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Single step first synthesis of a 3,6-dihydro-1,2-dithiin from its parent 1,4-dithioketone via a stereospecific rearrangement

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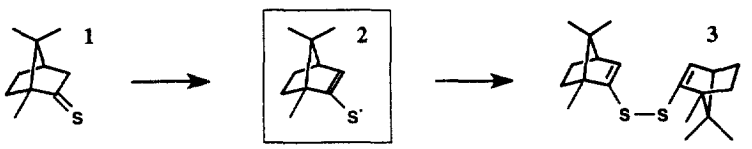
Abstract: The one step conversion of bis-thiocamphor into its corresponding 3,6-dihydro-1,2-dithiin was performed via a stereospecific rearrangement. Proof of the reaction stereospecificity was established by full characterization of the final product. Some speculative mechanistic avenues are exposed. © 1997 Elsevier Science Ltd

New synthetic methods directed towards the disulfide linkage are of great importance, in order to widen the potential access to biologically active cyclic disulfides.[1]

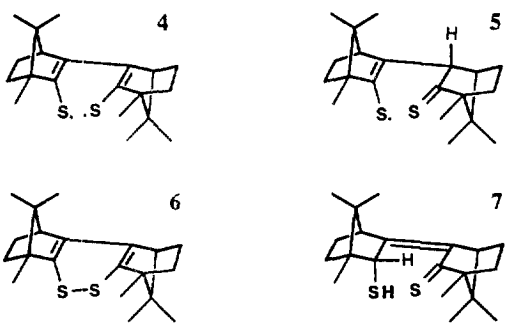
Campbell *et al.*,[2] reporting the preparation of bis-thiocamphor (**8**) from thiocamphor (**1**), proposed a mechanism involving the intermolecular coupling of an *enethiyl radical* species (**2**) to form disulfide (**3**) (Scheme 1).



Scheme 1.

Considering enolizable thioketones as starting material, such a radical pathway would be a mild synthetic tool, offering an interesting and complementary alternative to the existing methods,[3] principally using basic deprotonation and oxidative conditions.

Hence, our recent efforts were oriented towards the exploration of the potential involvement of intermediates (**4**) and (**5**) respectively in the preparation of compounds (**6**)[4] and (**7**).[5]



With the same purpose, we studied the action of iodine on bis-thiocamphor (**8**). This allows us now to report the preparation of disulfide (**9**) from (**8**) with a 52% isolated yield, in only one synthetic step (Scheme 2). This reaction necessitated both light and heat activation at the same time to proceed successfully.[6] Although, the use of half an equivalent of iodine gave good results, the best yields were obtained when a full equivalent was used instead (i.e. molecular ratio (**8**)/I_2: 1/1). On the other hand,

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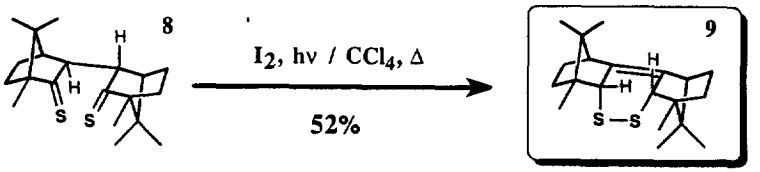
the reaction not being an oxidation was also expected to take place with a catalytic amount of iodine; however with these conditions (**9**) was not produced.



Scheme 2.

From a stereochemical standpoint, this rearrangement corresponds to a migration of two hydrogen atoms (beside the creation of a disulfide bond), along with the disappearance of two chiral centers and the creation of two new ones. The configuration of the stereocenters was certainly influenced by the geometric and energetic preferences for the resulting central heterocycle to be *cis*-fused rather than *trans*-fused with the two bicyclic camphor moieties.

This argument is supported (see Table 1) by values of ΔHf and dihedral angles (intra-cyclic C=C) for the three possible stereoisomeric disulfides, as a result of molecular modeling calculations.[7] Thus, it becomes even clearer that the endo/exo isomer would be thermodynamically favored, and would suffer less geometric distortion.

The configuration of (**9**) was unequivocally established through the absence of symmetry in the NMR spectra (PMR: 2 allylic protons (endo/exo) and 6 methyl groups; CMR: 20 signals), and confirmed by the X-ray crystallographic data.[8] This analysis notably revealed a quite shorter disulfide bond than usual (2.019 Å) with a CSSC dihedral angle of 44.9°, which might have biological activity consequences,[1] as abnormal S–S bond length and/or CSSC torsion angle values enhance the S–S bond reactivity.[8,9]

The complete mechanistic elucidation still remains elusive at the present time. At first, a purely radical mechanism could have been invoked. For example, the enethiyl radical (**5**)[2,5] could undergo a 6-endo-trig-like S-addition on the second thiono group to establish the key disulfide bond (Scheme 3). However, a 1,2-hydrogen shift would be then required to complete the reaction. This feature is rather unlikely, the literature suggesting such a possibility only in the cases of either spectroscopic experiments[10] or theoretical studies.[11] More likely is a pathway involving a sulfenyl iodide like (**10**) which could be formed either from intermediates (**5**) or (**11**). Then, an intramolecular nucleophilic displacement of the iodide by the thione would afford the disulfide bond (Scheme 3).

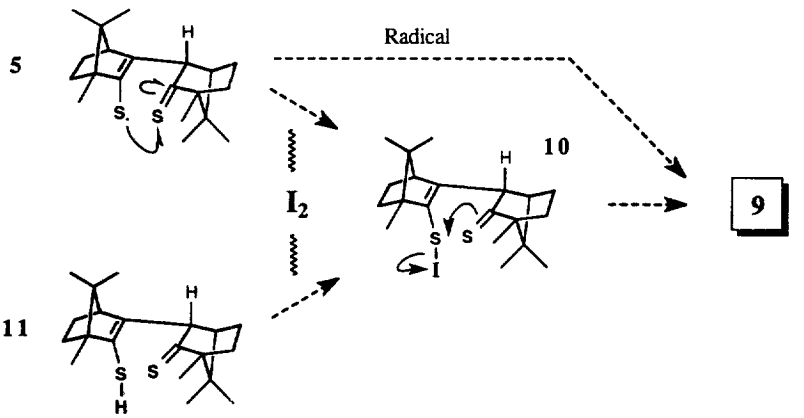
At this point, it is noteworthy that a 12% mixture consisting of dithiin (**6**), thiophen (**12**) and trithiepin (**13**) was also isolated (Scheme 4). The already reported disproportionation of (**6**) explains the formation of compounds (**12**) and (**13**),[3a,4] which was favored by the use of both UV and heat.

To determine whether dithiin (**6**) was only a byproduct or had to be considered as a key intermediate en route to disulfide (**9**), freshly prepared (**6**)[3a,4] was submitted to the same reaction conditions (I_2, HI, in refluxing CCl_4, under long UV). The fact that (**9**) was not produced under these circumstances, and that compounds (**12**) and (**13**) were the only significant products formed, led us to conclude that (**6**) was actually only a byproduct.

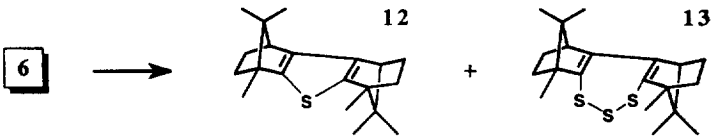
Therefore, we report a new rearrangement which constitutes a useful tool from both synthetic and stereoisomeric standpoints.[12]

Table 1.

Disulfide	ΔHf (kcal/mole)	C-C=C-C (°)
(9) endo/exo	**20.7**	**2.7**
endo/endo	25.8	17.6
exo/exo	27.0	16.4

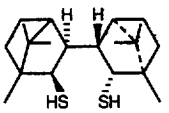


Scheme 3.



Scheme 4.

Moreover, disulfide (**9**) may be considered as a significant contribution to the recent efforts aimed at synthesizing and studying a new class of chiral auxiliaries (1,4-dithiols), such as 2,2′-dimercapto-1,1′-binaphtyl,[13] and compounds (**16**) and (**17**).[14] In that respect, the impact of the geometrical restriction imposed by the tetrasubstituted double bond in (**18**) [easily attainable from (**9**)] would be worth future studies.



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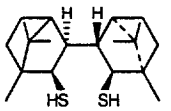

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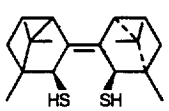

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Experimental section

Preparation of 2-(endo),2′-(exo)-epidithio-3,3′-bibornanylidene (9)

To a refluxing solution of bisthiocamphor (**8**) (100 mg, 0.3 mmol) in carbon tetrachloride (10 ml) maintained under irradiation (sunlamp), was added iodine (75 mg, 0.3 mmol). After 20 min of contact in these conditions, the irradiation was ceased and the reaction allowed to cool down to room temperature. After washing with a saturated solution of sodium thiosulfate (3×10 mL) and drying over magnesium sulfate, the organic phase was concentrated *in vacuo*. The resulting residue was then purified by flash-chromatography on silica gel (hexane) to afford (**9**) as a white solid (52 mg, 52%); mp (uncorrected; methanol) 113–114°C. $[\alpha]_D^{20}$=+28.8 (c=1, EtOH) ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 3.26 (s, 1H), 3.06 (s, 1H), 2.43 (d, 2H, J=3 Hz), 1.89–1.67 (m, 4H), 1.49–1.20 (m, 4H), 1.08 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.89 (s, 6H), 0.86 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm C=C: 138.75, 137.47; CH: 59.97, 55.21, 51.90, 51,39; C quat.: 51.30, 50.99, 49.88, 48,00; CH_2: 37.51, 29.89, 28.02, 25.91; CH_3: 21.11, 19.75, 19.30, 18.97, 14.33, 13.34. EIMS (70 eV): m/z=M^+ ($C_{20}H_{30}S_2$): 334 (42%); $C_{20}H_{30}$: 270 (100%); $C_{19}H_{27}$: 255 (16%); $C_{18}H_{26}$: 242 (25%); $C_{17}H_{23}$: 227 (23%).

Acknowledgements

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6. This reaction cannot be accounted for by a "photochemical rearrangement" for it was already shown[5] that under direct irradiation bis-thiocamphor was inert under long UV wavelength, which is the present case with the sunlamp source/pyrex glassware conditions.
7. MacSPARTAN 1.1.3, Wavefunction, Inc., 18401 Von Karman ave. suite 370, Irvine, CA 92715, USA. The displayed values were obtained at the AM1 semi-empirical level with geometry optimization. They do not intend to represent the reality in all its accuracy, but rather, wish to express a quantifiable trend (the calculations being performed with the same parameters).
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