A General Methodology for the Synthesis of [2.2.1], [3.2.1+], and [4.2.1] Bridged Bicyclic Disulfide Systems

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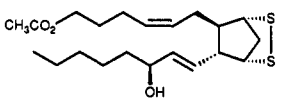
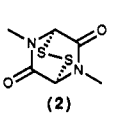
A general synthesis for bridged bicyclic disulfide compounds has been refined and expanded from [3.2.1] to [2.2.1] and [4.2.1] systems. The chemical reactivity of these novel compounds has been probed through esterification and S-oxidation reactions.

Introduction

Most of the known bridged bicyclic disulfide (or epidithia) compounds have important biological activity. Two of the more common examples are the prostaglandin epidithia analogues **1**[1] and the family of fungal toxins characterized by the epidithiadioxopiperazine system **2**; gliotoxin (**3**) is the most widely studied.[2] There have been three reported syntheses of the prostaglandin bicyclic disulfides;[1] the synthesis of epidithiadioxopiperazine (ETP) compounds has been led by Kishi[3] and Ottenheijm.[4] Other syntheses of novel bridged bicyclic disulfide compounds have been reported but their application to a general synthesis for this system is not possible.[5]



(1)



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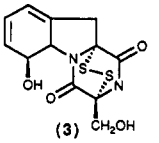
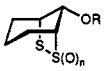


(3)

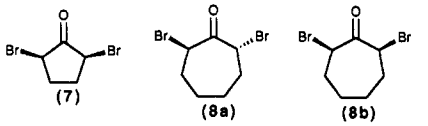
Results and Discussion

The synthesis of *syn*-2,3-dithiabicyclo[3.2.1]octan-8-ol (**4**) was first achieved by Wilson and co-workers in 1971.[6] We recently reported the crystal structure of the *p*-nitrobenzoate derivative **5** and its thiosulfinate ester **6** which confirmed the configuration about C8 (OH syn to the disulfide linkage) and the near-zero dihedral angle about the S–S bond.[7] We now wish to describe the synthesis of [2.2.1] and [4.2.1] bridged bicyclic disulfide compounds using this methodology.

The synthesis of these molecules begins with an α,α'-dibromocycloalkanone which must possess the cis configuration. This class of compounds has been previously investigated by Hoffmann and Vinter[8] who suggested that both 2,5-dibromocyclopentanone (**7**) and 2,7-dibromocycloheptanone (**8**) were in the trans configuration. An earlier report[9] implied the existence of the cis isomers of **7** and **8**; however, no experimental details were provided.



(4) R = H, n = 0
(5) R = -C(O)-C_6H_4-NO_2, n = 0
(6) R = -C(O)-C_6H_4-NO_2, n = 1



(7) (8a) (8b)

The syntheses of dibromocycloalkanones **7** and **8** were performed in glacial acetic acid with the addition of 2 equiv of bromine to the corresponding cycloalkanone. Only one isomer of **7** was isolated in crystalline form whereas the crude solid from the preparation of **8** was shown (^{1}H NMR) to consist of two isomers in a ratio of 2:1 (**8a**:**8b**). Slow recrystallization of this crude mixture provided **8a** as a white crystalline solid that had spectral data and a melting point consistent with the results reported by Hoffmann[8] for the trans isomer. Confirmation of the assignment of **8a** as the trans isomer was obtained by carrying out the synthesis of the [4.2.1] bridged bicyclic compound using the crude mixture containing both isomers, **8a** and **8b**, and, in a separate experiment, using pure **8a**. The latter experiment was not successful, whereas the former produced the desired bicyclic compound (vide infra).

The configuration of the isomer obtained in the synthesis of dibromocyclopentanone (**7**) was confirmed by the synthesis of the dithiocyanato derivatives. The addition of 2 equiv of potassium thiocyanate to **7** produced a crude product that contained a mixture of two isomers, **9a** and **9b**, in a ratio of 4:1 (Scheme I). Recrystallization of this mixture provided fine needles of **9a** which were subjected to an X-ray crystallographic investigation in order to determine the configuration of the two thiocyanate groups. The ORTEP[10] drawing of **9a** is shown in Figure 1 where the thiocyanate groups are clearly cis. This confirms that the two bromine atoms in **7** were also in the cis configuration. The production of a small amount of the trans isomer (**9b**) in this reaction can be explained by an S_N2 epimerization of one of the thiocyanate groups by another thiocyanate nucleophile.[11]

(1) (a) Miyake, H.; Iguchi, S.; Itoh, H.; Hayashi, M. *J. Am. Chem. Soc.* **1977**, *99*, 3536. (b) Greene, A. E.; Padilla, A.; Crabbe, P. *J. Org. Chem.* **1978**, *43*, 4377. (c) Ghosh, S. S.; Martin, J. C.; Fried, J. *J. Org. Chem.* **1987**, *52*, 862.

(2) For reviews see: (a) Brewer, D.; Hannah, D. E.; Taylor, A. *Can. J. Microbiol.* **1966**, *12*, 1187. (b) Taylor, A. In *Biochemistry of Some Foodborne Microbial Toxins*; Mateles, R. I., Wogan, G. N., Eds.; M.I.T. Press: Cambridge MA, 1967; p 69. (c) Taylor, A. In *Microbial Toxins*; Ciegler, A. Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. VII, p 337. (d) Kirby, G. W.; Robins, D. J. In *The Biosynthesis of Mycotoxins*; Stein, P. S., Ed.; Academic Press: New York, 1980; p 301. (e) Turner, W. B.; Aldridge, D. C. *Fungal Metabolites II*; Academic Press: New York, 1983; p 417.

(3) (a) Kishi, Y.; Fukuyama, T.; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490. (b) Kishi, Y.; Fukuyama, T.; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6492. (c) Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havle, M. *J. Am. Chem. Soc.* **1973**, *95*, 6493. (d) Nakatsuka, S.; Fukuyama, T.; Kishi, Y. *Tetrahedron Lett.* **1974**, 1549.

(4) Ottenheijm, H. C. J.; Herscheid, J. D. M.; Kerkhoff, G. P. C.; Spande, T. F. *J. Org. Chem.* **1976**, *41*, 3433.

(5) (a) McCabe, P. H.; Stewart, A. *J. Chem. Soc., Chem. Commun.* **1980**, 100. (b) Jubran, N.; Cohen, H.; Koresh, Y.; Meyerstein, D. *J. Chem. Soc., Chem. Commun.* **1984**, 1683. (c) Kolly, S.; Meier, H.; Rihs, G.; Winkler, T. *Helv. Chem. Acta* **1988**, *71*, 1101.

(6) Wilson, R. M.; Buchanan, D. N.; Davis, J. E. *Tetrahedron Lett.* **1971**, 3919.

(7) Folkins, P. L.; Harpp, D. N.; Vincent, B. R. *J. Org. Chem.* **1991**, *56*, 904.

(8) Hoffmann, H. M. R.; Vinter, J. G. *J. Org. Chem.* **1974**, *39*, 3921.

(9) Prager, R. H.; Tippett, J. M. *Tetrahedron Lett.* **1973**, 5199.

(10) Johnson, C. K. ORTEPII. *Report ORNL-5138*, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.

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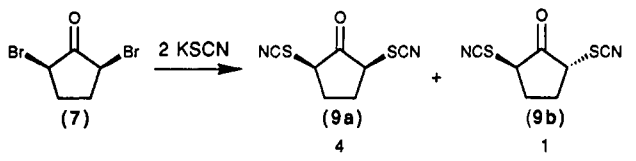
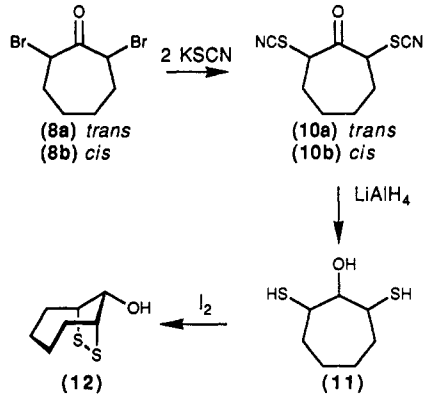
Scheme I



Scheme II



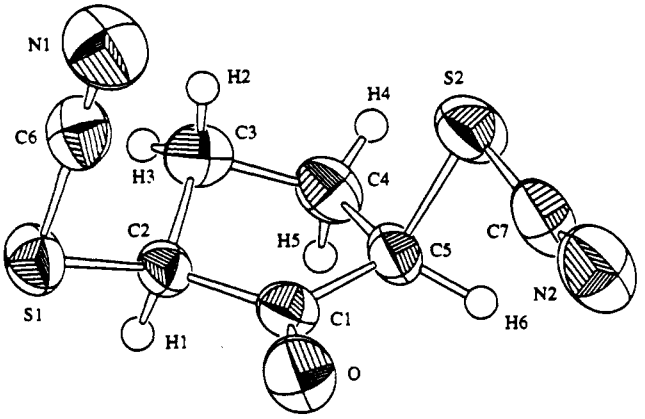
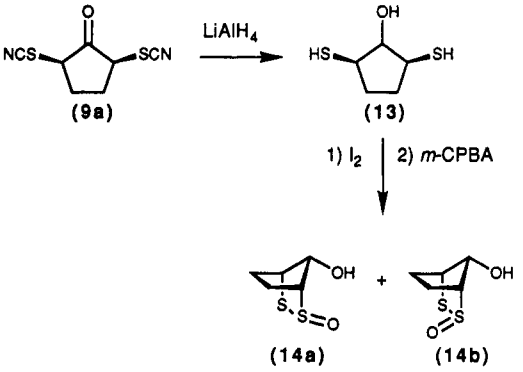


Figure 1. ORTEP plot of **9a**.

The synthesis of 2,7-dithiocyanatocycloheptanone (**10**) was performed by the addition of 2 equiv of potassium thiocyanate to the crude mixture of **8a** and **8b** using acetone as the solvent (Scheme II). Although refluxing temperatures were required to force the reaction to completion, a quantitative yield of a mixture of the cis and trans isomers **10a** and **10b** was obtained. The ratio of **10a**:**10b** remained the same as it was in the original mixture of **8a** and **8b**. Reduction of **10a** and **10b** was carried out using lithium aluminum hydride to give dithiol alcohol **11** which was immediately oxidized to *syn*-2,3-dithiabicyclo-[4.2.1]nonan-9-ol (**12**) using iodine under high dilution conditions (Scheme II). The yield of **12** based on the amount of *cis*-2,7-dithiocyanatocycloheptanone (**10b**) present in the original mixture ranged from 70 to 80%. The major side product in the oxidation step was a polymer formed by inter- rather than intramolecular oxidation.[6] The extent of this side reaction was less in the [4.2.1] bicyclic case than in the [3.2.1] system where the best yields were in the range of 50%.[6,7]

The synthesis of a [2.2.1] bridged bicyclic system was not as straightforward. When the procedures described above were repeated on *cis*-2,5-dithiocyanatocyclo-

Scheme III



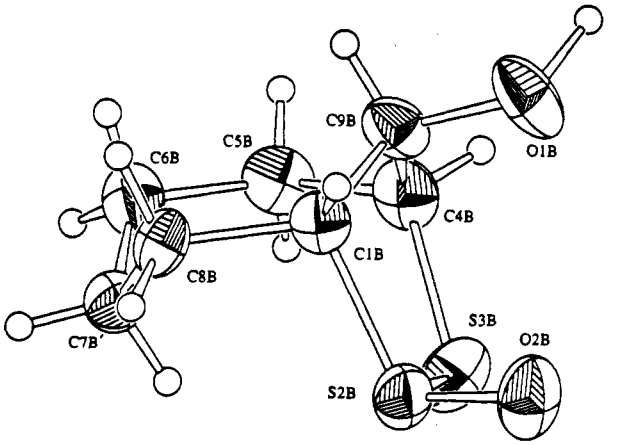


Figure 2. ORTEP plot of **17**.

pentanone (**9a**) all attempts at isolating a bicyclic disulfide compound led to polymerization.[12] In order to obtain the [2.2.1] bicyclic disulfide ring system using the above methodology, we thought that oxidation to a thiosulfinate ester might provide the stability required for isolation procedures. It is known that cyclic disulfides are readily oxidized to their corresponding thiosulfinate esters. This has been explained in terms of removing the destabilizing effect of the interaction between the two adjacent lone pairs of electrons on the sulfur atoms by replacement of one lone pair with an oxygen atom.[7,13] The lone pairs of electrons on the two sulfur atoms in a bridged bicyclic disulfide are forced to be parallel due to the dihedral angle of ca. 0° about the S–S bond. Any means for removing some of the interaction between these lone pairs is expected to add to the stability of the resulting molecule.

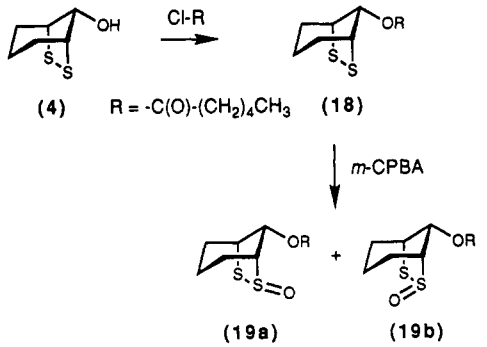
Reduction of **9a** was performed using lithium aluminum hydride, and the resulting dithiol alcohol **13** was immediately oxidized under high dilution conditions using iodine (Scheme III). Polymerization usually occurred when the solution was concentrated; thus, the solvent (ether) was removed under reduced pressure at room temperature until about 100 mL remained. Methylene chloride was then added and the remaining ether carefully removed. This solution was then cooled to 0 °C, and a solution containing 1 equiv of *m*-CPBA added. The resulting thiosulfinate ester **14** (Scheme III) was stable enough to be purified by column chromatography on silica gel and fully characterized. It was isolated as a mixture of exo and endo isomers (**14a** and **14b**) in a ratio of 4:1 (12%). The idea that the destabilization caused by the adjacent lone pairs

(11) This proposal was confirmed by the addition of KSCN to **9a** under the same conditions used for the initial substitution reaction. This resulted in isomerization of **9a** and the isolation of a mixture containing **9a** and **9b** in a ratio of 1:2.4.

(12) Polymerization was also a problem in the synthesis of 1,2-dithiolane via iodine oxidation of 1,3-propane dithiol (Gleason, J. G.; Ph. D. Thesis, McGill University, Montréal, Québec, Canada).

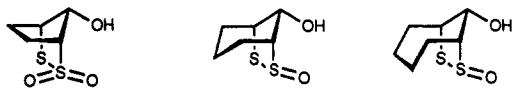
(13) Frisell, C.; Bergson, G. *Ark. Kemi* **1966**, *25*, 263.

Scheme IV



is removed by replacement with oxygen seems to be valid. This proposal was also supporting by oxidizing **14** to the corresponding thiosulfonate ester **15**. This compound was very stable and could be left at room temperature in ambient light for several weeks without any sign of decomposition. Thiosulfinate **14** had to be kept in the freezer to prevent decomposition.[14]

Oxidation of the [3.2.1] and [4.2.1] bridged bicyclic disulfides, **4** and **12**, to their corresponding thiosulfinate esters, **16** and **17**, using *m*-CPBA was also performed.[14]



This reaction was found to proceed in excellent yield (>90%) and gave the exo diastereomer as the only isolated product in both examples. The orientation of the sulfinyl oxygen in **17** was confirmed by X-ray crystallography; the ORTEP[10] drawing is shown in Figure 2. This molecule had a large amount of packing disorder in the region from C5–C8 that was only partially resolved by the structure refinement program (see Experimental Section). The important S–S bond and bridgehead regions were all well-resolved and thus provided an accurate representation of the positioning of these atoms.

The orientation of the sulfinyl oxygen in **16** was confirmed by derivation with *p*-nitrobenzoyl chloride and comparison of the spectral data with that of **6**.[7] The isolation of the exo isomer as the sole product suggested that the endo face is blocked by the ring hydrogens preventing attack by the oxidizing agent from this direction. The smaller ring in the [2.2.1] bicyclic structure did not hinder attack from the endo direction as much as the [3.2.1] and [4.2.1] rings, thus providing a small amount of the endo isomer **14b**. Esterification of [3.2.1] bicyclic **4** with *n*-hexanoyl chloride provided **18** as a yellow oil (Scheme IV). *m*-CPBA oxidation of **18** gave the only example in the [3.2.1] and [4.2.1] bicyclics where a small amount of the endo isomer **19b** was produced directly (Scheme IV). The long chain on the exo face apparently reduces the preference for oxidation to occur only from this direction.[15]

Access to the endo isomers was obtained by heating the thiosulfinates either neat or in solution. Refluxing a solution of [3.2.1] bicyclic **16** in benzene (80 °C) resulted in isomerization and produced a mixture containing *exo*-**16** and *endo*-**16** in a ratio of 1.2:1. A small amount of thiosulfonate **20** was also detected (by ^{1}H NMR).[16] Isomerization of [4.2.1] thiosulfinate **17** did not proceed as readily as **16**. Refluxing in toluene (110 °C) produced a mixture containing *exo*-**17** and *endo*-**17** in a ratio of 6:1. Once again, a small amount of the corresponding thiosulfonate (**21**) was detected.

Conclusion

A versatile and relatively simple synthesis of an unusual and important class of compounds has been refined and generalized. The starting materials are readily available and the yields are reasonable enough to allow production of these compounds on a moderate scale. Derivatization at the hydroxyl functionality plus oxidation at the sulfur atoms allows for further modifications for probing the chemical reactivity of these novel structures. Investigations of this type are being examined in our laboratory.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. X-ray crystallography was performed by Dr. James Britten at the Department of Chemistry, McGill University.

***cis*-2,5-Dibromocyclopentanone (7).** A solution of cyclopentanone (9.51 g, 0.113 mol) was dissolved in glacial acetic acid (50 mL), stirred, and cooled to 3 °C as Br_2 (36.1 g, 0.226 mol) was added (dropwise). N_2 was blown over the reaction and bubbled through a NaOH solution to neutralize the HBr formed. The reaction mixture was then poured onto ice and neutralized to pH 5. The product was extracted into $CHCl_3$ and the organic layer washed several times with H_2O and 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated to a yellow oil. This oil was redissolved in *n*-pentane/$CHCl_3$ and allowed to crystallize at 0 °C to give fine, off-white crystals (4.9 g, 18%) of **7**: mp 64–65.5 °C (lit.[8] mp 67 °C); R_f ($CHCl_3$) 0.50; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.47 (m, 2× H3 and H4, 4 H) and 4.26 (m, H2 and H5, 2 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 31.4 (C3 and C4), 43.4 (C2 and C5) and 204.6 (C1) ppm; IR ($CHCl_3$) 1759 (C=O) cm^{-1}; MS [EI, direct inlet, 30 °C] *m/z* (relative intensity, assignment) 244 (21.9, $C_5H_6{}^{81}Br_2O^{\bullet+}$), 242 (47.8, $C_5H_6{}^{79}Br{}^{81}BrO^{\bullet+}$), 240 (28.9, $C_5H_6{}^{79}Br_2O^{\bullet+}$).

***cis*- and *trans*-2,5-Dithiocyanatocyclopentanone (9a and 9b).** A solution of **7** (1.32 g, 5.46 mmol) in dry acetone (75 mL) under N_2 was stirred at rt as KSCN (1.06 g, 10.9 mmol) in dry acetone (75 mL) was added all at once. The solution was allowed to stir for 1 h, and then the white precipitate (KBr) was filtered and the acetone removed under reduced pressure. The resulting yellow solid was partitioned between H_2O and $CHCl_3$ and the organic layer dried over $MgSO_4$ and evaporated to give a yellow solid (0.90 g, 90%). Recrystallization from hexanes/CH_2Cl_2 provided off-white crystals shown to contain **9a** and **9b** (0.80 g, 80%) in ~4:1 ratio (^{1}H NMR), respectively. A second, slower recrystallization from pentane/$CHCl_3$ (10:1) gave yellow needles which contained only one isomer (**9a**), confirmed to be in the cis configuration by X-ray crystallography: mp 92–93 °C; R_f ($CHCl_3$) 0.10. **9a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30–2.77 (m, 2× H3 and H4, 4 H) and 3.94–4.02 (m, H2 and H5, 2 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.1 (C3 and C4), 48.5 (C2 and C5), 109.00 (SCN) and 201.9 (C1) ppm; IR (KBr) 1761 (C=O) and 2154 (SCN) cm^{-1}; MS [EI, direct inlet, 120 °C] *m/z* (relative intensity, assignment) 198 (6.9, $M^{\bullet+}$), 140 (31.6, $M^{\bullet+}$ – $^{\bullet}$SCN), 139 (29.9, $M^{\bullet+}$ – HSCN). **9b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05–2.95 (m, 2× H3 and H4,

(14) Details on some of the preceding oxidation chemistry has recently been carried out; See: Folkins, P. L.; Harpp, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 8998.

(15) It is of interest to note that the hindered nature of the endo sulfinyl oxygen of **19b** permits a more rapid elution (as compared to **19a**) on silica gel. This is in accord with the observations of Johnson; see: Johnson, C. R.; Diefenbach, H.; Keiser, J. E.; Sharp, J. C. *Tetrahedron* **1969**, *25*, 5649.

(16) Thiosulfinates are known to disproportionate into thiosulfonate and disulfide (cf. Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921, 3929). Any disulfide formed in this experiment likely polymerized due to the high temperatures used.

4 H) and 3.68–3.79 (m, H2 and H5, 2 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.4 (C3 and C4), 48.9 (C2 and C5), 108.96 (SCN) and 202.0 (C1) ppm; IR (KBr) 1750 (C=O) and 2154 (SCN) cm^{-1}; MS same as **9a**.

Isomerization of *cis*-2,5-Dithiocyanatocyclopentanone (9a). A sample of **9a** (0.50 g) in 30 mL dry acetone and a solution of 201 mg (1 equiv) of KSCN in acetone (15 mL) was stirred under N_2 for 4 h. The solvent was the removed under reduced pressure, and the crude material was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over $MgSO_4$ and evaporated to dryness to yield a yellow oil. This material was dried under vacuum for 24 h (quantitative recovery), and a ^1H NMR spectrum revealed that the ratio of cis/trans (**9a:9b**) was 1:2.4.

***cis*-2,5-Dimercaptocyclopentanol (13).** A slurry of $LiAlH_4$ (0.56 g, 14.8 mmol) in THF (50 mL) was stirred and cooled at 0 °C under N_2 as a solution of **9a** (0.50 g, 2.53 mmol) in 25 mL of THF was added dropwise. After the addition was complete, the solution was allowed to warm to rt and stirred overnight. The excess $LiAlH_4$ was then quenched with EtOAc (20 mL) and allowed to stir for another 4 h. TLC ($CHCl_3$) indicated that all the starting material had been consumed. The characteristic foul smell of a dithiol was also noted. This reaction mixture was used without further workup for the next oxidation step.

Preparation of *syn*-2,3-Dithiabicyclo[2.2.1]heptan-7-ol *S*-Oxides (14a and 14b). The quenched reaction mixture containing **13** (0.415 g, 2.53 mmol) was added simultaneously with a solution of I_2 (0.642 g, 2.53 mmol) in anhydrous ether (30 mL) to 2 L of refluxing anhydrous ether under N_2. After the addition was complete, the solution was cooled to rt and a 2.5% aqueous NaOAc/HOAc buffer solution (200 mL) was added and the ether layer separated, washed with H_2O (4×), and dried over $CaCl_2$. The solvent was evaporated to a volume of ~100 mL under reduced pressure at rt.[17] Freshly distilled CH_2Cl_2 (20 mL) was added, and the remaining ether was carefully removed under reduced pressure at rt. This solution was then cooled to 0 °C, and a solution of *m*-CPBA (0.55 g, 2.53 mmol) was added dropwise. The product was purified by flash chromatography using 9:1 CH_2Cl_2/EtOAc as the eluent, collecting 10-mL fractions. The two isomers (0.0516 g, 12%) of **14** were found in fractions 20–45 in a ratio of 4:1 for **14a:14b**: R_f (9:1 CH_2Cl_2/EtOAc) 0.20. **14a**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.95–2.0 (m, 2× H5 and H6, 4 H), 3.86 (dd J_1 = 5.94 Hz, J_2 = 2.45 Hz, H4, 1 H), 4.21 (s, H1, 1 H), 4.61 (d, J_{OH-H7} = 10.0 Hz, O*H*, 1 H) and 5.05 (d, J_{H7-OH} = 10.0 Hz, H7, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.2 (C5), 27.8 (C6), 57.2 (C4), 64.6 (C1) and 86.6 (C7) ppm; IR ($CDCl_3$) 882, 900 and 929 cm^{-1}; HRMS [EI, direct inlet, 70 °C] *m/z* for $M^{\bullet+}$ ion calcd for $C_5H_8O_2S_2$ 163.996 57, found 163.996 62. **14**:[18] ^1H NMR (200 MHz, $CDCl_3$) δ 1.8–2.3 (m, 2× H5 and H6, 4 H), 2.7–2.9 (m, H4, 1 H), 3.8 (dd, H1, 1 H) and (4.92, t, H7, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 60.5 (C4), 66.8 (C1) and 83.5 (C7) ppm; MS same as **14a**.

***syn*-2,3-Dithiabicyclo[2.2.1]heptan-7-ol *S*,*S*-dioxide (15):** mp 131–132 °C; R_f (9:1 CH_2Cl_2/EtOAc) 0.19; ^1H NMR (200 MHz, $CDCl_3$) δ 2.14–2.29 (m, 3 H), 2.50–2.57 (m, 1 H), 3.56–3.58 (m, H4, 1 H), 3.68 (d, J_{OH-H7} = 11.5 Hz, O*H*, 1 H), 4.20 (m, H1, 1 H) and 4.56 (dm, J_{H7-OH} = 11.5 Hz, H7, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.5 (C5), 28.3 (C6), 29.7 (C4), 61.9 (C1), and 67.2 (C7) ppm; IR ($CDCl_3$) 881, 924, and 1137 (SO_2) cm^{-1}; HRMS [EI, direct inlet, 240 °C] *m/z* for $M^{\bullet+}$ ion calcd for $C_5H_8O_3S_2$ 179.991 49, found 179.991 48.

***syn*-2,3-Dithiabicyclo[3.2.1]octan-8-ol *S*-Oxide (16).** A solution of **4** (0.219 g, 1.35 mmol) in $CHCl_3$ (10 mL) and this solution was stirred and cooled at 0 °C as *m*-CPBA (0.291 g, 1.35 mmol) was slowly added during 15 min. The resulting solution was then stirred for a further 30 min at rt. The product was purified directly by column chromatography using 1:1 hexanes/EtOAc as the eluent, collecting 10-mL fractions. Compound **20** was found in fractions 38–80 and was isolated as a white solid (0.211 g, 88%). NMR spectroscopy indicated the presence of only one isomer. Derivatization of this compound with *p*-nitrobenzoyl chloride and comparison of the spectral data with those of compound **6** indicated that the sulfinyl oxygen in **16** was in the exo configuration: mp 181–182 °C, sealed tube; R_f (1:1 hexanes/EtOAc) 0.10; ^1H NMR (200 MHz, $CDCl_3$) δ 1.2–1.7 (m, 2× H5 and H6, 4 H), 2.01–2.14 (m, 2× H7, 2 H), 4.07 (br s, H4, 1 H), 4.14 (br s, O*H*, 1 H), 4.68 (br s, H8, 1 H) and 4.75 (br s, H1, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.0 (C6), 24.7 (C5), 29.9 (C7), 64.2 (C4), 77.2 (C1) and 84.7 (C8) ppm; IR ($CDCl_3$) 1038, 1061 (S=O) and 3450 (OH) cm^{-1}; HRMS [EI, direct inlet, 120 °C] *m/z* for $M^{\bullet+}$ ion calcd for $C_6H_{10}O_2S_2$ 178.012 223, found 178.012 27.

***syn*-2,3-Dithiabicyclo[3.2.1]octan-8-ol *S*,*S*-dioxide (20):** white solid; mp 190 °C (sublimation); R_f (3:1 CH_2Cl_2/EtOAc) 0.39; ^1H NMR (200 MHz, $CDCl_3$) δ 1.6–2.5 (m, 2× H5, H6 and H7, 6 H), 3.43 (d, J_{OH-H8} = 10.5 Hz, O*H*, 1 H), 3.54 (br s, H4, 1 H), 4.30 (dm, J_{H8-OH} = 10.5 Hz, H8, 1 H) and 4.55 (br s, H1, 2 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.8 (C6), 26.5 (C5), 31.4 (C7) 62.9 (C4), 69.7 (C1) and 75.5 (C8) ppm; IR ($CDCl_3$) 753, 909, 1134 (SO_2), 1283 and 1315 (SO_2) cm^{-1}; HRMS [EI, direct inlet, 70 °C] *m/z* for $M^{\bullet+}$ ion calcd for $C_6H_{10}O_3S_2$ 194.0071, found 194.0074.

***syn*-2,3-Dithia-8-(*n*-hexanoyloxy)bicyclo[3.2.1]octane (18).** Compound **4** (0.178 g, 1.10 mmol) in freshly distilled pyridine (2 mL) was cooled to 0 °C under N_2. To this was added *n*-hexanoyl chloride (0.150 g, 1.10 mmol) via syringe. This was allowed to stir overnight at rt. Ether (5 mL) was then added, and the resulting solution was washed several times with 5% $NaHCO_3$ and H_2O, dried over $MgSO_4$, and evaporated to dryness. The resulting oil was pumped under high vacuum to remove residual pyridine and unreacted disulfide. This was then subjected to flash column chromatography for further purification using chloroform as the eluent. The first fraction was collected to give a yellow oil (0.204 g, 84%): R_f ($CHCl_3$) 0.53; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, *J* = 5 Hz, 3× H6′, 3 H), 1.26–1.34 (m, 2× H3′, H4′, and H5′ and 2× H5, H6, and H7, 12 H), 2.36 (t, $J_{H2'-H3'}$ = 7.4 Hz, 2× H2′, 2 H), 3.97 (br s, H1 and H4, 2 H) and 5.39 (t, $J_{H8-H1} = J_{H8-H4}$ = 1.7 Hz, H8, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.8 (C6′), 16.5 (C6) 22.2 (C5′), 24.5 (C4′), 31.1 (C3′), 33.3 (C5 and C7), 34.3 (C2′), 54.4 (C1 and C4), 82.2 (C8) and 173.3 (C=O) ppm; IR (neat) 1730 (C=O) cm^{-1}; MS [EI, direct inlet, 40 °C] *m/z* (relative intensity, assignment) 260 (34, $M^{\bullet+}$), 28 (100, $CO_2^{\bullet+}$ or $C_2H_4^{\bullet+}$).

***syn*-2,3-Dithia-8-(*n*-hexanoyloxy)bicyclo[3.2.1]octane *S*-Oxides (19a/19b).** To a solution of 2,3-dithia-8-(*n*-hexanoyloxy)bicyclo[3.2.1]octane (**18**) (0.0248 g, 0.254 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (0.027 g, 0.254 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After the addition was complete, the solution was allowed to warm to rt and was stirred for a further 30 min. The product was purified by column chromatography using 3:1 hexanes/EtOAc as the eluent, collecting 10-mL fractions. Fractions 7–12 were shown to contain the endo isomer **19b**, and fractions 15–27 contained the exo isomer **19a**. The overall yield of *S*-oxide was 90%. Exo *S*-oxide **19a** (0.028 g, 79%): R_f (3:1 hexanes/EtOAc) = 0.13; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, $J_{H6'-H5'}$ = 6.5 Hz, 3× H6′, 3 H), 1.2–2.2 (m, 2× H3′, H4′, and H5′ and 2× H5, H6, and H7, 12 H), 2.35 (t, $J_{H2'-H3'}$ = 7.6 Hz, 2× H2′, 2 H), 4.1 (br s, H4, 1 H), 4.6 (br s, H1, 1 H) and 5.5 (t, $J_{H8'-H1} = J_{H8'-H4}$ = 1.5 Hz, H8, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.9 (C6′), 17.5 (C6), 22.2 (C5′), 24.2 (C4′), 24.8 (C3′) 30.2 (C5), 31.2 (C2′), 34.1 (C7), 59.4 (C4), 75.3 (C1), 83.4 (C8) and 173.5 (C=O) ppm; IR (neat) 1084 (S=O) and 1743 (C=O) cm^{-1}; HRMS [EI, direct inlet, 40 °C] *m/z* for $M^{\bullet+}$ ion calcd for $C_{12}H_{20}O_3S_2$ 276.085 39, found 276.085 51. Endo *S*-oxide **19b** (0.0028 g, 11%): R_f (3:1 hexanes/EtOAc) = 0.21; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, $J_{H6'-H5'}$ = 6.5 Hz, 3× H6′, 3 H), 1.2–2.2 (m, 2× H3′, H4′, and H5′ and 2× H5, H6, and H7, 12 H), 2.35 (t, $J_{H2'-H3'}$ = 7.6 Hz, 2× H2′, 2 H), 4.04 (br s, H4, 1 H), 4.60 (br s, H1, 1 H) and 5.50 (t, $J_{H8-H1} = J_{H8-H4}$ = 1.5 Hz, H8, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.8 (C6′), 16.7 (C6), 22.2 (C5′), 22.6 (C4′), 24.4 (C3′), 30.7 (C5), 31.1 (C2′), 34.1 (C7), 58.1 (C4), 67.2 (C1), 82.1 (C8), and 172.7 (C=O) ppm; IR (neat) 1088 (S=O) and 1734 (C=O) cm^{-1}; HRMS [EI, direct inlet, 40 °C] *m/z* for $M^{\bullet+}$ ion calcd for $C_{12}H_{20}O_3S_2$ 276.085 39, found 276.085 51.

***trans*- and *cis*-2,7-Dibromocycloheptanone (8a and 8b).** Cycloheptanone (4.75 g, 0.0424 mol) was dissolved in glacial acetic acid (150 mL), along with two drops of HBr (50%) to initiate the

(17) Removal of all of the ether under vacuum at 0 °C gave a yellow oil which was shown by ^1H NMR spectroscopy to contain a species that may have been the disulfide. However, all attempts to purify this mixture resulted in polymerization.

(18) NMR data were difficult to resolve from the peaks of **14a**. Only positions for H1, H4, and H7 along with C1, C4, and C7 could be assigned with certainty.

reaction, and bromine (13.55 g, 0.0848 mol) was added (dropwise) at 10 °C. The solution was then allowed to warm to rt and stirred for a further 2 h, at which time it was neutralized to pH 6 with $NaHCO_3$. The product was then extracted into ether and the ether layer washed with H_2O (3×) and 5% $NaHCO_3$ (3×) and then dried over $MgSO_4$ and evaporated under reduced pressure to a yellow oil. This oil was redissolved in petroleum ether/EtOAc (1:1) and allowed to crystallize at −15 °C for 24 h. The white crystals formed were collected to yield 5.32 g (46%) of a crude mixture containing the trans and cis isomers of **8** in a ratio of 2:1, respectively. Recrystallization from petroleum ether/EtOAc (1:1) resulted in the isolation of the trans isomer **8a** only: mp 70–71 °C (lit.[8] mp 70 °C); R_f (CH_2Cl_2) 0.68; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40–2.55 (m, 2× H3–H6 for **8a** and **8b**, 16 H), 4.61 (dd, J_1 = 8.52 Hz, J_2 = 4.29 Hz, H2 and H7 for **8b**, 2 H) and 4.71 (dd, J_1 = 10.34 Hz, J_2 = 4.86 Hz, H2 and H7 for **8a**, 2 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 26.4 (C4 and C5, **8b**), 27.0 (C4 and C5, **8a**), 33.8 (C3 and C6, **8b**), 35.0 (C3 and C6, **8a**), 49.7 (C2 and C7, **8a**), 51.7 (C2 and C7, **8b**), and 198.5 (C1, **8a**) ppm; IR ($CHCl_3$) 1728 (C=O, **8a**) and 1701 (C=O, **8b**) cm^{-1}. The crude mixture containing both isomers was used for the next step of the reaction sequence.

***cis*- and *trans*-2,7-Dithiocyanatocycloheptanone (10a and 10b).** 2,7-Dibromocycloheptanone (**8a** and **8b**) (2.09 g, 7.73 mmol) was dissolved in dry acetone (100 mL), and a solution of KSCN (1.520 g, 15.4 mmol) in dry acetone (50 mL) was added all at once under an atmosphere of nitrogen. The solution was refluxed for 4 h and cooled and the precipitated KBr filtered. The acetone was evaporated under reduced pressure and the resulting solid partitioned between H_2O and $CHCl_3$. The organic layer was washed, dried over $MgSO_4$, and evaporated to a yellow oil (1.38 g, 80%) containing a 2:1 mixture of two isomers (**10a**:**10b**): R_f (CH_2Cl_2) 0.20; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42–2.60 (m, 2× H3–H6 for **10a** and **10b**, 16 H), 4.21 (dd, J_1 = 11.97 Hz, J_2 = 4.36 Hz, H2 and H7 for **10b**, 2 H) and 4.59 (dd, J_1 = 7.68 Hz, J_2 4.48 Hz, H2 and H7 for **10a**, 2 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 25.5 (C4 and C5, **10a**), 27.7 (C4 and C5, **10b**), 31.9 (C3 and C6, **10a**), 32.0 (C3 and C6, **10b**), 54.7 (C2 and C7, **10b**), 57.6 (C2 and C7, **10a**), 110.0 (SCN, **10b**), 111.1 (SCN, **10a**), 200.2 (C1, **10b**) and 201.2 (C1, **10a**) ppm; IR ($CHCl_3$) 1712 (C=O) and 2159 (SCN) cm^{-1}; MS [EI, direct inlet, 30 °C] m/z (relative intensity, assignment) 226 (11.3, $M^{\bullet+}$).

***syn*-2,3-Dithiabicyclo[4.2.1]nonan-9-ol (12).** 2,7-Dithiocyanatocycloheptanone (**10a** and **10b**) (1.30 g, 5.78 mmol) was dissolved in dry THF (20 mL) and added to a slurry of $LiAlH_4$ in dry THF (100 mL) at 0 °C under an atmosphere of nitrogen. The reaction mixture was then allowed to warm to rt and stirred overnight. The unreacted $LiAlH_4$ was quenched with EtOAc (50 mL) at 0 °C, and the solution was once again stirred overnight. No further workup procedures were carried out, and the mixture was used directly for the proceeding oxidation step. The quenched reaction mixture containing 2,7-dimercaptocycloheptanol (**11**) was added simultaneously with a solution of I_2 (1.46 g, 5.8 mmol) in anhydrous ether (50 mL) to 2 L of refluxing anhydrous ether under an atmosphere of nitrogen. The addition of iodine normally lagged behind that of the dithiol alcohol and was continued until the yellow color of iodine persisted, at which time the mixture was cooled to rt and a 5% aqueous HOAc/NaOAc buffer solution (200 mL) was added. The organic layer was separated, washed with H_2O (4 × 200 mL), dried over $MgSO_4$ and evaporated to dryness to give a yellow solid. The product was purified via flash column chromatography using $CHCl_3$ as the eluent. Fractions 6–11 were combined to yield (after recrystallization from hexane/CH_2Cl_2) 0.212 g (63%)[19] of **12** as yellow crystals: mp 120–122 °C (sealed tube); R_f ($CHCl_3$) 0.20; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35–1.50 (m, 2 H), 1.68–1.92 (m, 4 H), 1.93–2.09 (m, 2 H), 2.76 (d, J_{OH-H9} = 11.5 Hz, O*H*, 1 H), 3.88–3.92 (m, H1 and H4, 2 H) and 4.55 (d, J_{H9-OH} = 11.6 Hz, H9, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.0 (C6 and C7), 33.4 (C5 and C8), 61.93 (C1 and C4), and 82.31 (C9) ppm; IR (KBr) 939, 1049 and 3300 (OH) cm^{-1}; UV ($CHCl_3$) μ_{max} 357 nm (ε = 131); MS [EI, direct inlet, 30 °C] m/z (relative intensity, assignment) 176 (95, $M^{\bullet+}$), 112 (100, $M^{\bullet+} - S_2$). Anal. Calcd for $C_7H_{12}OS_2$: C, 47.69; H, 6.86; S, 36.37. Found: C, 47.51; H, 6.84; S, 36.02.

***syn*-2,3-Dithiabicyclo[4.2.1]nonan-9-ol *S*-Oxide (17).** 2,3-Dithiabicyclo[4.2.1]nonan-9-ol (**12**) (30.9 mg, 0.175 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and cooled to 0 °C under an atmosphere of nitrogen. To this was added (dropwise) a solution of *m*-CPBA (30.2 mg, 0.175 mmol) in dry CH_2Cl_2 and the solution allowed to warm and stirred for 1 h. An aqueous solution of $NaHSO_3$ (25 mg in 25 mL) was added, and the organic layer was separated, washed with 5% $NaHCO_3$ (3×) and H_2O, dried over $MgSO_4$, and evaporated to dryness under reduced pressure to give 31.5 mg (90%) of **17** as a white solid. Recrystallization from ethanol gave clear prisms of **17**, and the structure was confirmed by X-ray crystallography: mp 130–131 °C; R_f ($CHCl_3$) 0.10; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24–1.40 (m, 2 H), 1.50–1.99 (m, 4 H), 2.15–2.30 (m, 2 H), 4.38 (dd, J_1 = 10.75 Hz, and J_2 = 2.50 Hz, H4, 1 H), 4.85 (br s, O*H*, 1 H), 5.02 (t, J = 3.49 Hz, H9, 1 H) and 5.07 (br s, H1, 1 H); ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 23.3 (C6), 23.7 (C7), 24.2 (C5), 30.9 (C8), 68.1 (C4), 78.0 (C1), and 86.8 (C9) ppm; IR ($CDCl_3$) 1056 (S=O) and 3450 (OH) cm^{-1}. Anal. Calcd for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29. Found: C, 43.55; H, 6.24.

***syn*-2,3-Dithiabicyclo[4.2.1]nonan-9-ol *S*,*S*-dioxide (21):** white semisolid; R_f (4:1 $CHCl_3$/EtOAc) 0.10; ^1H NMR (200 MHz, $CDCl_3$) δ 1.7–2.45 (m, 2× H5, H6, H7, and H8, 8 H), 3.60 (d, J_{OH-H9} = 11 Hz, O*H*, 1 H), 3.75 (d, J = 9 Hz, H4, 1 H), 4.55 (d, J_{H9-OH} = 11 Hz, H9, 1 H), and 4.62 (br s, H1, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 22.9 (C6), 23.9 (C5), 24.7 (C7), 33.9 (C8), 64.3 (C4), 74.2 (C1), and 75.1 (C9) ppm; IR ($CDCl_3$) 909, 1127 (SO_2) and 1292 (SO_2) cm^{-1}; HRMS [EI, direct inlet, 80 °C] m/z for $M^{\bullet+}$ ion calcd for $C_7H_{12}O_3S_2$ 208.022 79, found 208.022 85.

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Supplementary Material Available: X-ray data for compounds **9a** and **17**, 200-MHz ^1H spectra for compounds **9a** and **20**, and 300-MHz ^{13}C spectra for compounds **14a**, **15**, **16**, **18**, **19a**, **19b**, **10a**, and **21** (57 pages). Ordering information is given on any current masthead page.

(19) Based on the amount of **10a** present in the starting material.