Synthesis and Structural Characterization of Cis- and Trans-Fused 4a,5,6,7,8,8a-Hexahydro-2*H*,4*H*-1,3-benzodithiines and Their 2-Methyl and 2,2-Dimethyl Derivatives

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Both cis- and trans-fused 4a,5,6,7,8,8a-hexahydro-2*H*,4*H*-1,3-benzodithiine together with their 2-methyl and 2,2-dimethyl derivatives were prepared as racemates from the appropriate dithiols obtained via multistep syntheses. The products were characterized by ^{1}H and ^{13}C NMR, mass spectrometry, and for two of the cis-fused compounds by X-ray diffraction. ^{1}H,^{1}H vicinal coupling constants indicated that all compounds attain chair−chair conformations as their predominant conformations. All three trans-fused isomers exist in totally biased chair−chair conformations and are essentially conformationally locked, whereas the cis-fused compounds are conformationally mobile and can potentially attain either the *S-in* or the *S-out* conformation. The interconversion of the conformers is fast on the NMR time-scale at ambient temperatures, but at 213 K 4a*r*,5,6,7,8,-8a*c*-hexahydro-1,3-benzodithiine freezes out into a 83:17 mixture of the *S-in* and *S-out* forms, respectively. Both 2*c*-methyl-4a*r*,5,6,7,8,8a*c*-hexahydro-1,3-dithiine and the dimethyl derivative adopt almost exclusively the *S-in* conformer at ambient temperature whereas 2*t*-methyl-4a*r*,5,6,7,8,-8a*c*-hexahydro-1,3-dithiine is a 5:1 mixture of the *S-out* and *S-in* conformers.

Introduction

The syntheses and spectroscopic analyses (NMR, MS, and X-ray) of various carbocyclane-fused five- and six-membered heterocycles have been the subject of intense and active study over the years and continues to this day unabated.[1,2] For example, cyclohexane-fused 1,3-dioxanes, first described with regard to their NMR spectroscopy sometime ago,[3] have received recent attention as part of a fresh study[4] on the spectroscopy of (bi)cyclic 1,3-dioxa compounds. Extending our previous studies of these and related systems to the 1,3-dithia analogues is a natural course, and these compounds in their own right have received considerable attention with regard to structure,[5] conformational analysis,[6] thermodynamics,[7] and spectroscopy,[6,8,9] complementing work on related compounds such as the 1-thia-[10] and 1,4-dithiadecalins.[11] Although the full understanding of the conformational behavior of even monocyclic systems[12] is far from complete, bicyclic decalin systems continue to attract considerable interest with regard to their interesting conformational behavior.[13] In this vein, we report here a study on the conformational behavior of cis- and trans-fused 4a,5,6,7,8,8a-hexahydro-2*H*,4*H*-1,3-benzodithiines and their 2-methyl and 2,2-dimethyl derivatives. Although some substituted derivatives of *trans*-2-mercaptomethyl cyclohexanethiol have been synthesized earlier,[14,15] none of the aforementioned compounds have been previously reported. Starting appropriately either from diol **1** which is not commercially available but which was readily prepared applying literature methodology,[16] or compound **2** which was also prepared using specific literature methods[17,18] (see Scheme 1), the polysulfides

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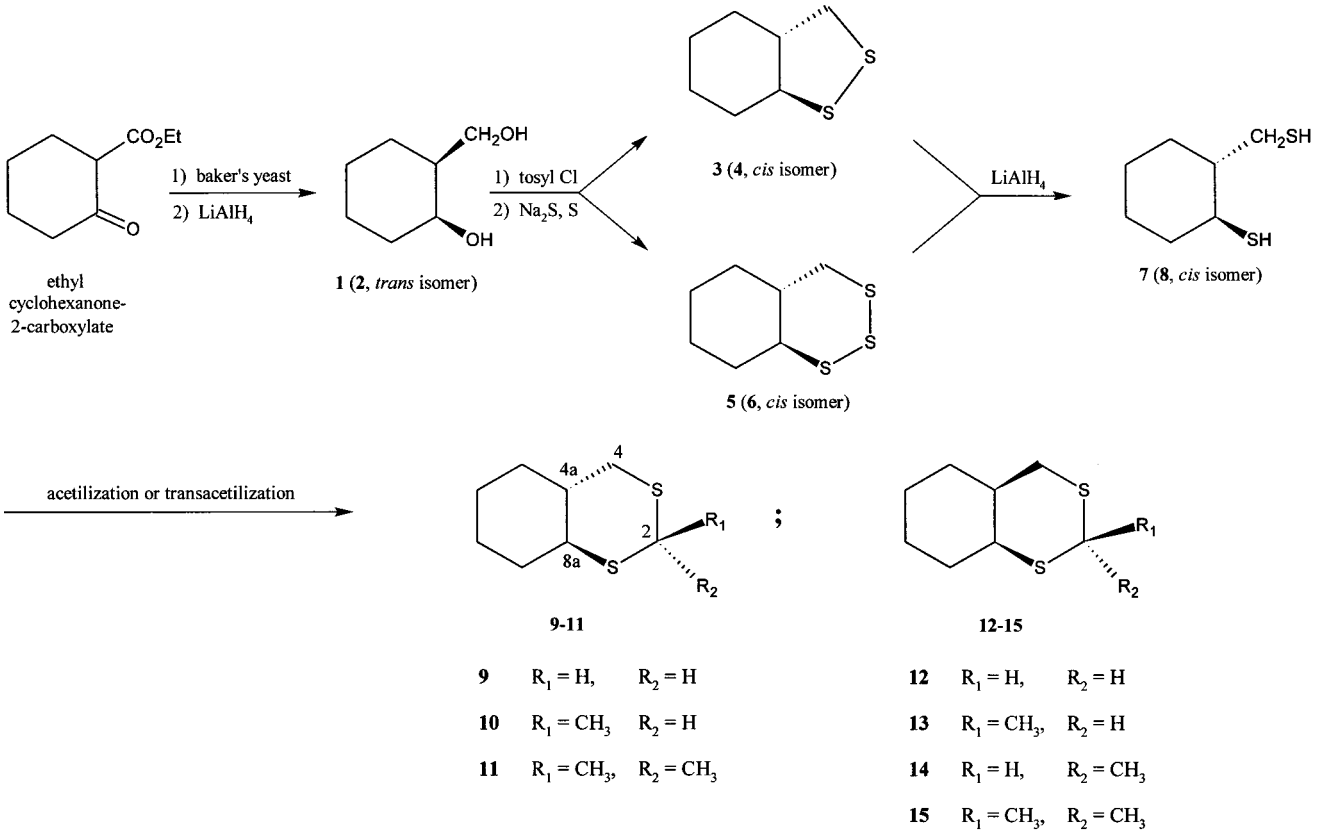
Scheme 1. The Reaction Scheme Leading to the Compounds 9−15 Examined in This Study. The Numbering System in Use Is Also Indicated



3−**6** were produced which were subsequently reduced to the dithiols **7** and **8**. From **7** and **8**, the dithiines of interest, **9**−**15**, were readily prepared for this study using standard acetalization and transacetalization procedures. The conformations adopted by the compounds were primarily determined by ^{1}H NMR spectroscopy and were further examined by ^{13}C NMR, mass spectrometry, and for comparison in the solid state by single-crystal X-ray diffraction (for compounds **12** and **13**).

Results and Discussion

Synthesis of Trans-Fused (4a*r*,8a*t*)-Hexahydro-1,3-dithiines (9−11). Starting from commercially available ethyl cyclohexanone-2-carboxylate (see Scheme 1), reduction of this racemic ketone using bakers' yeast[16] provided the 1-hydroxyl ester diastereoselectively in good yield which upon treatment with $LiAlH_4$ provided *cis*-2-hydroxymethyl cyclohexanol (**1**). Ditosylation of this diol followed by treatment with sodium sulfide and sulfur to displace the oxygens with sulfur provided a mixture of two novel bicyclic polysulfides, **3** and **5**, the reaction proceeding with inversion of configuration at C-1. Polysulfides **3** and **5** were readily separable by column chromatography and have been characterized by ^{1}H and ^{13}C NMR and MS. Reduction of either a mixture of the two or separately provided the *trans*-2-mercaptomethyl cyclohexanethiol (**7**). The unsubstituted parent *trans*-fused hexahydro-1,3-benzodithiine (**9**) and its 2,2-dimethyl-substituted derivative (**11**) were then prepared by standard acetalization of this *trans*-dithiol **7** using paraformaldehyde or acetone, respectively, under acid-catalyzed conditions. The 2-methyl derivative (**10**) with relative configuration of (2*t*,4a*r*,8a*t*) was alternatively obtained by transacetalization from diethyl acetal by treatment with the dithiol **7**. As anticipated, the C-2 epimer of **10** with relative configuration (2*c*,4a*r*,8a*t*) was not observed at all in the reaction products since an axially oriented methyl group would render it unstable[2,19] by ca. 8 kJ mol^{-1} relative to **10** leading to a population of less than 5% under equilibrium conditions. Furthermore, kinetic control appears to favor the formation of the more stable epimer and equilibration appears to require rather drastic conditions (cf. **13** and **14**, vide infra). All three trans-fused compounds, **9**−**11**, were produced as racemates.

Synthesis of Cis-Fused (4a*r*,8a*t*)-Hexahydro-1,3-dithiines (12−15). *trans*-2-(Hydroxymethyl)cyclohexanol (**2**) (prepared using literature methodology[17,18]) was ditosylated followed by treatment with sodium sulfide and sulfur similarly to **1** to provide a mixture of two cis-fused, bicyclic polysulfides, **4** and **6** (see Scheme 1). Reduction of the mixture of the two polysulfides **4** and **6** provided *cis*-2-mercaptomethyl cyclohexanethiol (**8**). The three compounds **12**, **13**, and **15** were all readily prepared by transacetalization from either diethyl formal, diethyl acetal, or acetone dimethylacetal, respectively, by treatment with the dithiol **8** under acid-catalyzed conditions. Somewhat surprisingly, the C-2 epimer of **13** with relative configuration (2*t*,4a*r*,8a*c*) (**14**) was not isolated from the reaction of **8** with diethyl acetal and, based on the significant presence of both the *S-in* and *S-out* conformations for compound **12** (vide infra), it was expected that **13** and **14** should be of comparable stability and that **14** should therefore be present to a significant

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Table 1. ^{1}H Chemical Shifts (ppm) for Compounds 9−15 at 298 K

compound	2ax	2eq	Me-ax	Me-eq	4ax	4eq	4a	5ax	5eq	6ax	6eq	7ax	7eq	8ax	8eq	8a
9	4.14	3.41	-	-	2.55	2.53	1.69	1.06	1.63	1.40	1.76	1.34	1.76	1.34	1.75	2.63
10	4.20	-	-	1.46	2.61	2.60	1.53	1.04	1.71	1.40	1.79	1.34	1.77	1.34	1.78	2.64
11	-	-	1.82	1.55	2.80	2.49	1.51	1.09	1.72	1.40	1.79	1.36	1.78	1.30	1.69	2.81
12 (*S-in*)[a]	4.13	3.55	-	-	3.16	2.70	1.95	2.46	1.36	1.36	1.85	1.52	1.46	1.78	1.78	3.41
12 (*S-out*)[a]	4.22	3.20	-	-	3.36	2.34	2.40	1.69	1.68	1.43	1.46	1.39	1.86	2.15	1.85	2.87
13	4.11	-	-	1.49	3.13	2.70	1.83	2.44	1.26	1.34	1.82	1.54	1.44	1.81	1.78	3.39
14 (*S-out*)[b]	4.16	-	1.455	-	3.43	2.42	n.d.[d]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.08	n.d.	2.93
14[c]	4.19	-	-	1.46	3.19	2.53	2.19	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.99
15	-	-	1.78	1.60	3.31	2.58	1.84	2.38	1.22	1.33	1.79	1.54	1.42	1.84	1.74	3.51

[a] At 213 K. [b] At 208 K for the 77:23 mixture of epimers **13** and **14**. [c] At 333 K for the 77:23 mixture of epimers **13** and **14**, conformationally averaged spectrum of the *S-out* (78 ±2%) and *S-in* forms (22%). [d] n.d., not detected.

Table 2. ^{13}C Chemical Shifts (ppm) for Compounds 9−15 at 298 K

compound	C2	C4	4a	C5	C6	C7	C8	C8a	CH_3
9	32.67	36.24	43.09	34.07	26.36	26.43	32.58	47.81	-
10	43.02	37.59	41.83	33.52	26.44	26.31	32.0.49	48.46	20.54 (eq)
11	47.04	33.80	42.25	33.42	26.52	26.39	32.15	44.29	30.51 (eq) 31.45 (ax)
12 (*S-in*)[a]	33.04	37.19	33.71	23.83	26.03	20.61	32.55	43.72	-
12 (*S-out*)[a]	24.97	27.27	35.47	34.78	19.59	27.05	27.56	40.82	-
13	43.91	38.45	32.94	24.05	26.37	20.91	32.60	45.27	20.91 (eq)
13[b]	43.99	38.59	33.36	24.36	26.55	21.09	32.82	45.50	20.94 (eq)
13 (*S-in*)[c]	43.83	38.06	32.09	23.59	25.91	20.60	32.09	44.98	20.93 (eq)
14[b,d,e]	36.10	30.17	34.96	32.22	21.56	26.19	29.92	42.19	21.13
	(35.74)	(30.10)	(34.82)	(31.88)	(21.12)	(26.25)	(29.45)	(42.23)	(21.34)
14 (*S-out*)[c]	35.08	28.94	34.37	33.83	19.60	27.15	28.40	42.81	20.29 (eq)
14 (*S-in*)[c]	37.93	34.00	36.34	25.34	26.20	23.24	32.95	40.27	24.84 (ax)
15	47.10	34.35	32.79	23.94	26.07	20.98	32.08	40.62	31.19 (eq) 30.92 (ax)

[a] At 213 K. [b] At 348 K for the 77:23 mixture of epimers **13** and **14**. [c] At 208 K for the 77:23 mixture of epimers **13** and **14**. [d] Conformationally averaged spectrum of the *S-out* (77%) and *S-in* forms (23%). [e] In parentheses are given the population-weighted average shift values of the *S-in* and *S-out* forms of **14** at 208 K based on the conformer ratio of 77:23 at 348 K.

extent at equilibrium. As has been demonstrated earlier, the equilibration of 1,3-dithianes can be achieved using either CF_3COOH[19] or boron trifluoride etherate[15,19] at relatively high temperatures; thus, an NMR sample of **13** treated with a catalytic amount of CF_3COOH in $CDCl_3$ at elevated temperatures (200 °C) for an extended period of time (overnight) yielded an equilibrium mixture consisting of ca. 77 ± 2% **13** and 23 ± 2% **14**. Therefore, equilibrium had not been attained in the synthetic preparation, and furthermore, kinetic control must have also been in effect to account for this result. Compound **14** was not isolated but was analyzed from the mixed solution by ^{1}H and ^{13}C NMR. All four cis-fused compounds, **12**−**15**, were produced as racemates.

Conformational Analysis. Chemical shift assignments were based on the standard application of DQF−COSY, CHSHF, NOE difference, and HSQC-TOCSY experiments. In addition, ^{13}C EXSY experiments facilitated the ready assignment of the ^{13}C resonances of the minor conformer of **12** after the assignments of the major conformer had been made. ^{1}H chemical shifts and ^{1}H,^{1}H coupling constants were extracted using PERCH[20] NMR software. The ^{1}H and ^{13}C chemical shifts are presented in Tables 1 and 2, respectively. Stereochemical conclusions were based on ^{1}H,^{1}H vicinal coupling constants (see Table 3) which indicate that all compounds are dominated by chair−chair conformations. The results of NOE difference experiments supported these conclusions.

Trans-Fused (4a*r*,8a*t*)-Hexahydro-1,3-dithiines. As expected, these three compounds are each conformationally locked in chair−chair conformations and dynamic processes were not in effect (see Figure 1). In compound **9**, irradiation of the proton resonating at 4.14 ppm resulted in an enhancement of the H-4ax and H-8a protons, which indicates that these protons are all axially orientated. Long-range w-coupling was also observed between the H-2eq and H-4eq protons of **9**, indicating their stereochemical dispositions and the chair conformation of the heteroring. In compound **11**, irradiation of the overlapping H-4ax and H-8a protons resulted in an enhancement of the methyl signal resonating at 1.82 ppm, indicating that this C-2 methyl group is axially orientated.

Cis-Fused (4a*r*,8a*c*)-Hexahydro-1,3-dithiines. The unsubstituted parent dithiine **12** provided only broad signals for both ^{1}H and ^{13}C NMR at ambient temperature. At 213 K, coalescence had been traversed and both conformations gave rise to separate subspectra (see Tables 1 and 2). Based on the values of the vicinal ^{1}H,^{1}H coupling constants (Table 3) at this temperature, in particular the vicinal couplings to the H-4a and H-8a protons, it was clear that the major conformer (83%) is the chair−chair *S-in* conformer and the minor form (17%) is the chair−chair *S-out* conformer (see Figure 1). The increased stability of the latter conformer in comparison to the corresponding conformers in analogous compounds[1] composed of oxygen and/or nitrogen instead of sulfur is due to the much longer C−S bond which reduces the diaxial interactions between CH_2-4 and H-6ax, and between CH_2-2 and H-8ax (Figure 1). For example, in the 1,3-dioxa analogue no conformational equilibrium was observed and the *O-in* conformer predominated[3] exclusively as the diaxial interactions are too severe and

(20) see for example, Laatikainen, R.; Niemitz, M.; Weber, U.; Sundelin, J.; Hassinen, T.; Vepsäläinen, J. *J. Magn. Reson., Ser. A* **1996**, *120*, 1, or the program website at http://www.uku.fi/perch.html.

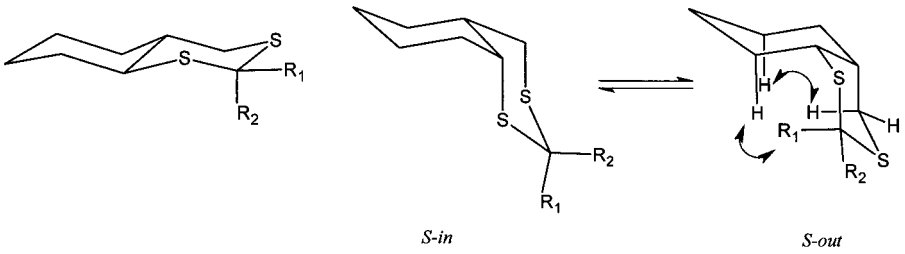
Table 3. ^{1}H,^{1}H-Coupling Constants (Hz) for Compounds 9−15 at 298 K

compound	2ax,2eq	2eq,4eq	4ax,4eq	4a,4ax	4a,4eq	4a,5eq	4a,5ax	5ax,5eq	5ax,6eq
9	−13.9	1.9	−13.8	10.8	2.9	3.9	11.9	−13.3	3.6
10	7.0[a]	−	−14.0	10.7	3.2	3.6	11.9	−13.3	3.4
11	−	−	−14.4	11.4	2.9	4.0	11.9	−13.3	3.9
12 (*S-in*)[b]	−13.9	2.3	−14.0	3.0	3.6	3.4	12.0	−13.3	3.8
12 (*S-out*)[b]	−14.1	−	−14.1	12.3	3.1	2.6	5.1	−14.9	6.9
13	7.0[a]	−	−14.1	3.2	3.6	3.2	12.0	−13.3	3.9
14 (*S-out*)[c]	6.8[a]	−	−13.9	12.7	3.1	n.d.[f]	n.d.	n.d.	n.d.
14[d]	6.9[a]	−	−14.3	10.8	3.3	2.8	5.4	n.d.	n.d.
15	−	−	−14.4	3.3	3.8	3.2	11.7	−13.3	3.9

	5eq,6eq	5ax,6ax	5eq,6ax	6ax,6eq	6ax,7eq	6ax,7ax	6eq,7eq	6eq,7ax	7ax,7eq
9	2.0	13.3	3.2	−13.1	4.0	12.9	3.2	3.7	−14.2
10	1.5	13.1	2.9	−13.5	4.4	12.5	2.1	5.1	−14.7
11	2.0	13.0	3.6	−13.1	4.1	13.1	2.7	3.9	−13.7
12 (*S-in*)[b]	3.0	13.4	3.8	−12.7	3.7	13.4	2.2	4.0	−14.2
12 (*S-out*)[b]	4.8	12.4	3.4	−15.1[e]	3.9	11.7	4.1	4.6	−14.5
13	3.0	13.2	4.0	−13.3	3.9	13.2	2.8	3.8	−13.6
14 (*S-out*)[c]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
14[d]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
15	2.5	13.05	4.05	−13.3	3.8	13.1	4.1	4.0	−13.5

	7ax,8eq	7ax,8ax	7eq,8eq	7eq,8ax	8ax,8eq	8a,8ax	8a,8eq	4a,8a
9	3.7	13.1	2.3	4.4	−13.1	12.1	3.6	10.1
10	3.5	11.7	2.2	4.2	−12.6	12.2	3.5	10.1
11	3.5	13.0	2.0	3.8	−13.1	12.1	3.6	10.4
12 (*S-in*)[b]	2.4	14.8	3.5	2.8	−14.0	4.7	2.0	2.3
12 (*S-out*)[b]	2.9	12.7	2.4	3.4	−13.9	13.1	3.7	3.0
13	3.9	13.8	3.35	4.2	−14.15	4.2	2.4	3.0
14 (*S-out*)[c]	n.d.	12.8	n.d.	3.4	−13.6	13.1	3.5	3.5
14[d]	n.d.	n.d.	n.d.	n.d.	−14.0	10.6	4.0	3.9
15	4.0	13.6	2.7	4.1	−14.6	4.5	2.7	3.2

[a] 2ax,2CH_3. [b] At 213 K. [c] At 208 K for the 77:23 mixture of epimers **13** and **14**. [d] At 333 K for the 77:23 mixture of epimers **13** and **14**, conformationally averaged spectrum of the *S-out* (78 ±2%) and *S-in* forms (22%). [e] Standard deviation ±0.4 Hz. [f] n.d., not detected.



S-in *S-out*

trans-fused compounds

9 R_1 = H, R_2 = H

10 R_1 = CH_3 R_2 = H

11 R_1 = CH_3, R_2 = CH_3

cis-fused compounds

12 R_1 = H, R_2 = H, *S-in*:*S-out*, 83:17 at 213 K

13 R_1 = CH_3, R_2 = H

14 R_1 = H, R_2 = CH_3 *S-in*:*S-out*, 77:23 at 348 K

15 R_1 = CH_3, R_2 = CH_3

Figure 1. The chair−chair conformation adopted by the trans compounds (**9**−**11**) and the *S-in* and *S-out* conformations adopted by the cis compounds (**12**−**15**) with the axial−axial interactions responsible for the conformational preference and resulting shift in equilibrium indicated.

completely disfavor the *O-out* conformer. Based on the 83:17 conformational equilibrium of **12** at 213 K, the *S-in* conformer is 2.8 kJ mol^{-1} more stable than the *S-out* conformer.

The synthetic procedure provided only one 2-monomethyl epimer, **13**. This molecule also clearly adopts a biased *S-in* conformation as indicated by the ^{1}H,^{1}H coupling constants at ambient temperature, and in this conformation the 2-methyl substituent is equatorially orientated. In comparison to **12**, the *S-in* conformation should be even more favored over the *S-out* conformation as the methyl group would change from an equatorial position in the former to an axial position in the latter. Upon going down in temperature though, the presence of another conformer was clearly evident from the broadening and then resharpening of the signals in both the ^{1}H and ^{13}C NMR spectra. However, the minor conformer was not observable at lower temperatures due to its low concentration which is reduced drastically with decreasing temperatures. Lacking direct observation of the minor conformer precludes its explicit identification since it can be either the *S-out* conformer (where there is a large syn-axial interaction between the 2ax-Me and CH_2-8) or the 3,8a-twist form, which for monocyclic 1,3-dithiane[19] is disfavored enthalpy-wise by ca. 16.7 kJ mol^{-1} in comparison to the chair form. Using the isomeric

2-*tert*-butyl-2,4-dimethyl-1,3-dithianes (of which one is completely in the twist form and the other has an axial 2-methyl[19]) as model compounds whereby $\Delta H_{CT} = 20.2$ kJ mol^{-1} and $\Delta S_{CT} = 14.3$ J K^{-1} mol^{-1}, it is possible to estimate that the contribution of the *S-in* form to **13** at 298 K is ca. 98%, approximating to a 9.6 kJ mol^{-1} difference in free energy between the two conformers. This is also borne out by the vicinal ^{1}H,^{1}H coupling constants (see Table 3) which also provide a value of 98% for the *S-in* conformer based on *J* values taken from **12** for the *S-out* and *S-in* conformers. An equilibrium composed of the *S-in* and *S-out* chair−chair forms would therefore imply that the *syn*-axial interaction between the 2-axial methyl and CH_2-8 in the latter would be 9.6−3.2 = 6.4 kJ mol^{-1}, which in fact is virtually equal to that between the axial 2-methyl and the axial H-4 and H-8a hydrogens of the *S-in* conformer of **14** (vide infra).

Compound **14** at ambient temperature is clearly in a dynamic equilibrium as evidenced by the breadth of the signals in the ^{1}H and ^{13}C NMR. At 208 K, coalescence had been traversed and both conformations gave rise to separate subspectra (see Tables 1 and 2). Because the sample was analyzed as a mixture of compounds (**13** and **14**) it was difficult to discern the signals of the minor conformer of **14**, particularly in the ^{1}H NMR spectrum. Based on the values of the vicinal ^{1}H,^{1}H coupling constants (Table 3) at this temperature, in particular the vicinal couplings of the H-4a and H-8a protons, it was clear that the major conformer is the chair−chair *S-out* conformer (cf. **12**) which enables an equatorial orientation of the 2-methyl group and therefore the minor form is the *S-in* chair−chair conformation (see Figure 1). Since the conformational energy of an axial 2-methyl in 1,3-dithianes[2,19] is usually considered to be ca. 8 kJ mol^{-1}, the *S-in* conformer of **14** was also expected to be observable to some degree based on an energy difference of 2.8 kJ mol^{-1} between the two conformers of **12** as this would place the *S-in* conformer 5.2 kJ mol^{-1} in energy above that of the *S-out* conformer. However, the interaction of the axial 2-methyl in the *S-in* conformation of **14** is not necessarily equal to that in 1,3-dithianes as there can exist a palpable entropy difference between the more stable *S-out* and the less stable *S-in* conformer of **14**. A sufficient number of ^{1}H chemical shifts (see Table 1) and vicinal coupling constants (see Table 3) for the *S-out* form of **14** at 208 K were solved and for the conformationally averaged spectrum at 333 K. Two vicinal coupling constants at 333 K allow evaluation of the conformational equilibrium between the *S-out* and *S-in* forms, namely $^3J_{4a,4ax} = 10.8$ Hz and $^3J_{8a,8ax} = 10.6$ Hz, both of which are clearly smaller than the limiting values for the *S-out* form of **14** (12.7 and 13.1 Hz, respectively) indicating that some of the *S-in* conformer must be present (the respective model couplings $J_{4a,4eq}$ and $J_{8a,8eq}$ from **12** (*S-in*) are 3.6 and 2.4 Hz). From these values the proportion of the *S-out* conformer for **14** at 333 K is calculated to be 78 ± 2% and therefore the *S-out* conformer of **14** is 3.5 kJ mol^{-1} more stable than the *S-in* form at 333 K. Taking into account that for the unsubstituted cis-fused compound **12** the ratio of the *S-in* and *S-out* conformers at 213 K was 83:17 (which corresponds to a free energy difference of 2.8 kJ mol^{-1}) and assuming that there is no significant entropy term, the conformational energy of an axial 2-methyl in the *S-in* conformer is 6.3 kJ mol^{-1}. This value is somewhat smaller than that for monocyclic 1,3-dithiane and this could be attributed to some entropy difference between the *S-out* and *S-in* forms of these bicyclic 1,3-dithia derivatives and/or small contributions from twist-boat conformations which are known to be relatively low energy and also clearly favored by entropy (vide supra).[19] An estimate of the population for the *S-in* form of **14** is approximately 12% at 208 K, thus precluding total solution of its ^{1}H spectrum (in the equilibrium mixture of the epimers the amount of **14** in total was ca. 23%, i.e., less than 3% of the material weight of the sample is in the *S-in* form at 208 K).

By comparison to the previous arguments for **13**, the 2,2-dimethyl derivative, **15**, should also have its *S-out* conformer raised in energy by 9.6 kJ mol^{-1}. In this case, however, the twist form is excluded since it cannot be attained without having a pseudoaxial methyl group at C-2.[2] Indeed, the conformational equilibrium is practically as biased as it is for **13**. At ambient temperature the molecule is almost exclusively in the *S-in* conformation as evidenced by the pertinent coupling constants, but the presence of another conformer was clearly in evidence upon going down in temperature as the signals in both the ^{1}H and ^{13}C NMR spectra first broadened and then sharpened. However the presence of the minor conformer was again indiscernible at these lower temperatures as its concentration was again too low for it to be observed directly. The *O-out* conformer of the dimethyl 1,3-dioxa analogue was, similarly to the parent 1,3-dioxa analogue, also severely energetically disfavored.[3] However, the fact that the *S-out* conformer appears to be present in this case (**15**) as the minor conformer in the dynamic equilibrium supports the conformational equilibrium existing mainly between the *S-in* and *S-out* chair−chair forms for **13** as well with twist conformations being of only minor importance in both cases.

The ^{13}C NMR chemical shifts of compounds 9−15 are listed in Table 2, and the assignments are based on the standard application of 2-D experiments. The distinct ^{13}C chemical shifts of the *S-in* and *S-out* forms of **12** (an 83:17 mixture at this temperature, respectively) were obtained below coalescence at 213 K. The chemical shifts of **13** having the biased *S-in* conformation with the equatorial 2-methyl were determined at three temperatures (348, 298, and 208 K). The shift differences between 348 and 208 K vary from less than 0.2 up to 1.3 ppm, indicating a clear temperature effect. It was possible to assign the ^{13}C shifts for both the major *S-out* form with an equatorial 2-methyl and the minor *S-in* form with an axial 2-methyl of **14** at 208 K although several impurity signals of similar intensity complicated this task in the case of the latter conformer. The task was made easier by the fact that the population-weighted average shifts for the 77:23 mixture of the *S-out* and *S-in* forms of **14** at 348 K were also measured (see Table 2). These were also estimated based on the ^{13}C shifts for the separate forms at 208 K, and the agreement between the found and calculated (Table 2) average shifts for **14** at 348 K is surprisingly good in consideration of the temperature effects mentioned above.

It was also insightful to compare the ^{13}C chemical shifts of C-2, C-4, C-4a, and C-8a of **10** and **11** with those obtained using substituent effects derived for monocyclic dithianes[2] and the parent shifts for **9**. For compounds **13**−**15**, the parent shifts are those of the *S-in* and *S-out* forms of **12**. In the main, a good or at least satisfactory agreement was generally forthcoming although in some cases the ring fusion exhibits, especially for the *S-in*

forms, small shift effects which are obviously not present in the monocyclic alkyl-substituted 1,3-dithianes.[2]

Mass Spectra of Compounds 9−15. The fragmentation patterns of compounds **9**−**13** and **15** under electron impact were in accord with earlier studies on the behavior of 2-alkyl- and 2-aryl-1,3-dithianes,[21] i.e., fragmentation is dominated by the heterocyclic part and not by any means by the fused carbocycle. The molecular ion is very strong and often the base peak of the spectrum (see Table S1, Supporting Information). Very little loss of H$^{\bullet}$ occurs from **9** and **12** whereas all of the other compounds yielded strong $[M - CH_3]^+$ fragments. The ion $C_7H_{11}S_2^+$ is an interesting one; in each case it results from loss of the C-2 unit of the dithiane ring following a hydrogen transfer (R_1R_2C + H, i.e., CH_3 from **9** and **12**, C_2H_5 from **10** and **13**, and C_3H_7 from **11** and **15**) and is consistent with the observations on the monocyclic dithianes.[21c] Other common fragments observed were the $[M - HS]^+$, $[M - CH_3S]^+$, and $[M - R_1R_2CS]^{+\bullet}$ ions. The loss of HS from the latter ion gave in all cases the abundant ion $C_7H_{11}^+$ at *m*/*z* 95.[21]

To distinguish cis- and trans-fused isomers a priori based on their mass spectra is certainly not a trivial problem, but it can be accomplished.[22,23] For **13** and **15** the $C_7H_{11}^+$ ion is the most abundant ion, but for **10** and **11** the relative abundance of this ion was only 66 and 53, respectively. For **9** and **12** the abundances of the $[M - CH_3S]^+$ ion are clearly different, namely 10 vs 43%, respectively. Thus, there is some indication that a basis for determining the fusion site stereochemistry exists.

X-ray Crystal Structure Determination of 12 and 13. 1,3-Dithiane structures do not appear to have been rigorously examined by X-ray analysis, and there is only one study[5] in the literature that actually reports a structure which is closely related to the structures examined here (**12** and **13**). The solid-state structure of (2*t*,4a*r*,8a*t*)-2-(*p*-chlorophenyl)-hexahydro-1,3-dithiine (a phenyl-substituted analogue of compound **10**) is unexceptional, and both rings are in near idealized chair conformations.[5] Thus, it provides a reference basis set for the internal structure of the compounds examined in this work in terms of bond lengths and bond angles. Although the compound crystallized in the monoclinic $P2_1/n$ space group in comparison to the triclinic $P\bar{1}$ space group for both **12** and **13**, the packing of the molecules indicated little or no intermolecular interactions apart from van der Waals forces, and this result is translatable to the two compounds examined here. The primary interest for these studies was the solid-state conformational preference of compound **12,** and for comparative purposes the structure of compound **13** was also determined, which is depicted in Figure 2. Suitable crystals of **13** amenable for X-ray analysis were obtained without difficulty from methanol solution by slow evaporation, and the compound crystallized out in the triclinic $P\bar{1}$ space group. Needless to say the enantiomeric molecule depicted in Figure 2 comprises half the unit cell with the other enantiomer constituting the other half of the unit cell. There was a regular arrangement of similarly

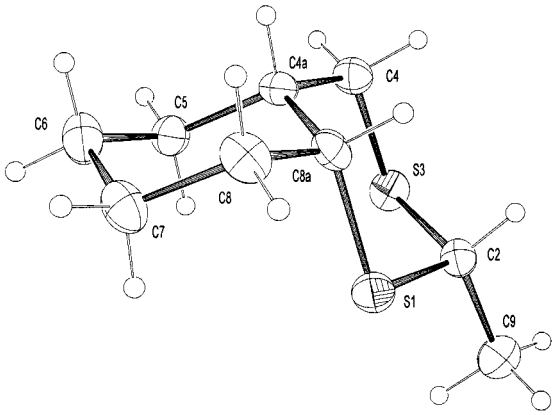


Figure 2. The X-ray crystallographic structure of **13**. The adopted conformation in the solid state is the same as the major conformer adopted in solution (*S*-*in*). The cif file of this structure is available as Supporting Information.

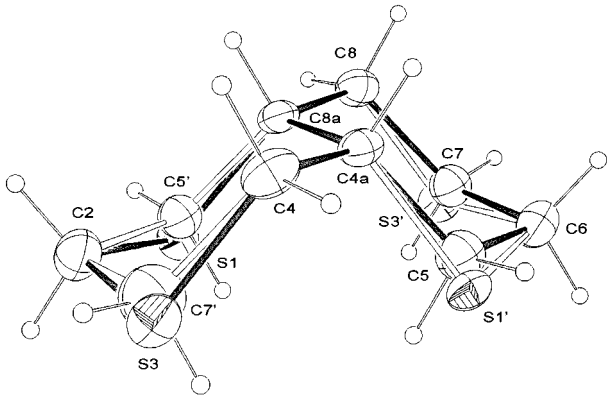


Figure 3. The unbiased refinement of the X-ray analysis of **12**. The overlaid structures result from irregular stacking of the molecules with two parallel orientations possible. The enantiomers crystallized separately but within the one unit cell ($P\bar{1}$ space group).

orientated molecules in the crystal lattice and refinement was obtained uneventfully. Both six-membered rings each conform to an almost ideal chair conformation, and the preferred conformation is the same as the predominant conformer adopted in solution, namely *S*-*in*. The bonding parameters—lengths and angles—are unexceptional and are otherwise normal in comparison to (2*t*,-4a*r*,8a*t*)-2-(*p*-chlorophenyl)-hexahydro-1,3-dithiine.[5]

Compound **12** was, by comparison, quite problematic in that suitable crystals were difficult to obtain despite the variety of solvents (polar, nonpolar, aromatic, etc.), and even sublimation, that were used to effect crystallization. The propensity of the compound was to form thin, needlelike crystals emanating from the one central point and to "twin" excessively, although acceptable crystals were finally obtained by slow evaporation from acetonitrile solution. These crystals were similar to the needlelike crystals grown by sublimation, and X-ray analysis indicated both to have the same unit cell. Randomness was also evident at the packing level as the compound crystallized out in a random manner with respect to the orientation of the idealized ring planes about a C_{2v} axis orthogonal to this same plane. By solving the structure without any prior bias the refinement yielded the result depicted in Figure 3, and this was the only acceptable result that could be obtained. The

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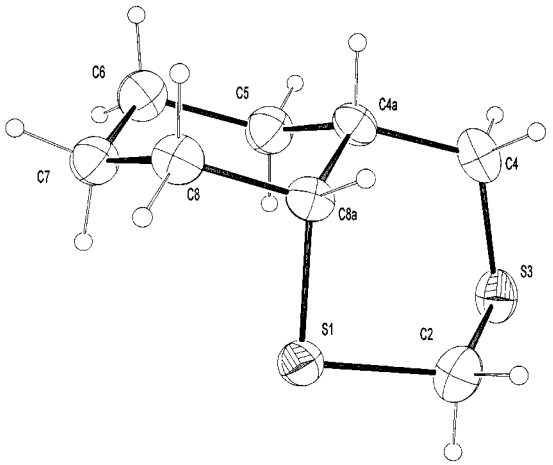

Figure 4. The X-ray crystallographic structure of **12**. The adopted conformation in the solid state is the same as the major conformer adopted in solution (*S-in*). The cif file of this structure is available as Supporting Information.

contributions of each of the two overlaid structures is approximately equal. Obviously two molecules cannot occupy the same space, and the solution is a result of random stacking. If the molecules can stack with only minimal intermolecular forces in effect, this could lend itself either to a random disposition of molecules on top of one another (a systematic or regular stacking arrangement would otherwise lend itself to refinement) but with only two possible orientations related by a 2-fold axis, or to a regular stacking in the column that with additional molecules becomes increasingly lopsided which is corrected at irregular intervals by a reversal of orientation of an incoming molecule. Both possible explanations imply a minimal level of intermolecular interaction not only between adjacent stacked molecules, but also between columns of molecules. Depicted in Figure 4 is the crystal structure of one molecule of **12**. The depiction is enantiomeric, and this moiety comprises one-half of the unit cell with the other enantiomer comprising the other half (triclinic $P\bar{1}$ space group). This is also true for the overlaid refinements, i.e., both enantiomers do not appear to cocrystallize in the one column. Again both six-membered rings each conform to an almost ideal chair conformation, and the preferred conformation is the same as the predominant conformer adopted in solution, namely *S-in*. Similarly too, the bonding parameters—lengths and angles—are unexceptional and are otherwise normal in comparison to both **13** and (2*t*,4a*r*,8a*t*)-2-(*p*-chlorophenyl)-hexahydro-1,3-dithiine.[5]

Experimental Section

NMR spectra were acquired on either a JEOL Alpha 500 or JEOL Lambda 400 NMR spectrometer equipped with either a 5 mm normal configuration tunable probe or a 5 mm inverse probe operating at 500.16 MHz (or 399.78 MHz) for ^{1}H and 125.78 MHz (or 100.54 MHz) for ^{13}C. Spectra were recorded at 298 K in $CDCl_3$, or where warranted by dynamic effects, using variable temperature NMR (208−348 K). Both ^{1}H and ^{13}C spectra were referenced internally to tetramethylsilane (0 ppm for both). For 1-D proton spectra, spin analysis was performed using PERCH software[20] for the extraction of ^{1}H chemical shifts and ^{1}H,^{1}H coupling constants. NOE difference measurements were acquired at lower resolution using saturation times of 6−8 s. DEPT 135° and selective INEPT (9 ms soft rectangular pulse; optimized on 5−7 Hz for $^nJ_{HC}$) spectra were acquired with similar conditions as for the 1-D carbon spectra but with a postacquisition delay time of 3 s.

2-D CHSHF (^{1}H-{^{13}C}, optimized on 145 Hz for $^1J_{HC}$), HMBC (^{1}H-{^{13}C}, optimized on 8 Hz for $^nJ_{HC}$), and EXSY spectra (^{13}C nucleus; 500 ms mixing time) were all acquired in magnitude mode. DQF−COSY and HSQC-TOCSY (optimized on 145 Hz for $^1J_{HC}$; spin lock times, 15−60 ms; proton field strength attenuated to 8.3 kHz) experiments were both acquired in phase-sensitive mode. For all 2-D spectra, the spectral widths and resolution were appropriately optimized from the 1-D spectra.

Mass spectra were acquired on a VG ZabSpec mass spectrometer operating in the EI^+ mode (direct insert probe, 70 eV). Fragmentation routes were confirmed by metastable ion analysis.

X-ray structures for compounds **12** and **13** were determined using essentially the same methodology as described in ref 24 and according to the principles outlined in the references therein (refs 29−33). Single-crystal data collections were performed at ambient temperature on a Rigaku AFC5S diffractometer using graphite monochromatized Mo Kα radiation ($\lambda = 0.71069$ Å). The unit cell parameters were determined by least-squares refinement of 25 carefully centered reflections. Data reduction and subsequent calculations were performed using *teXsan for Windows*.[25] The structures were solved by direct methods using the *SIR92* program[26] and full-matrix least-squares refinements on F^2 were performed using the *SHELXL-97* program.[27] For compound **12**, heavy atoms were refined anisotropically while hydrogen atoms were included at fixed distances with fixed displacement parameters from their host atoms. For compound **13**, heavy atoms were refined with anisotropic displacement parameters while hydrogen atoms were refined isotropically. Figures were drawn using *Ortep-3 for Windows*.[28] The crystal data for compounds **12** and **13** are summarized in the Supporting Information together with the cif files.

Synthesis. *trans*-2-(Mercaptomethyl)cyclohexanethiol (7).[14,15] Commercially available ethyl cyclohexanone-2-carboxylate (Fluka) was stereoselectively reduced using bakers' yeast[16] to the *cis*-1-hydroxy ester followed by reduction with $LiAlH_4$ affording *cis*-2-(hydroxymethyl)cyclohexanol,[17,18] **1**. Compound **1** was then ditosylated using standard methodology,[14,15,29] and a solution of this ditosylate (4.04 g, 9.2 mmol in 10 mL DMF) was added to a stirred suspension of 3.31 g $Na_2S{\cdot}9H_2O$ (10.2 mmol; freshly recrystallized from 90% aq ethanol) and 450 mg (10.2 mmol) of sulfur in 15 mL of DMF. The mixture was heated to 75 °C and stirred for 34 h, poured into ice−water, extracted with hexane, dried over Na_2SO_4, and concentrated.

Column chromatography (silica gel, gradient elution with hexane/hexane−ether 10:1) afforded the novel bicyclic disulfide *trans*-1,2-dithiahydrindane, **3** (420 mg, 28% yield), as a yellow oil. HRMS: $M^{+\bullet}$, 160.0377; calcd for $C_7H_{12}S_2$, 160.0380. ^{1}H NMR ($CDCl_3$) δ ppm: 3.34 (dd, 1H, $J = 9.6$, $J = 7.1$, H_{eq}-CHS), 2.89 (ddd, 1H, $J = 11.8$, $J = 10.8$, $J = 3.7$, H_{ax}-CS), 2.75 (dd, 1H, $J = 10.7$, $J = 9.6$, H_{ax}-CHS), 2.21−2.09 (m, 2H), 1.95−1.10 (m, 7H). MS (EI, 70 eV): 160 ($M^{+\bullet}$, 35), 95 (100), 67 (23), 55 (8), 41 (11). The novel bicyclic trisulfide *trans*-1,2,3-trithiadecalin, **5** (290 mg, 15% yield), was obtained as a white solid. Mp 66 °C. HRMS: $M^{+\bullet}$, 192.0101; calcd for $C_7H_{12}S_3$, 192.0101. ^{1}H NMR ($CDCl_3$) δ ppm: 3.13−3.05 (m, 1H, CH−S), 3.08 (dd, 1H, $J = 14.0$, $J = 11.1$, H_{ax}-CHS), 2.72 (dd, 1H, $J = 14.0$, $J = 2.6$, H_{eq}-CHS), 1.90−1.74 (m, 4H), 1.57−1.51 (m,

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5H). ^{13}C NMR ($CDCl_3$) δ ppm: 26.43, 26.94, 32.49, 34.93, 41.11, 42.81, 53.28. MS (EI, 70 eV): 192 ($M^{+\bullet}$, 79), 127 (21), 95 (100), 94 (13), 93 (30), 81 (19), 79 (10), 67 (24), 55 (9). The polysulfides **3** and **5** were then reduced with $LiAlH_4$ to afford the dithiol **7** in 60% yield (bp 84−86 °C/2 mmHg; liter.[14] 114−116 °C/10 mmHg) which was then subsequently used without purification for the syntheses of compounds **9**−**11**.

***cis*-2-(Mercaptomethyl)cyclohexanethiol (8).** *trans*-2-(Hydroxymethyl)cyclohexanol[17,18] was first ditosylated to provide an oily product (yield 70%) which was then further converted to the *cis*-dithia analogue using sodium disulfide in DMF (80 °C, 3 days). Reduction with $LiAlH_4$ in ether provided the dithiol **7** in 60% yield (based on the ditosylate). Bp 82−84 °C/2 mmHg; purity 99% by GC.

(4a*r*,8a*t*)-Hexahydro-1,3-benzodithiine (9). A mixture of dithiol **7** (250 mg, 1.5 mmol), paraformaldehyde (270 mg, 9 mmol), and *p*-toluenesulfonic acid (25 mg, 0.15 mmol) in 5 mL of toluene was refluxed under nitrogen for 30 min, diluted with hexane, and then washed consecutively with 2 M NaOH and water. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel, gradient elution with hexane/hexane−CH_2Cl_2 10:1) to yield 160 mg (60%) of **9** as white crystals, mp 119 °C. HRMS: $M^{+\bullet}$, 174.0536; calcd for $C_8H_{14}S_2$, 174.0537. NMR and MS results in Tables 1−3 and 4, respectively.

2,2-Dimethyl-(4a*r*,8a*t*)-hexahydro-1,3-benzodithiine (11). A solution of dithiol **7** (180 mg, 1.1 mmol) and *p*-toluenesulfonic acid (17 mg, 0.1 mmol) in 5 mL of acetone was refluxed for 8 h under nitrogen, concentrated, and purified by column chromatography (silica gel, gradient elution with hexane/hexane−CH_2Cl_2 10:1) to yield 140 mg (60%) of **11** as a clear liquid. HRMS: $M^{+\bullet}$, 202.0835; calcd for $C_{10}H_{18}S_2$, 202.0850. NMR and MS results in Tables 1−3 and 4, respectively.

General Transacetalization Procedure for the Preparation of Hexahydro-1,3-benzodithiines 10, 12, 13, and 15. 10 mmol of **7** or **8** and 20 mmol of diethyl acetal (or diethyl formal or acetone dimethylacetal) were dissolved in 30 mL of benzene followed by a catalytic amount of *p*-toluenesulfonic acid. The alcohol that formed was removed slowly by azeotropic distillation. After the reaction was complete, the residue was taken up in ether, washed with $NaHCO_3$ solution, and dried over $MgSO_4$. The crude products were purified by vacuum distillation followed by recrystallization from hexane.

(2*t*,4a*r*,8a*t*)-2-Methyl-hexahydro-1,3-benzodithiine (10): yield 60%; mp 60−61 °C (hexane); HRMS, $M^{+\bullet}$, 188.0705; calcd for $C_9H_{16}S_2$, 188.0693. NMR and MS results in Tables 1−3 and 4, respectively.

(4a*r*,8a*c*)-Hexahydro-1,3-benzodithiine (12): yield: 60%; bp 104−110 °C/2 mmHg; mp 81−82 °C (hexane); HRMS, $M^{+\bullet}$, 174.0543; calcd for $C_8H_{14}S_2$, 174.0537. NMR and MS results in Tables 1−3 and 4, respectively.

(2*c*,4a*r*,8a*c*)-2-Methyl-hexahydro-1,3-benzodithiine (13): yield: 65%; bp 95−96 °C/2 mmHg; mp 65−66 °C (hexane); purity 95% by GC; HRMS, $M^{+\bullet}$, 188.0697; calcd for $C_9H_{16}S_2$, 188.0693. NMR and MS results in Tables 1−3 and 4, respectively.

(2*t*,4a*r*,8a*c*)-2-Methyl-hexahydro-1,3-benzodithiine (14). To ca. 15 mg of **13** in ca. 0.8 mL of $CDCl_3$ were added increasing portions (final amount ca. 2 μL) of CF_3CO_2H, and the reaction was monitored by ^{1}H NMR with respect to time and elevated temperatures. Overnight heating at approximately 200 °C was found to be necessary to force the reaction along, resulting in an equilibrium mixture of **13** and **14** (77:23) being obtained. **14** was not isolated from this mixture, and the sample was used directly for the NMR measurements, the results of which are summarized in Tables 1−3.

2,2-Dimethyl-(4a*r*,8a*c*)-hexahydro-1,3-benzodithiine (15): yield: 58%; bp 103−105 °C/2 mmHg; mp 43−44 °C (hexane); HRMS: $M^{+\bullet}$, 202.0861; calcd for $C_{10}H_{18}S_2$, 202.0850. NMR and MS results in Tables 1−3 and 4, respectively.

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Supporting Information Available: Detailed NMR experimental conditions, mass spectral data (Table S1), and X-ray crystallographic data (including the cif files) for compounds **12** and **13** is available free of charge via the Internet at http://pubs.acs.org.

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