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Supporting Information:

Table S1. Elemental compositions and relative intensities of the fragments in the mass spectra of compounds **A-E**.

		A	B	C	D	E
Formula	m/z	1 RI:1175	3/4 RI:1472	2 RI:1516	6 RI:1727	5 RI:1748
$C_8H_{16}S_4^{+}$	240	-	-	-	39	62
$C_8H_{16}S_3^{+}$	208	-	100	82	-	-
$C_4H_8S_3^{+}$	152	100	59	100	100	100
$C_8H_{15}S^{+}$	143	-	13	-	-	-
$C_4H_8S_2^{+}$	120	-	28	26	24	59
$(C_3H_6S_2)^{+}$	106	2	12	42	1	-
S_3^{+}	96	4	1	1	-	-
$C_4H_8S^{+}$	88	27	53	41	24	26
$C_4H_7S^{+}$	87	52	94	87	56	55
$C_3H_5S^{+}$	73	10	10	8	2	19
S_2^{+}	64	13	4	3	4	4
$C_2H_3S^{+}$	59	21	27	32	11	15
$C_4H_7^{+}$	55	38	95	76	54	82
CHS^{+}	45	17	19	18	9	10

C_3H_5^+	41	19	27	29	17	23
C_3H_3^+	39	18	21	20	13	16

Figure S1. MS spectra of 4,4-dimethyl-1,2,3-trithiolane (1).

Scheme X. MS spectra of 4,4,6,6-tetramethyl-1,2,5-trithiepane (2).

Scheme X. MS spectra of 3,3,7,7-tetramethyl-1,2,5,6-tetrathiocane (**5**).

Scheme X. MS spectra of 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**).

Scheme X. MS spectra of 5,5-dimethyl-1,2,3,4-tetrathiane (**7**).

Scheme X. MS spectra of methyl-1,2-propanedithiol (**8**).