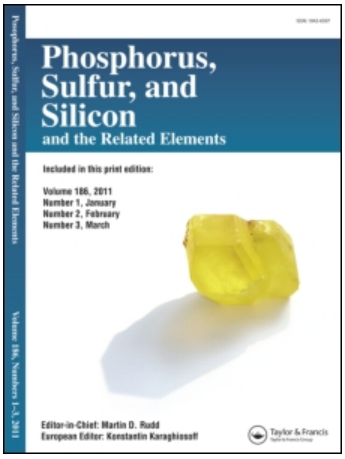

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S_2 in Drug Synthesis

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S_2 IN DRUG SYNTHESIS[1]

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SUMMARY

Two convenient methods for the preparation of S_2 have been developed and a third, based on binaphthyl chemistry, is delineated. Although S_2 additions to acyclic 1,3-dienes afford 1,2-dithiin Diels-Alder adducts, cyclic 1,3-dienes give bicyclic trisulfides. A [3,3] sigmatropic rearrangement initiated from an additional S_2 addition to the Diels-Alder adduct produced with cyclic dienes is proposed to account for the latter result. S_2 also adds to strained olefins. However, it does not participate in the "ene" type reactions that plague singlet oxygen chemistry. Several of the 1,2-dithiin adducts, prepared from S_2 additions, have been found to have antimicrobial properties, and more importantly, some also to inhibit the *in vitro* HIV infection of H9 type tissue cells.

INTRODUCTION

The 90° preferred geometrical disposition of the substituents about a disulfide bond can be attributed to the minimization of sulfur-sulfur lone pair interactions[2] and is thought to exert a profound influence in defining the "biologically active" conformational orientation of the cystine amino acid containing peptides such as insulin, malformin A, oxytocin, vasopressin and other disulfide natural products.[3] The extent to which this occurs is of considerable interest and

has been the subject of numerous studies that have quantified a 10-18 kcal/mol barrier in the rotation of a S-S bond through the cisoid geometry (Figure 1).[2]

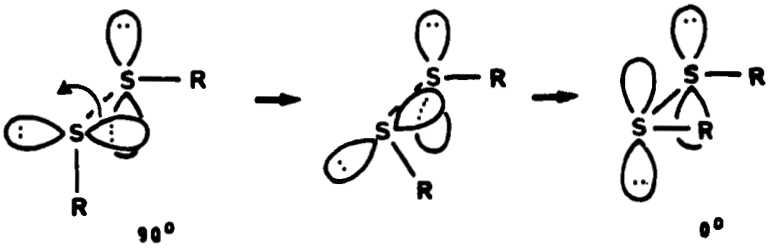
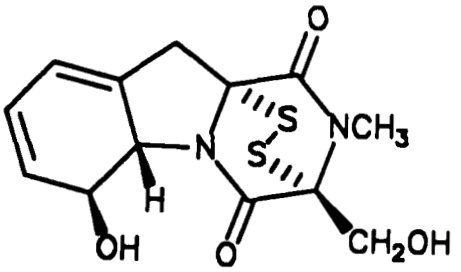


FIGURE 1 Sulfur-Sulfur lone pair interactions.

The consequence of this cost in energy is best reflected in the synthetic difficulty that is experienced when constructing S-S bonds in cyclic systems. It can be formidable and, at times, the limiting synthetic factor. For example, reference to the total synthesis of gliotoxin (1), by Kishi and co-workers,[4] can be made to illustrate this point.



1

Based on several examples, scattered in the literature, there is ample evidence to suggest that the strain imposed on the S-S bond in cisoidal constrained

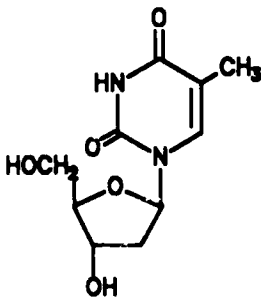
disulfides is partly relieved by a lengthening of that bond.[2a,d,3c,d,5] This "conformationally induced" weakening (calculated to be of the order of at least 15 kcal/mol relative to the unstrained 90° conformer)[5] is, to a large extent, responsible for the accelerated rate that cyclic disulfides undergo the thiol-disulfide exchange reaction compared to acyclic analogues (eq. 1).[2a,6]

$$RSSR + R'SH \rightleftharpoons R'SSR + RSH \qquad (1)$$

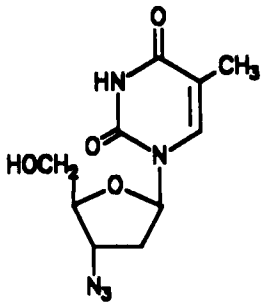
Since the introduction of penicillin to the clinic in 1941,[7a] more than 7,000 natural and over 30,000 (semi) synthetic antibiotics have been evaluated.[7] Of these, approximately 100 can be said to have gained clinical importance.[7b,c] On the other hand, even though intensive efforts have been made, particularly during the last 5 years, only a handful of therapeutically (prophylactic) useful antiviral agents have been reported.[7,8]

Part of the reason why so comparatively little advancement has been made with antivirals is that, unlike bacteria which have unique growing and replicating processes that lend themselves to specific chemical intervention, viruses have the advantage of hiding in the commonality of their host cell. Discrimination against the host or normal cell in virology is also a

problem found in cancer chemotherapy. Not surprisingly then, candidate anticancer and antiviral drugs are often screened for both of these malicious afflictions. Indeed, 3'-azido-3'-deoxythymidine (AZT),[9a] a drug currently used in the treatment of some AIDS[9] patients, was first introduced as an anticancer drug.[7a] Once incorporated into the viral transcriptase enzyme, its mode of action is believed to be that of a premature chain terminator because it lacks the 3'-hydroxy group, as found on thymidine, necessary for the phosphorylation step in the DNA chain growing sequence.[9a]



THYMIDINE



AZT

α,β-Unsaturated carbonyl compounds have also been explored for these purposes. They readily add sulfhydryl groups of enzymes and thereby remove these important biocatalysts from further action (Figure 2).[10] Unfortunately, this usually is a nonspecific reaction that is capable of capturing a host of other nucleophiles and therefore, has found little practical application. However, since sulfhydryl groups abound many of

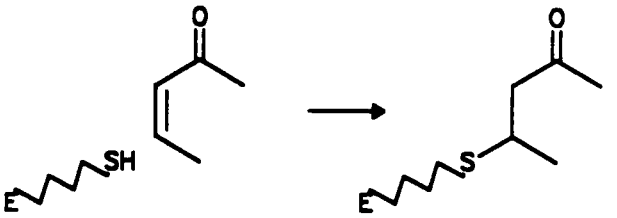
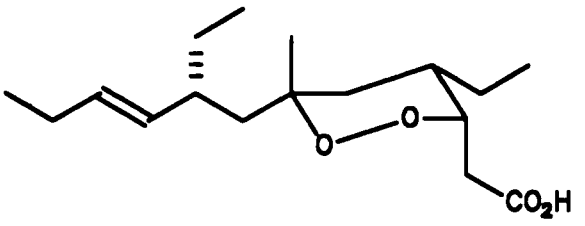


FIGURE 2 Sulfhydryl Michael additions.

the key enzymes, they offer excellent potential sites for functional interference. If some discriminatory and non-cell toxic process could be formulated to selectively recognize sulfhydryl units, it would become a powerful handle in the design and synthesis of anti-viral and anticancer drugs.

Mercaptans are, of course, functionally the same. Therefore, how can they be used to discriminate one thiol-bound enzyme from another? We believe that the thiol-disulfide exchange reaction, we alluded to earlier, if incorporated into 1,2-dithiane analogues of certain naturally occurring peroxides such as, plakortic acid,[11] will posses this attribute.[12] Further, the kinetically favored intramolecular reversibility of



plakortic acid

this reaction (Figure 3) could work to free the small, innocent, and sterically less demanding thiol-bound

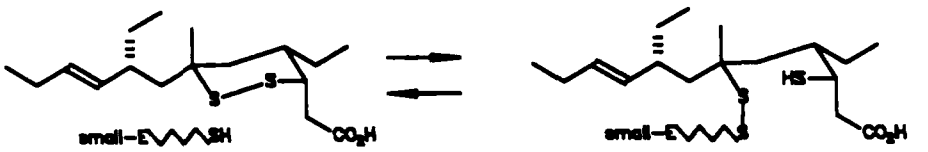
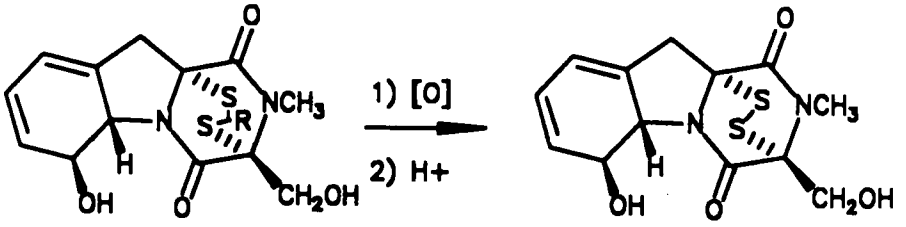


FIGURE 3 Sulfhydryl trans-sulfuration.

enzymes that inadvertently get snared. However, larger enzymes, such as viral RNA polymerase, should become trapped sufficiently long enough to effectively stop the viral replicating process.[12] In a hostile environment, survival of the virus depends on its ability to produce competitively more aggressive enzymes. Thus, in competition with the viral polymerase for the disulfide bait, the less efficient mamalian polymerase should be spared this pitfall.

RESULTS AND DISCUSSION

In his total synthesis of gliotoxin, Kishi introduced us to a novel and elegant method for the genesis of a S-S bond.[4] A Pummerer type rearrangement[13] of a dithia acetal derivative of anisaldehyde, cleverly used to protect the sensitive mercapto moiety throughout the synthesis (Figure 4), was designed and gracefully executed to accomplish the transformation in high



R = p–$CH_3OC_6H_4$

FIGURE 4 Gliotoxin synthesis.

yield. However, this procedure cannot readily be applied to the dithiaplakortic acid synthesis and alternative methodology had to be sought.

Since creation of the S-S bond is a problematic step, the ideal situation would be to avoid it altogether. It is difficult not to note that the disulfide unit in gliotoxin and dithiaplakortic acid constitutes part of a six-membered ring. A ring size that is directly accessed by the Diels-Alder reaction. In fact, in designing a synthesis for the natural product myrcene disulfide[14] (2, Figure 5), it is almost impossible to ignore this route.

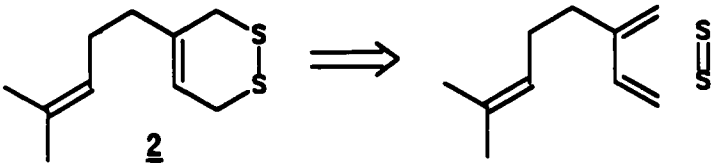


FIGURE 5 Retrosynthesis of myrcene disulfide.

Although the Diels-Alder addition of singlet oxygen (O_2) to 1,3-dienes is a well developed synthetic reaction,[15] the corresponding diatomic form of sulfur, hitherto our work,[16] had only been described[17] to exist in the vapor phase of elemental sulfur heated at 1000° K. After considerable effort in designing and preparing organometallic reagents[18] that could deliver a discrete number of sulfur atoms, we explored the possibility of using these reagents to mimic the phosphine ozonide procedure, used for the emission of singlet oxygen, for the preparation of S_2 (Figure 6).[16a] The

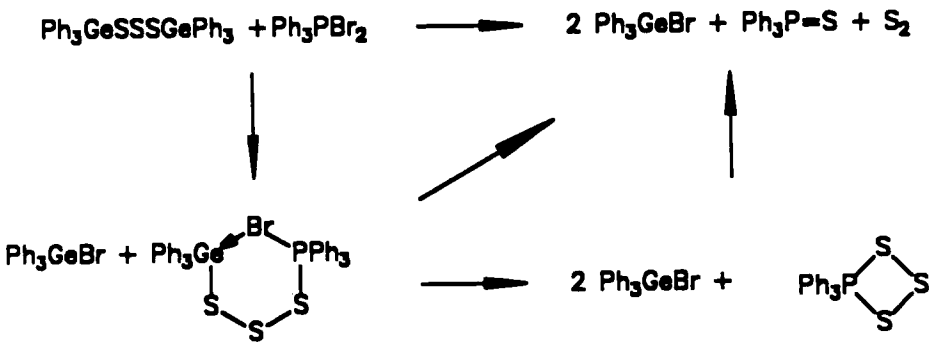


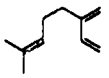
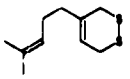
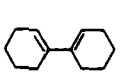
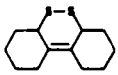
FIGURE 6 Organometallic route to S_2.

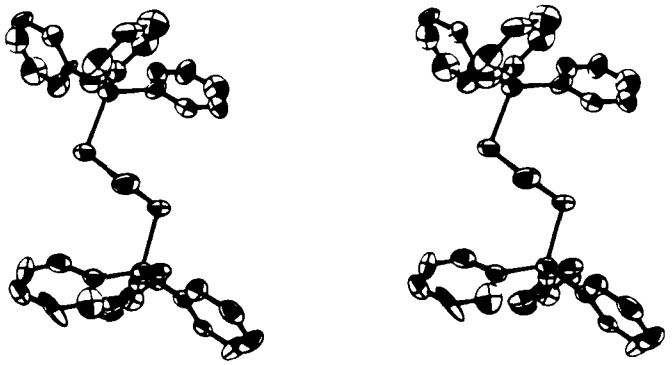
approach was successful and, for the first time, a direct entry into the synthesis of 1,2-dithiins *via* the Diels-Alder reaction (Table 1) became available.

Because "activated" elemental sulfur also adds to acyclic 1,3-dienes,[14,19] it was essential for us to be

able to differentiate the two processes. Firstly, the integrity of the sulfur content in *bis*-triphenylgermanium trisulfide (our S_3 source) was unequivocally established through X-ray crystallography.[18a]

TABLE 1 S_2 additions to acyclic 1,3-dienes.

olefin	product	isolated % yield	mp. °C
		60	oil
		85	101–102
		75	oil
		70	oil



Stereoview of $[(C_6H_5)_3Ge]_2S_3$

Although treatment of acyclic 1,3-dienes with "activated" elemental sulfur is known to afford 1,2-dithiin

adducts (in modest yield), substantial amounts of the mono and polysulfurated homologues are also produced by this method.[14,19] From the many experiments that we have carried out on S_2 additions to acyclic 1,3-dienes, the addition, by our methodology, always gives the 1,2-dithiin adduct as the sole sulfur containing organic product in the reaction. *This is a very important distinction.* Subsequent to the publication[16] of our procedures for the preparation of S_2, several additional methods for the purported preparation of this highly reactive diatomic species have appeared.[20] From our experience in this area, we conclude that those *methods*[20e,g,21] *that give mixtures of sulfurated products are, in effect, generating "activated" elemental sulfur* and it is the chemistry of this form of sulfur that is being observed with these techniques. Reports of methodology[20d,f] that claim to liberate S_2 without substantiation from trapping experiments must, for the time being, be discounted until such evidence is brought forth.

The organometallic route to S_2 is limited to a temperature range of -20 to 44° C. Although we have now optimized this procedure to give good to excellent yields of S_2 adducts, the temperature limitation prevents 1,4-substituted conjugated dienes from reacting

efficaciously. Since our synthesis of dithiaplakortic acid (Figure 7) involves this type of diene, an alter-

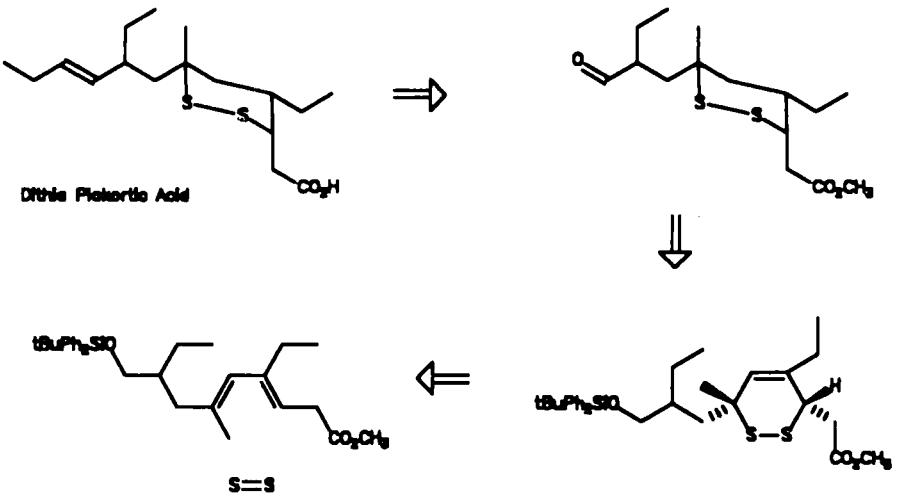


FIGURE 7 Retrosynthesis of dithiaplakortic acid.

nate source for S_2 that could accommodate a higher tolerance for temperature had to be devised. Using computer generated structures, we were able to calculate, from enthalpy differences,[16b] that conversion of the biphenyl diketone compound 3 (Figure 8), into its corresponding dithione derivative would result in a 37 kcal/mol favorable extrusion of S_2 in order to achieve the aromaticity of 9,10-diphenylphenanthrene 6. Although no precedent for this reaction could be found, treatment of diketone 3 with a highly reactive *in situ* form of B_2S_3[18b] in refluxing toluene, in the presence of 2,3-dimethylbutadiene, gave the expected S_2 adduct

in 60% isolated yield and a quantitative isolated yield

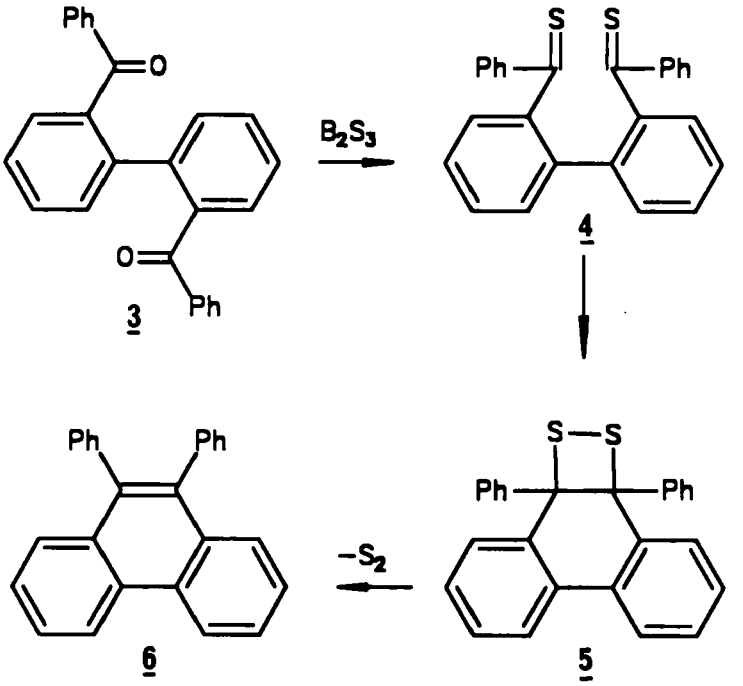
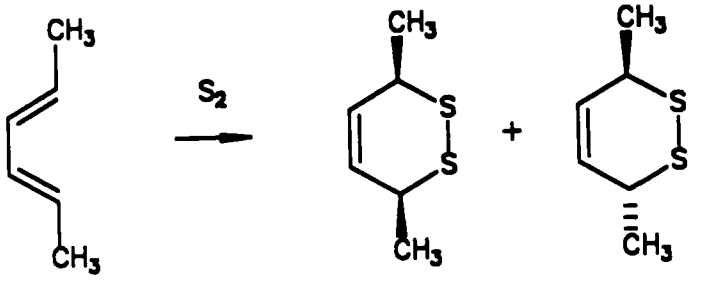


FIGURE 8 Biphenyl route to S_2.

of the phenanthrene derivative as the calculations predicted. Dithione or dithietane intermediates 4 and 5, respectively, did not survive isolation attempts.

Now that methodology for the preparation of S_2 has been established, its chemistry remains to be elucidated. Of primary concern to us, for the synthesis of dithiaplakortic acid, is the question of whether or not S_2 obeys the Woodward-Hoffmann rules[22] in cycloaddition reactions, and whether it would participate in the "ene" type chemistry that often plagues singlet oxygen [4+2] additions.

When the all trans isomer of 2,4-hexadiene was subjected to S_2 addition, the expected Diels-Alder adduct



was obtained in 52% isolated yield. No trace of the other adduct could be noted. The stereochemistry was firmly established by H NMR analysis of the saturated *cis*-2,5-dimethyl-1,2-dithiane product obtained by hydrogenation of the double bond through the thermal generation of diimide from naphthosyl hydrazine. At room temperature, a single doublet for the methyl protons is seen. However, below the coalescence temperature of -10° C (12.2 kcal/mol barrier to rotation), the two different doublets for the axial and equitorially restricted methyls are observed (Figure 9).

The diimide reduction of the double bond, without destroying the sensitive disulfide linkage, is a very important finding. This transformation is essential to our synthetic strategy and furthermore, since it can only be invoked in the very late stages of the synthesis, it would be catastrophic to find out that it

doesn't work! S_2 addition to the *cis-trans* isomer of 2,4-hexadiene affords only the non Diels-Alder adduct

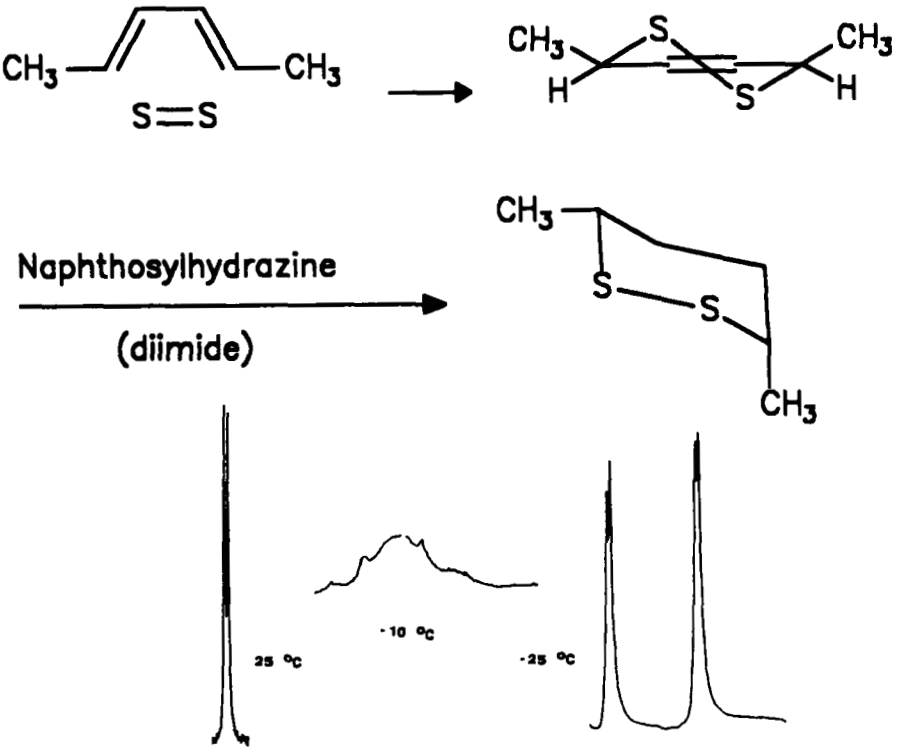
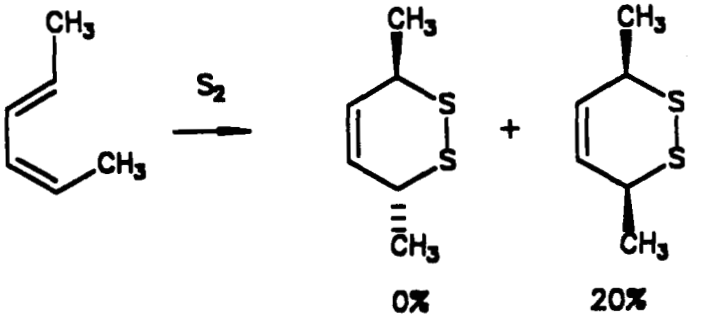
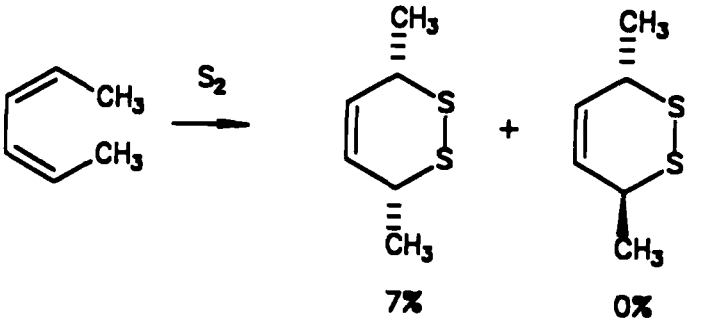


FIGURE 9 Diimide reduction of 1,2-dithiins.



in low (20%) yield. The expected Diels-Alder adduct is not observed. Interestingly, the results parallel those

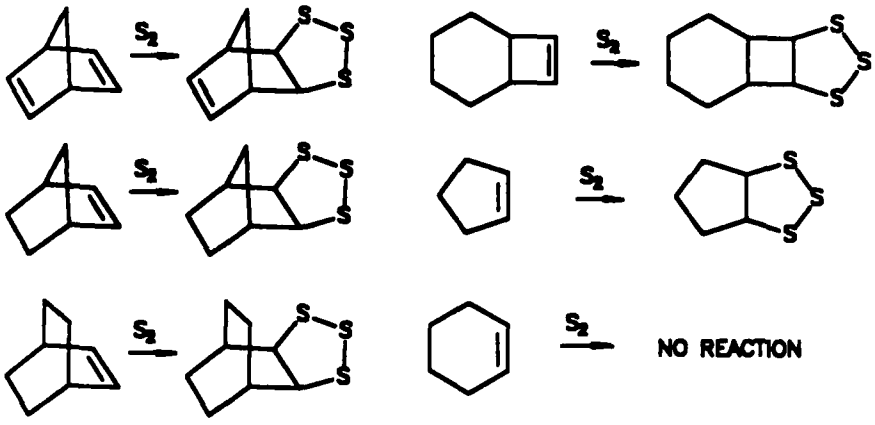
of singlet oxygen addition to these dienes.[15b] The all *cis* isomer, which is very sluggish toward Diels-Alder



additions, gave the expected adduct in 7% isolated yield, uncontaminated by any other sulfurated products.

We have never noted any [2+2] or "ene" type adducts to be formed by S_2 additions to acyclic 1,3-dienes. Strained olefins such as norbornadiene react with S_2 to give epitrisulfides (Table 2) in poor to good yield. At

TABLE 2 S_2 additions to strained olefins.



first we thought these to be episulfides, but independent synthesis of a few examples showed this not to be the case. The path that we think leads to epitrisulfide formation is depicted in figure 10. The second addition

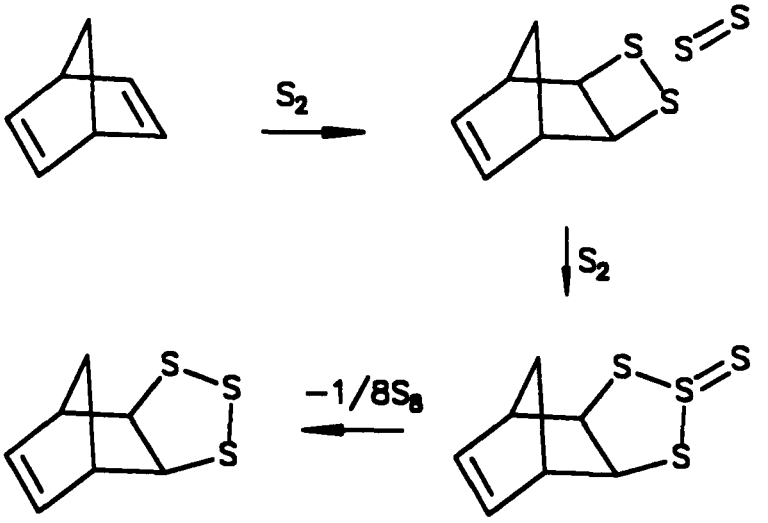
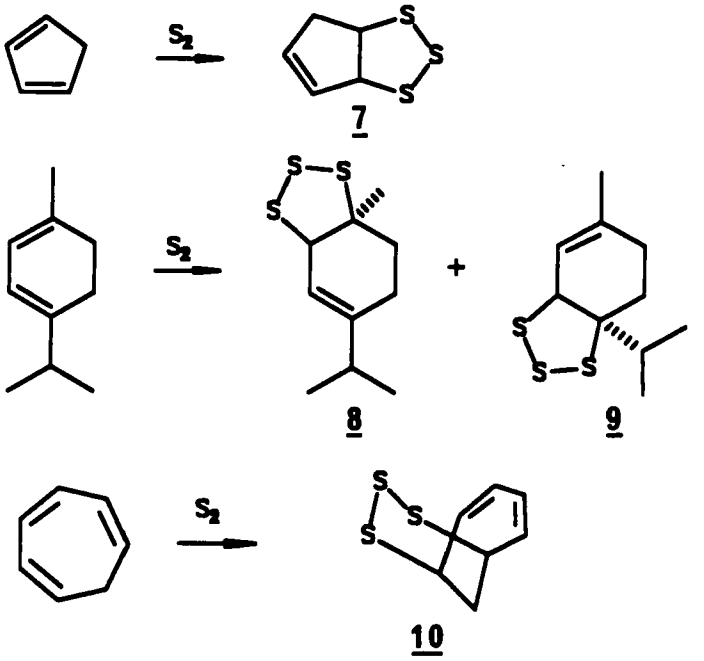


FIGURE 10 Pathway to epitrisulfide formation.

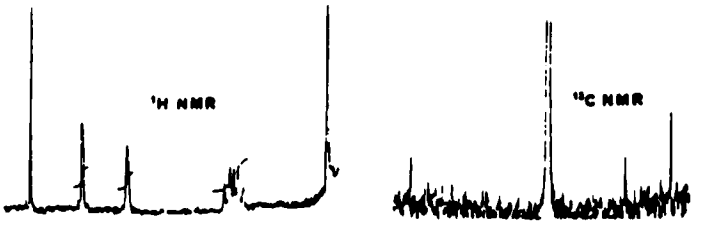
of S_2 to the highly strained S-S bond of the [2+2] adduct appears to be a very facile one. The characterization of these epitrisulfides proved to be instrumental to our being able to elucidate some of the chemistry that we observe when S_2 is added to cyclic 1,3-dienes.

For example, when cyclopentadiene is treated with S_2, bicyclic trisulfide 7 is obtained in 50% isolated yield. Similarly, α-terpinene gives a 42% yield of a

9:1 mixture of bicyclic trisulfides 8 and 9, respectively, and with cycloheptatriene the adduct 10 is obtained in 20% yield. Since, on one occasion, we



were able to isolate the Diels-Alder adduct from the addition of S_2 to cyclohexadiene (a reaction that



unfortunately we have not been able to reproduce)[23] and by H NMR analysis of the reaction mixtures there is spectroscopic evidence in support of Diels-Alder adduct formation, we think that the Diels-Alder adducts are intermediate products of these reactions. However, as noted with S_2 additions to strained olefins, a second equivalent of S_2 apparently rapidly inserts into the bridging S-S bond and that this then initiates a [3,3] sigmatropic rearrangement, to give after deposition of elemental sulfur, the bicyclic trisulfides that are isolated (Figure 11). For comments on branched bonded sulfur intermediates and possible modes of sulfur loss, see ref. 20b.

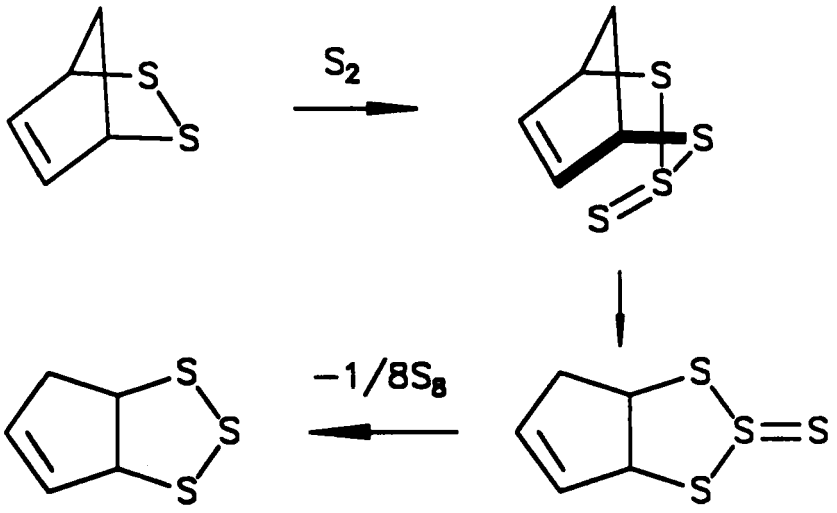


FIGURE 11 Bicyclic trisulfide formation.

We are presently carrying out experiments to deter-

mine the conditions necessary to inhibit this undesired second addition of S_2 to cyclic 1,3-dienes. The fact that the cyclohexadiene adduct was obtained is evidence that these conditions must exist. One area that we are emphasizing, is in the design and synthesis of an isolatable dithione or dithietane precursor to S_2. Although we have not yet accomplished this, we herein delineate some of our results to date.

In our synthetic strategy for the synthesis of dithiaplakortic acid, we are faced with several challenging problems. We have already addressed whether S_2 can be made available and whether it will undergo [4+2] cycloaddition reactions. Plakortic acid has four stereocenters, three in the heterocyclic unit and one on the side chain. It is believed that the relative ring stereochemistry is as shown but no information concerning the absolute stereochemistry or the relative or absolute stereochemistry of the stereocenter on the side chain is known.[11a]

From structure-activity relationship studies carried out on a number of marine natural peroxides similar to plakortic acid, the boxed in porion shown in figure 12 is thought to be necessary for biological activity.[11j] In a few cases where absolute stereochemistry has been determined, the configuration of carbon 6 is *S*.[11j,k]

Assuming that a common metabolite is involved, it is likely that the absolute configuration at carbon 6 of

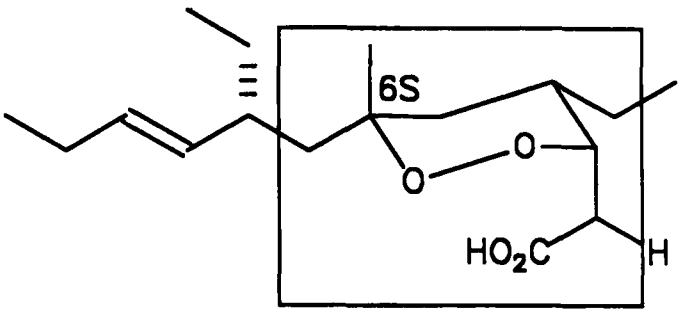


FIGURE 12 Bioactive part of plakortic acid.

plakortic acid will also be of the *S* configuration. The Diels-Alder addition of S_2 would then automatically define stereocenter 3 as *R* and the diimide reduction, expected to be from the least hindered side, to give the equitorial orientation of the ethyl appendage on carbon 4 (Figure 13) as *S*.

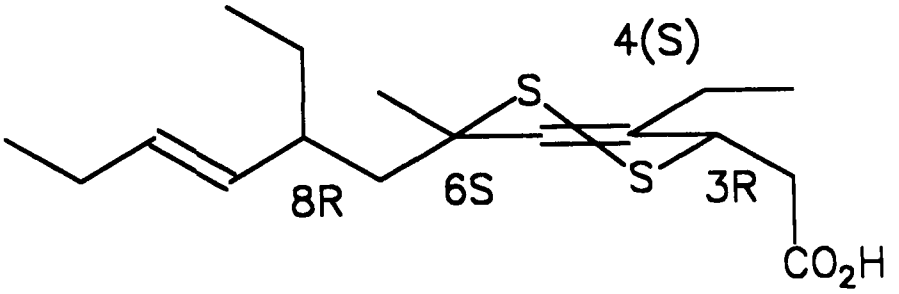


Figure 13 Stereochemistry of Diels-Alder adduct.

With the use of molecular modeling techniques, we generated and searched several thousand conformers of

the two diastereotopic Diels-Alder transition states (Figure 14), in which the ring stereochemistry was set to that described above and the configuration of the

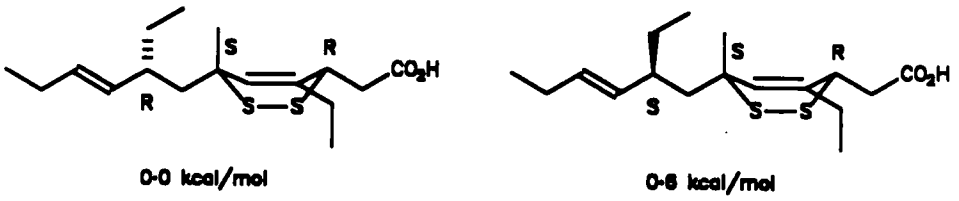


FIGURE 14 Diastereotopic transition states.

stereocenter at carbon 8 on the side chain fixed to *R* and then *S* in order to determine the relative differences of the global minima of the two states. The search netted a 0.6 kcal/mol in favor for the *R* configuration over the *S*. Thus, given the choice of having to synthesize all 16 possible diastereomers, we chose to synthesize the diastereoisomer having the *R*,*S*,*S*, and *R* configurations at carbons 3,4,6 and 8 respectively, based on these calculations. Although we are rapidly approaching the completion of this total synthesis, a few more steps still remain to be performed. In the end however, it will be interesting to see if molecular modeling techniques will have contributed, importantly, to this synthesis.

There are many examples of asymmetric induction in

the Diels-Alder addition of chiral or prochiral dienophiles to chiral dienes.[24] *Since successful addition of S_2 to conjugated dienes occurs only if the S_2 is generated in the presence of the diene,*[16,20a,b] *it is possible that the addition actually occurs through an intimate exchange rather than through contact with a "free" S_2 species.* If indeed this is what actually occurs then, even though S_2 itself is not chiral, if incorporated into a "stable" chiral precursor, we should see asymmetric induction in additions to chiral dienes. According to the same type of computer calculations[16b] we carried out in designing the biphenyl route to S_2, binaphthyl dithione derivative, 12, shown in figure 15, is calculated to have these desired properties.

Binaphthyl, itself, has a 23.8 kcal/mol[25a] barrier to rotation about the bridging bond. Substituted 2,2'-derivatives generally have higher rotational barriers and those derivatives that can be resolved do not racemize at room temperature (in some cases to well over 100° C).[25b] The prerequisite diketone 11 has only recently been prepared and conversion into the corresponding dithione using methodology we developed for the biphenyl analogue[16b,18b] is underway.

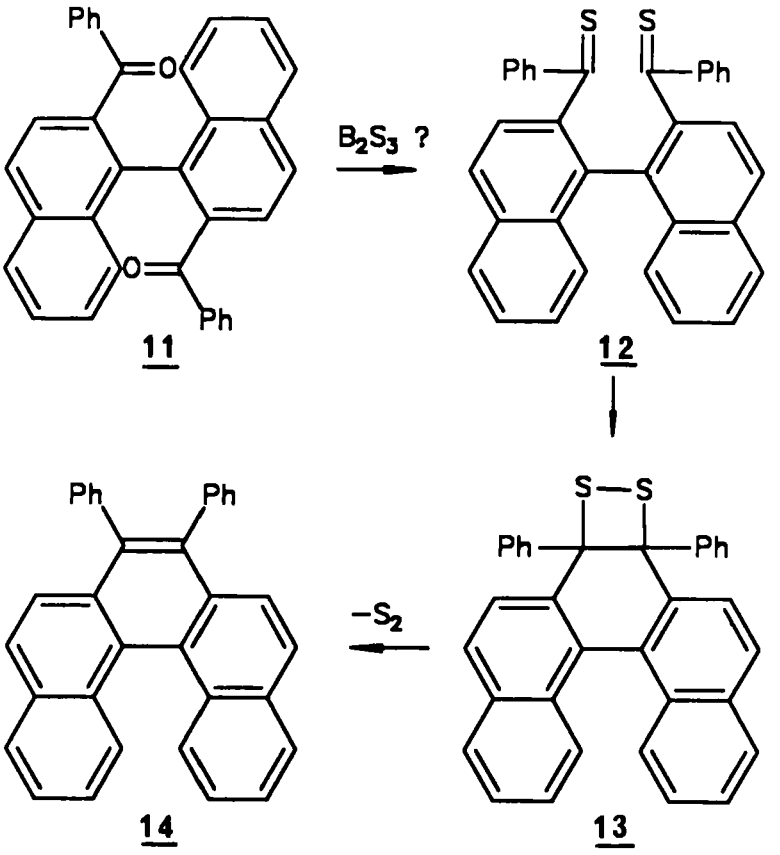
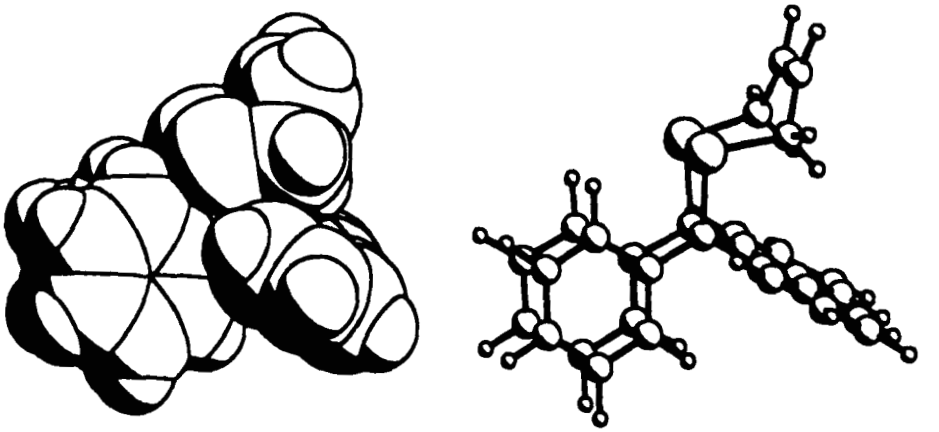


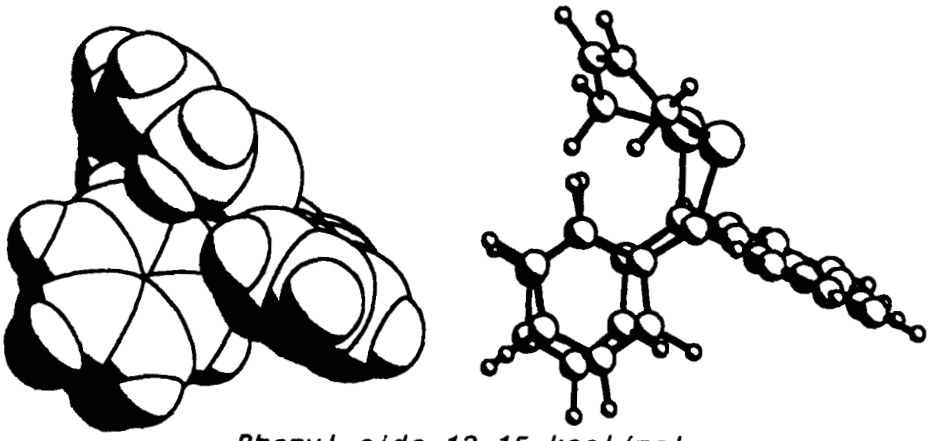
FIGURE 15 Binaphthyl approach to S_2.

From molecular modeling studies on the reaction of butadiene with the dithietane derivative 13 (Figure 16), the approach of the diene favors the binaphthyl side by 13 kcal/mol over that from the sterically more crowded phenyl direction. The calculations to determine asymmetric induction on the chiral diene leading to dithiaplakortic acid involve several thousands of conformers to be evaluated and, at present, this computer

intensive task is still being processed.



Naphthyl side 0.0 kcal/mol



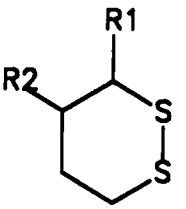
Phenyl side 13.15 kcal/mol

FIGURE 16 Pluto drawings of butadiene addition to 13.

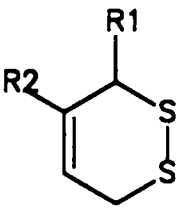
Calculations on the more simple system involving the addition of 1,3-pentadiene to one enantiomeric form of 13, yield a 0.1 kcal/mol difference between the two diastereotopic transition states. If borne out in the experiment, this would translate into a 10% enantiomeric excess for the reaction carried out at room tem-

perature.

Finally and most importantly, this whole exercise in S_2 chemistry was designed as a novel route to antiviral and anticancer drugs. Although the synthesis of dithiaplakortic acid has not yet been realized, we have prepared, in addition to those already described, several S_2 adduct intermediates of the type 11 and 12 and, for a variety of these, have had an opportunity to study some of them for their biological and chemical properties.



11



12

	R1	R2	R1	R2
a)	CH_2CO_2H	H	CH_2CO_2H	H
b)	$CH_2CO_2CH_3$	H	$CH_2CO_2CH_3$	H
c)	CH_2CH_2OH	H	CH_2CO_2OH	H
d)	CH_2CH_2OAc	H	CH_2CH_2OAc	H
e)	$CH_2CONHCH_2CO_2H$	H	H	CH_2CH_2OH
f)	$CH_2CONHCH_2CO_2CH_3$	H	H	CH_2CH_2OAc

Firstly, since the thiol-disulfide exchange reaction is what we have based our reasoning on for the anticipated biological activity in this class of compounds, three mercaptans; benzyl mercaptan, the amino acid cysteine and *t*-butyl mercaptan were treated with myrcene

disulfide (**2**) in methanol containing a catalytic amount of NaOH[6a] (Figure 17). Recalling that small, sterically

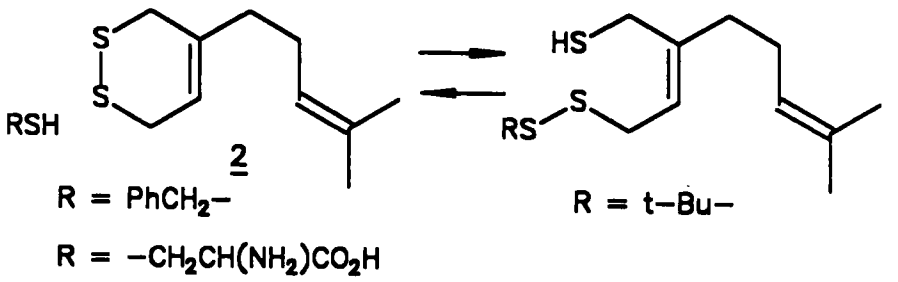


FIGURE 17 Based catalyzed thiol exchange with 2.

free thiol-bound enzymes should keep the equilibrium (Figure 17) to the left, we were delighted to note (NMR analysis), that with benzyl mercaptan or cysteine, even after a week at room temperature, the disulfide remained completely intact. On the other hand, *t*-butyl mercaptan was irreversibly exchanged in less than 10 hours!

When tested for antimicrobial properties, disulfides **2**, **11**, and **12** showed no activity against Gram negative bacteria (*E. Coli* and *Ps. aeruginosa*), fungi (*C. albicans*), or mycobacteria (BCG strain of *M. bovis*). However, against Gram positive bacteria (Oxford strain of *Staph. aureus*, *Staph. epidermis*, *Strep. pyogenes*, and *Strep. faecalis*), disulfides **2**, **12e** and **12f** are active.

Naturally, it is their antiviral activity, if any, (especially against HIV[9b]) that we are most interested in. Using concentrations of 50 to 100 μM, of the disulfides in DMSO, Table 3 outlines the results

TABLE 3 Inhibition studies against HIV infection.

Disulfide	% Infected H9 cells
2	15
11a	20
11b	90
11e	75
11f	30
12b	95
12d	TOXIC

observed after two weeks of infecting H9 tissue grown cells (changed twice weekly) with HIV. Compound 12d was found to be toxic and although none of these disulfides showed complete inhibition, compounds 2, 11a, and 11f are sufficiently active to warrant further study. It is also worth pointing out that these compounds are only model intermediates and since the thiol-disulfide exchange reaction is reversible, the more fully substituted dithiaplakortic acid is expected to be far more potent.

Since myrcene disulfide (2), which recorded the best activity against HIV, was also found to induce platelet aggregation, any potential clinical use is negated. The other disulfides, however, are completely neutral to

platelet aggregation. The dithiaplakortic acid model compound **11a**, which is similar to compound **2** in activity against HIV, importantly, does not express any toxic behavior towards normal cells. Methyl esterification of plakortic acid causes biodeactivation.[11g] Interestingly, the activity of compound **11a** against HIV, is also lost if methyl esterified (**11b**).

In conclusion, the results in hand are very promising for the goals we have targeted, and we anticipate, judging by the number of papers concerning S_2 chemistry that have already appeared in the short time since we introduced this new and exciting area of organosulfur chemistry, that more is yet to come.

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