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CYCLIC SULFIDES IN ORGANIC SYNTHESIS

E. VEDEJS* and G. A. KRAFFT
S. M. McElvain Laboratory of Organic Chemistry, Chemistry Department, University of Wisconsin, Madison, WI 53706, U.S.A.

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CONTENTS

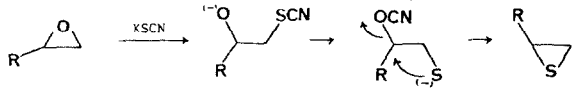
Many reactions of cyclic sulfur compounds have interesting synthetic potential, but relatively few have enjoyed widespread use. This review will include brief coverage of well established techniques, but the main emphasis will be to highlight recent developments having as yet undefined scope. The discussion is restricted to nonaromatic rings, typically having one or two sulfur atoms at the sulfide, sulfoxide, or sulfone oxidation state. Reactions where the cyclic nature of the sulfur substrate is coincidental to success and where comparable transformations are known with acyclic sulfur reagents will not be considered.

Simple cyclic sulfides with three to seven membered rings are commercially available, but more functionalized compounds of interest as synthetic intermediates must be prepared, usually from acyclic materials. The most general method involves base-induced ring closure of thiols having a suitably placed leaving group or other electrophilic functionality, an approach which can be adapted to any of the common ring sizes. Other methods tend to be highly specialized. The following summary selects some of the more important preparative methods, arranged according to ring size.

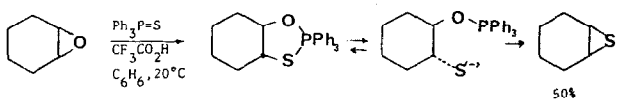
THIIRANES

Epoxides (or the parent alkenes) are the most convenient starting materials for preparation of simple thiiranes. The well known thiocyanate procedure remains the method of choice for epoxides having reasonable S_N2 reactivity (eqn 1).[2] A key intermediate step in this interesting reaction is intramolecular S to O cyanide migration, a process which activates oxygen as a leaving group. Similar mechanisms are involved in the thiirane syntheses in eqn (2) (nucleophile, $Ph_3P{=}S$; leaving group after S to O migration, $Ph_3P{=}O$.[3,4] Synthetically equivalent methods which begin directly with alkenes are also available. The examples of eqn (4) depend on the addition of S-protected sulfenyl chlorides to alkenes, followed by ring closure.

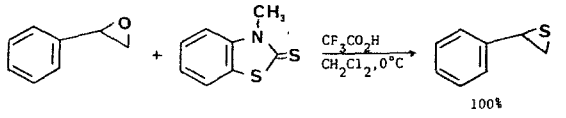
eq. 1[2]



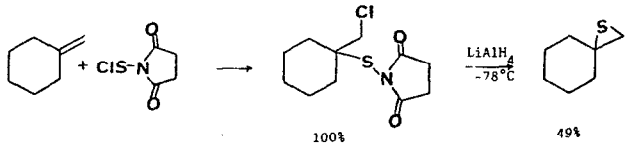
eq. 2[3]

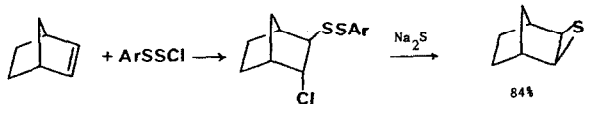


eq. 3[4]



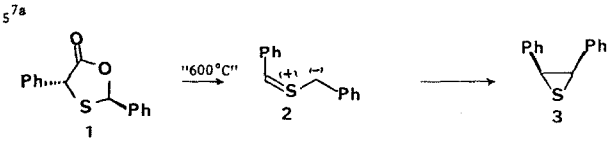
eq. 4[5]



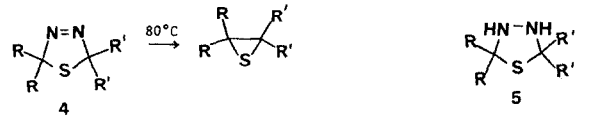


Thiocarbonyl ylides are important as intermediates in the preparation of thiiranes by thermal extrusion methods from heterocyclic precursors.[6] As illustrated by the flash vacuum pyrolysis of trans-2,4-diphenyl-1,3-oxathiolan-5-one **1** to cis-stilbene sulfide **3**, an intermediate ylide **2** undergoes conrotatory ring closure (eqn 5).[7a] Several other 1,3-oxathiolan-5-ones have been converted into thiiranes in excellent yield by this method.[7a] Thiadiazolines **4** are also useful precursors of thiocarbonyl ylides under conditions which permit isolation of thiiranes.[7b] Several methods are available for thiadiazoline preparation,[7b] including the oxidation of thiadiazolidines **5**[7b,8] or the cycloaddition between diazoalkanes and various thiocarbonyl compounds (eqn 7).[9]

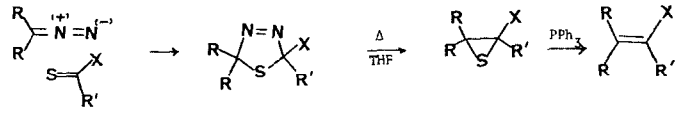
eq. 5[7a]



eq. 6[7,8]



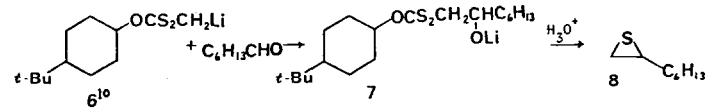
eq. 7[9]

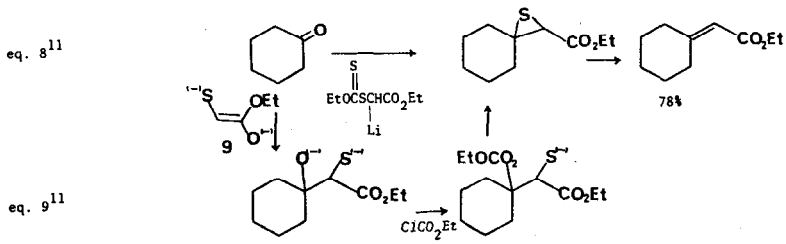


X=alkyl; aryl; OR" ; SR"

Isolation of alkyl-substituted thiiranes is usually not difficult. However, electron-withdrawing substituents (carbonyl; cyano; aryl; heteroatoms) promote the decomposition of thiiranes to alkenes. In the presence of trivalent phosphorus, extrusion of sulfur is efficient even for the alkyl derivatives. This sequence allows synthesis of highly substituted alkanes by "twofold extrusion" (first extrusion: CO_2 or N_2; second, S)[9] from 1,3-oxathiolan-5-ones or thiadiazolidines.

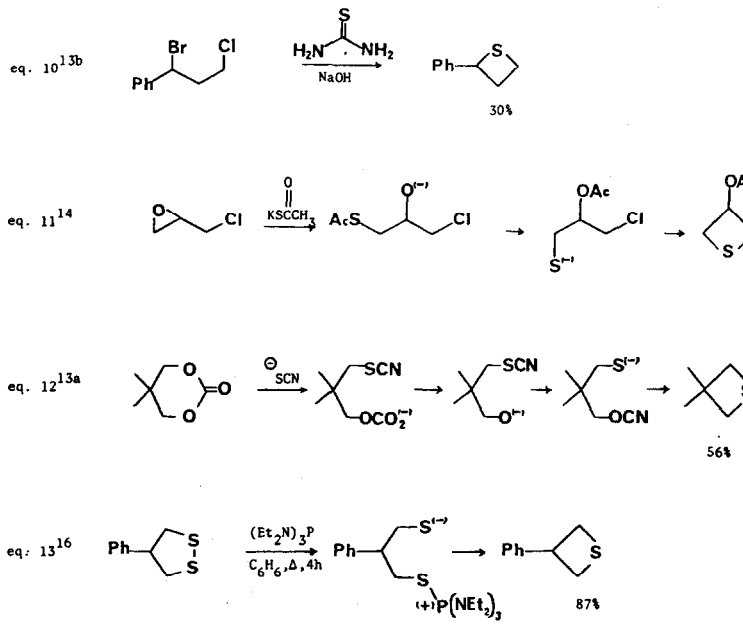
Thiiranes may also be prepared by condensation of carbonyl compounds with certain sulfur-stabilized carbanions.[10] For example, the lithiated xanthate **6** reacts with heptanal to give thiirane **8** (71%) via the adduct **7**. The transformation from **7** to **8** involves migration of the thiono ester fragment from sulfur to oxygen, a step which has close analogy in the thiirane syntheses of eqns (1)–(3). The method is of limited value for thiirane isolation because lithiation is difficult unless the starting $XSCH_2R$ has R^6 = H, C_6H_5, or $CH=CH_2$ (X = thiono ester, thiazole, pyridine, etc.). However, systems where R = anion stabilizing ester, cyano etc. are easy to deprotonate and are useful for generation of thiiranes as transient intermediates. As mentioned earlier, thiiranes having electron-withdrawing substituents are unstable and tend to lose sulfur spontaneously. The result is a synthesis of α,β-unsaturated esters, cyanides etc. starting from lithiated xanthates (eqn 8) or from dilithioethyl thioglycolate (eqn 9).[11] Analogous results have been obtained with phosphorothiolate carbanions.[12]





THIETANES

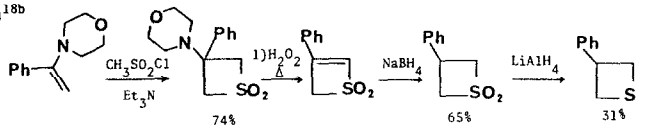
Relatively few methods have been described for synthesis of 4-membered sulfur-containing rings. Cyclization by nucleophilic displacement of γ-substituted alkanethiols is the most general method, and several variations are in use (eqns 10–13). The 1,3-dihalide + thiourea method (eqn 10) is the simplest if the dihalide is available.[13] The epichlorohydrin sequence illustrated in eqn (11) features an acyl transfer step from sulfur to oxygen.[14] A simpler method using $H_2S/Ba(OH)_2$ converts epichlorohydrin into thietan-3-ol, 39%.[15] A technique based on reaction of KSCN with a cyclic carbonate substrate (eqn 12)



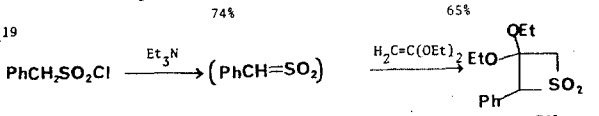
involves an S–O shift of cyanide.[13a] Less substituted cyclic carbonates react similarly, but the yields are quite low.[13a] The disulfide desulfurization example (eqn 13) illustrates a reaction of mechanistic interest which is limited by the availability of 1,2-dithiolanes (lipoic acid derivatives etc.).[16]

The other important route to thietane derivatives is based on the cycloaddition of sulfenes to electron-rich olefins (enol ethers, enamines).[17] Sulfenes may be generated from sulfonyl chlorides with triethylamine (eqns 14, 15)[18,19] or by reaction of diazoalkanes with sulfur dioxide (eqn 16).[20] The latter method is potentially complicated by the competing reaction of sulfene with the starting diazoalkane to give episulfone intermediates.[17] Conversion of sulfene cycloadducts to the sulfide oxidation state can be achieved using strong reducing agents ($LiAlH_4$), as in eqn (14), but yields are low. A closely related synthesis of mustelane (2,2-dimethylthietane) has also been reported,[21] although an approach using intramolecular cyclization of a chloromercaptan is more convenient.[22]

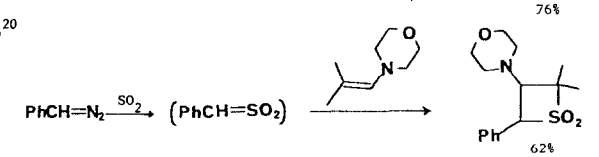
eq. 14[18b]



eq. 15[19]



eq. 16[20]



THIOLANES AND THIANES; GENERAL METHODS

Both 5-and 6-membered sulfides can be made by closely related sulfur-mediated techniques which will be discussed together in this section. Standard cyclizations which do not depend on the presence of sulfur are also available, and these may be found in other, more comprehensive summaries.[23]

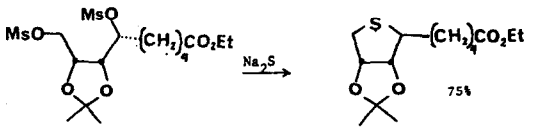
As usual, nucleophilic C–S bond formation is important for preparation of the 5- and 6-membered sulfides.[23] Many examples of cylization by the reaction of sulfide anion with dihalides, bis-mesylates etc. are known, as illustrated in the preparation of a biotin precursor (eqn 17) from carbohydrate starting materials.[24] Free thiolate is not essential for the ring forming step if the electrophilic functionality is reactive enough to attack a sulfide. An interesting example encountered in a synthesis of biotin illustrates the use of an acetal sulfur as the nucleophile in a cyclization initiated by attack of bromine on an alkene (eqn 18).[25] A related bromine-induced cyclization of a γ-δ-unsaturated thioamide has been used to prepare 5-bromomethyl-thiolan-2-one (eqn 19).[26] Unsaturated thiols or their S-acetate derivatives may also be cyclized by phenylselenium chloride, a process which appears to involve initial attack of electrophilic selenium at the double bond (eqn 20).[27]

A simple R–S–CH_3 group can also serve as the nucleophile in the cyclization step (eqn 21).[28] In this example, the equilibrium with an intermediate sulfonium salt is driven to the right by removal of methyl bromide. A similar S_N2' cyclization via free thiolate is highly stereospecific with C–S bonding anti to the departing mesitoate group (eqn 22).[29a]

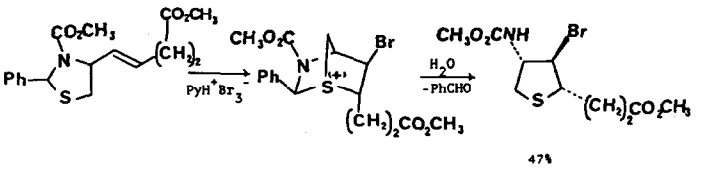
The 1,4-addition of thiolate to suitable Michael acceptors is a useful technique for preparation of cyclic sulfides. Intramolecular examples are especially facile (eqn 23),[29b] but the most important applications involve intermolecular mercaptide 1,4-addition followed by conventional cyclization of a difunctional sulfide intermediate. Convenient variations include standard Michael acceptors and typical carbonyl cyclizations (eqns 24, 25).

More esoteric techniques employ unusual Michael acceptors. Use of vinylphosphonium salts in this context allows an interesting synthesis of unsaturated thiolanes[32] or thianes[31b] based on intramolecular Wittig cyclization (eqn 26). Dimers are often used as the sources of α-thiohydroxy carbonyl reactants under basic conditions which serve to catalyze monomer formation and promote condensation–cyclization. Numerous examples of 2,5-dihydrothiophen synthesis by this method are described.[32] Nitroalkenes may also be used as reactive Michael acceptors with mercaptide anions. Several adap-

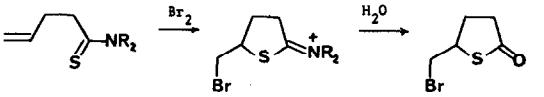
eq. 17[24]



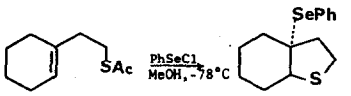
eq. 18[25]



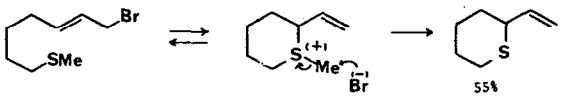
eq. 19[26]



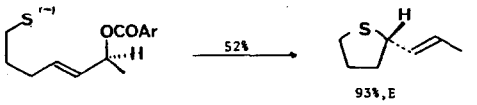
eq. 20[27]



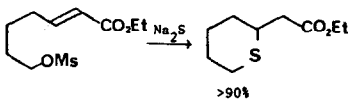
eq. 21[28]



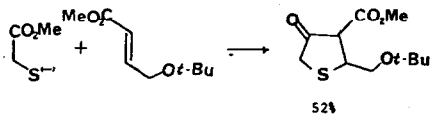
eq. 22[29a]



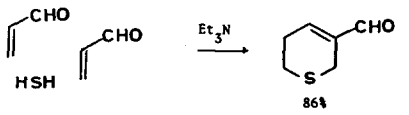
eq. 23[29b]



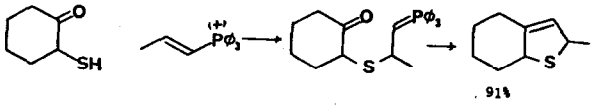
eq. 24[30]



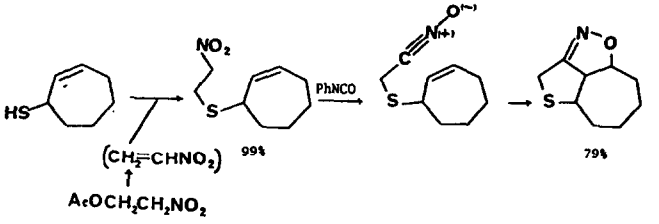
eq. 25[31]



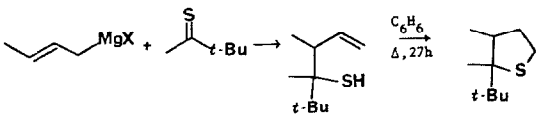
eq. 26[32]



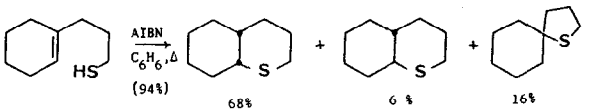
eq. 27[33a]



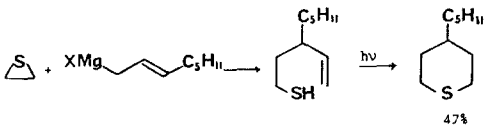
eq. 28[34]



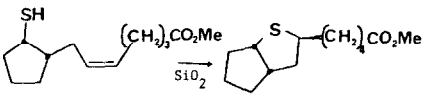
eq. 29a[35]



eq. 29b



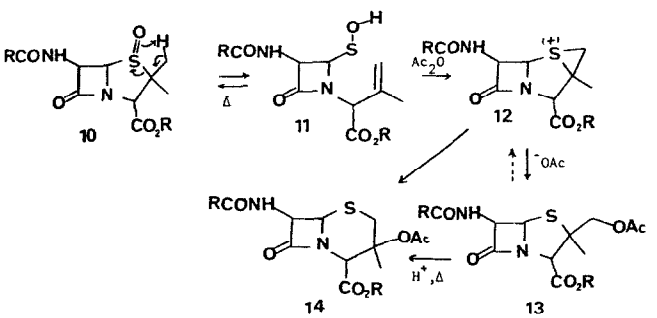
eq. 30[36]



tations for biotin synthesis are based on this idea,[33] one of which is the interesting sequence of eqn (27) where an intramolecular 1,3-dipolar cycloaddition closes the thiolane ring.

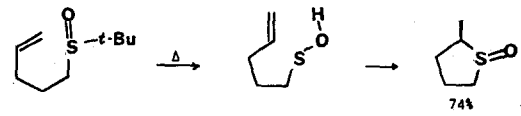
Cyclization of unsaturated mercaptans under free radical conditions is a promising method for synthesis of 5- and 6-membered cyclic sulfides.[34–37] There are few systematic studies in this area, and cyclization conditions vary considerably (heating, photolysis or heating with AIBN, exposure to silica gel etc.). In the case of β,γ-unsaturated alkenethiols, thiolanes are obtained (eqn 28).[34] The homologous γ,δ-unsaturated alkenethiols are capable of cyclization to both 5-membered or 6-membered rings (eqns 29, 30), but the factors governing the regiochemistry are not yet established.

Cyclization of various unsaturated sulfenic acid derivatives is probably the most important approach to synthesis of complex thiolanes or thianes. Much of the extensive progress in this area originates from the development of methods for conversion of penicillins into cephalosporins. This field has been reviewed in detail,[38] and only the key reactions will be summarised here. Pyrolysis of penicillin sulfoxide **10** at *ca.* 100° results in the reversible formation of a sulfenic acid **11** via 5-centre fragmentation.[38c] In the presence of electrophilic activating agents (acid catalysts or acetic anhydride), **11** may cyclize by an alternative ionic mechanism involving an episulfonium ion **12**. Nucleophilic cleavage of **12** under kinetic control gives mostly the thiolane (penicillin-type) product **13**, while harsher conditions (heating, TsOH catalysis) promote the formation of a thiane product (cephalosporin type) **14**.

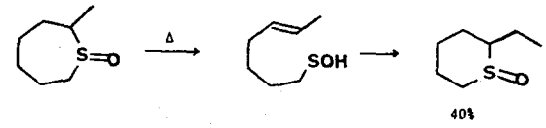


Each of the steps in the penicillin-cephalosporin interconversion sequence now has extensive analogy in simpler molecules. The intramolecular 3+2 cycloaddition of unsaturated sulfenic acids has been studied in representative systems.[39] (eqns 31, 32). Pyrolysis of branched alkylsulfoxides is the most convenient approach for generation of the unstable sulfenic acid intermediates, but an interesting alternative based on the thio-Claisen rearrangement has also been described (eqn 33). In this example, sulfenic acid [3+2]cyclization is observed upon simple heating to give **15**. If acetic acid is present, the sulfenic acid reacts by an ionic mechanism (episulfonium intermediate) to form **16**.

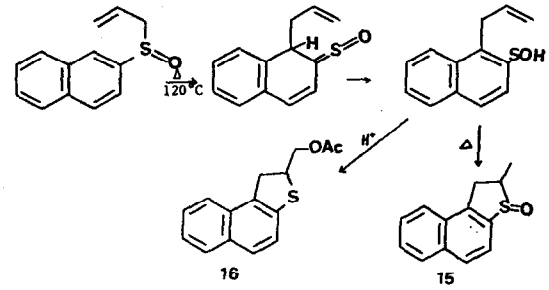
eq. 31[39a]



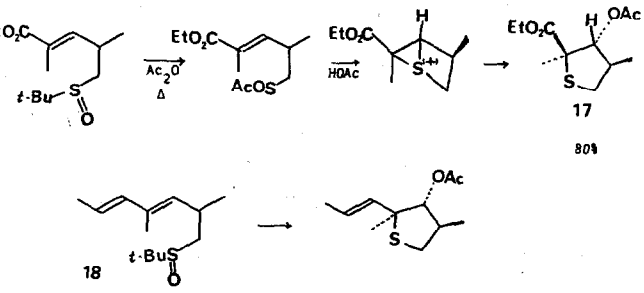
eq. 32[39b]



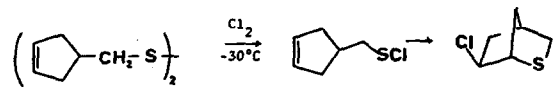
eq. 33[40]



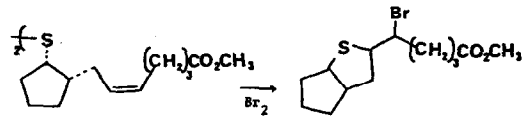
eq. 34[41,42]

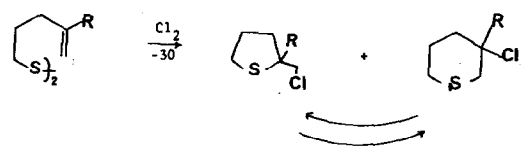


eq. 35[44]



eq. 36[36]





R=H, kinetic	80	:	20
Thermodynamic	18	:	82
$R=CH_3$, Kinetic	95	:	5
Thermodynamic	4	:	96

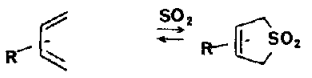
Numerous variations of the ionic cyclization via episulfonium intermediates are described. The process is quite general for systems C=C–(C)$_n$SX where n = 2–4 and X = a leaving group, and intramolecular trans addition to the alkene is observed. An example of highly selective cyclization is described in eqn (34) using the tert-butyl sulfoxide/acetic anhydride method for generation of the sulfenyl acetate intermediate.[41] A single cyclic product **17** is obtained, resulting from trans addition to the alkene via the less hindered episulfonium ion. Under similar conditions, the E,E diene **18** gives the 5-membered ring product in modest yield, but the E,Z diene **19** prefers to react at the disubstituted double bond to form thiane derivative **20**.[42]

Cyclization of unsaturated sulfenyl halides has been studied extensively. Early examples of such cyclization are reviewed under reactions of sulfur dichloride with dienes.[43] Interesting recent developments include the facile generation of sulfenyl halides from disulfides[44,36] (eqns 35, 36). Cleavage of the dissulfide linkage by halogen appears to be faster than addition of halogen to the double bond and rapid cyclization of the sulfenyl chloride occurs at low temperatures. As in the penicillin-derived sulfenic acetate cyclizations, the sulfenyl chloride reactions are subject to kinetic control at low temperatures. Ring size equilibration occurs via the episulfonium ion if the product β-chloroalkylsulfides are heated (eqn 27),[45] and the thiane ring system is more stable than the isomeric thiolane.

Several other mechanistically related cyclizations are described in the penicillin-cephalosporin literature.[38] Interesting specific examples include methods for cyclization of disulfides,[46,47] sulfenamides,[47] and an isolable trimethylsilyl sulfenate ester.[98]

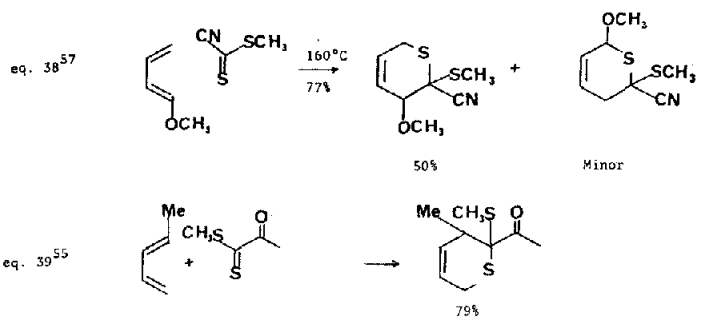
Methods via diene cycloaddition

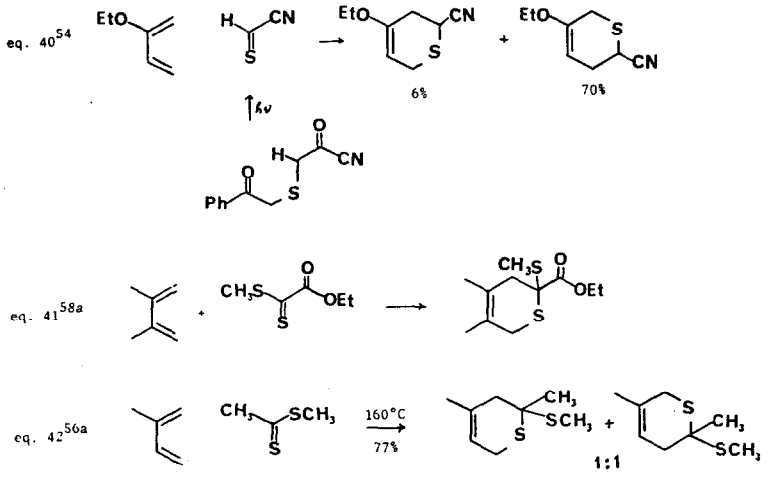
Five-membered cyclic sulfones are easily prepared from 1,3-dienes and sulfur dioxide. This well-known technique has been reviewed,[49] and continues to attract some interest.[50] Given the numerous alternative methods for thiolane synthesis, the SO_2 cycloaddition process is of interest primarily in connection with diene synthesis by the reverse reaction, to be discussed later.



The Diels–Alder type cycloaddition between dienes and thiocarbonyl compounds, on the other hand, leads directly to unsaturated thianes at the synthetically versatile sulfide oxidation state. There is considerable activity in this field. A list of reactive dienophiles includes $X_2C{=}S$ (X = Cl;[51a] X = 1,2,4-triazolyl[51c]) $R_2C{=}S$,[51b,52] RCH = S,[53,54,55] RC(SR′) = S,[55,56,52f] $CH_3SC(CN) = S$,[57,58] $R_2NC(CN) = S$,[59] $ArSO_2C(Ph) = S$,[60] as well as the related sulfines or thione S-imides.[61] In general, typical Diels–Alder reactivity criteria apply to both the diene and dienophile components. As usual, the reactivity of dienophiles is increased by electron demand ($RO_2CC(SR') = S$ more reactive than $CH_3C(SR') = S$, etc). With unsymmetrical dienes, the regiochemistry follows a consistent pattern for nearly all thiocarbonyl compounds studied to date (eqns 38–41). The major products can be rationalized in simple terms by assuming advanced S–C bonding relative to C–C bonding in the transition state. The relatively inert dithio-alkanoates react with little selectivity (eqn 42), but here the question of product equilibration by the relatively harsh conditions (3 days, 160°) has not been resolved.[56a]

Among the thiocarbonyl dienophiles, probably the most convenient reagent for general use is the cyanodithioformate ester $NCC(SCH_3) = S$.[57] This substance, which is a reactive dienophile at 0°, can be isolated if desired, and can also be conveniently prepared *in situ*.[58] However, the highly reactive



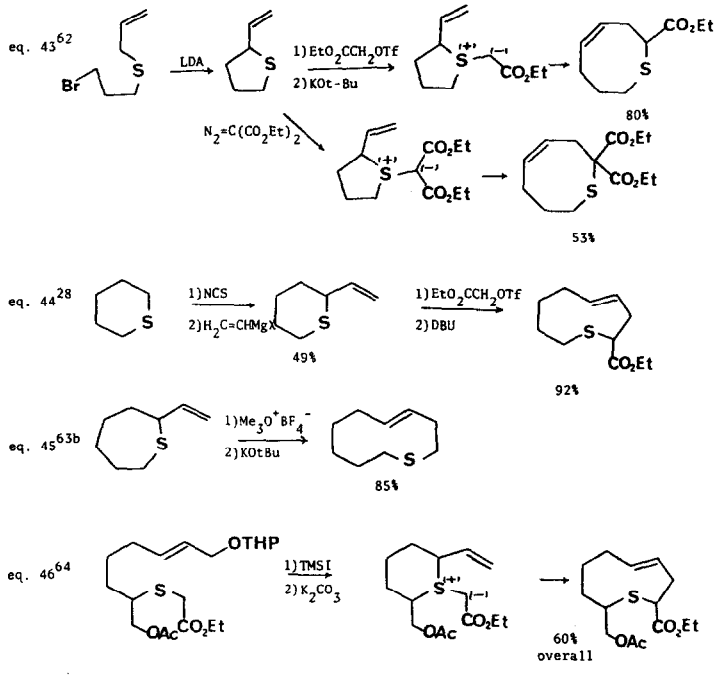


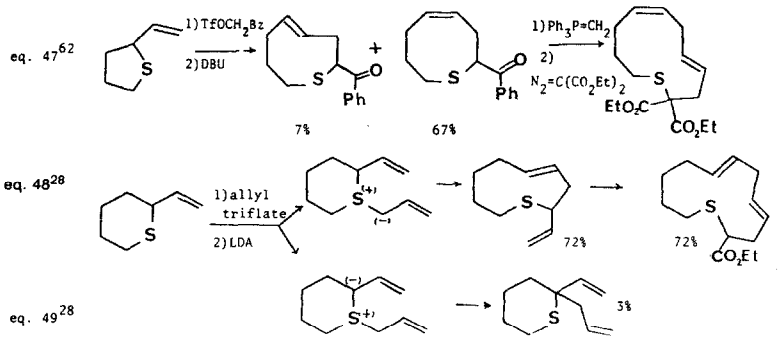
(non-isolable) thioaldehydes XCH = S[54] (X = RCO, RO_2C, Ph_2PO, CN, etc.) are more versatile, and better suited for rapid access to cycloadducts containing relatively fewer appendages.

MEDIUM AND LARGE RING SULFIDES

Cyclic sulfides of 8 or more members can be prepared conveniently using ring expansion methods. Several methods are available, depending on the ring size desired. To prepare 8–10 membered rings, α-vinyl thiolanes, thianes, or thiepanes may be converted to sulfur ylides by an alkylation-deprotonation sequence.[28,62,63] The resulting ylides undergo 2,3-sigmatropic shift at room temperature or below, resulting in ring expansion by three carbons (eqns 43–45). Both stabilized[28,62] and nonstabilized[63] sulfur ylides have been used in the rearrangement step. Stabilized ylide ring expansions are somewhat less susceptible to ylide side reactions such as α',β-fragmentation. In the 8-membered ring case, formation of the Z-olefin is strongly favored with stabilized ylides[62] while nonstabilized ylides afford E,Z-mixtures.[63] The olefin geometry is related to the stereochemistry of sulfonium ylide precursors.

The need for preparing the starting α-vinyl sulfide can be avoided if the desired target is an 8- or 9-membered ring. Intramolecular S-alkylation can be used in these examples to form the usual ylide intermediate for ring expansion (eqn 46) starting from an acyclic sulfide.[64]





Rings of 11 to 17 members have been prepared by repeatable adaptations of the 2,3-sigmatropic shift technique.[28,65] This operation is possible by a stepwise approach[62] (eqn 47), or by using a reagent CH_2=$CHCH_2X$ (X = leaving group) for S-alkylation followed by base-induced rearrangement (eqn 48).[28,65] In the latter case, the immediate product is an α-vinyl sulfide which is ready for further ring expansion by the same method. Success depends on kinetic control in the deprotonation step to ensure formation of the desired exocyclic ylide. Some of the endocyclic ylide isomer is formed even under the best conditions (minimal ylide equilibration by proton transfer) resulting in an alternative 2,3-sigmatropic shift (eqn 49).[28]

SYNTHETIC APPLICATIONS OF CYCLIC SULFIDES

Important synthetic uses of cyclic sulfides include studies where the desired end product retains sulfur in a ring (penicillins, cephalosporins, biotin, gliotoxin etc.) as well as cases where the sulfur is destined for complete removal. Since the most important examples of the first category (penicillins, cephalosporins) have been reviewed extensively, this discussion centers on applications where one or both ring sulfur bonds are ultimately cleaved. Simple applications are arranged according to the method used for C–S cleavage. A later section discusses reductive methods of sulfur removal in the context of complex natural product synthesis.

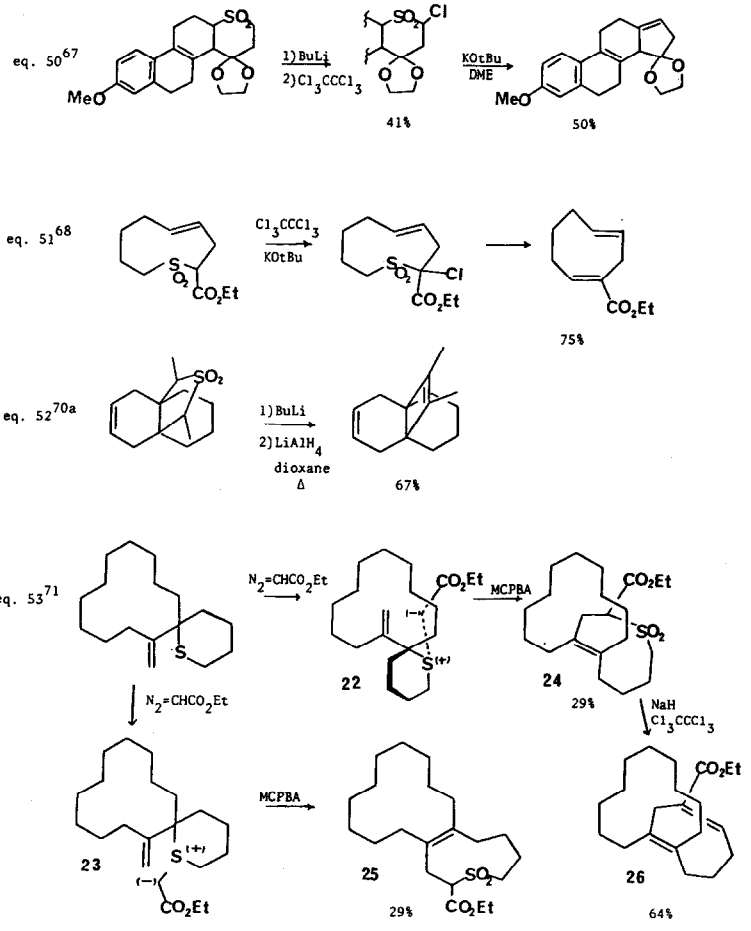
Sulfur-free rings from cyclic sulfides

The classical Ramberg–Bäcklund reaction of α-haloalkyl sulfones remains the most widely used technique for sulfur extrusion in cyclic systems and has been reviewed.[66] In general, two approaches are used to prepare the α-haloalkyl sulfone starting materials. Sulfides can be chlorinated at the α-carbon by positive chlorine donors, and oxidation of the resulting (labile) α-chloroalkylsulfides with m-chloroperbenzoic acid gives the α-chloroalkylsulfone. Alternatively, the sulfone anion may be chlorinated directly with positive halogen reagents. Upon base treatment, the α-chloroalkylsulfones afford alkenes via an unstable episulfone intermediate.[66] Interesting recent examples (eqns 50,[67] 51[68]) indicate the versatility of the method in synthesis of cyclic alkenes. The use of hexachloroethane as the positive chlorine donor is noteworthy because this reagent chlorinates sulfone anions smoothly without risk at other substituents. In the preparation of a derivative of cis, trans-cyclooctadiene (eqn 51) sulfone anion chlorination and Ramberg–Backlund SO_2 extrusion may be performed in a single operation. An alternative one-pot chlorination Ramberg–Bäcklund technique employs KOH/CCl_4.[69]

Alkenes of theoretical interest are commonly prepared by the Ramberg–Bäcklund method. Important results have been achieved in synthesis of propellanes[66,70a,b] 1,4-dimethyl Dewar-benzene,[70b] and other strained molecules.[66,70c] Propellanes and related systems have also been made by a reductive elimination technique (eqn 52[70a]), starting from cyclic sulfones. The mechanism of this method, which employs treatment of a sulfone with butyllithium followed by $LiAlH_4$, is unknown.

A most interesting recent application is in the "betweenanene" series (eqn 53). Reaction of the spiro-fused sulfide **21** with ethyldiazoacetate under conditions of carbenoid generation results in flexible ylide conformers **22** and **23**. Both conformers undergo 2,3-sigmatropic ring expansion to give a mixture of alkenes isolated as the sulfones **24** and **25** after oxidation (MCPBA). Sulfur extrusion via the chloroalkylsulfone converts **24** into the betweenanene **26**.[71]

Another well-established technique for sulfur extrusion is based on the Stevens rearrangement of sulfur ylides. This process is important for the synthesis of cyclophanes (eqns 54, 55). According to the most likely rationale, homolytic cleavage of a benzylic C–S bond in a possible ylide intermediate **27** is



followed by a rapid intramolecular radical recombination step to form **28**. Studies with acyclic Stevens rearrangements show that radical lifetimes are often short compared to diffusion from a solvent cage.[73] Thus, efficient C–C bonding in systems of unusual ring size such as the meta-cyclophane **28** is not viewed as an indication of a concerted (forbidden) process. A second Stevens rearrangement followed by sulfur alkylation and tert-butoxide-induced elimination results in the sulfur-free product (eqn 54).

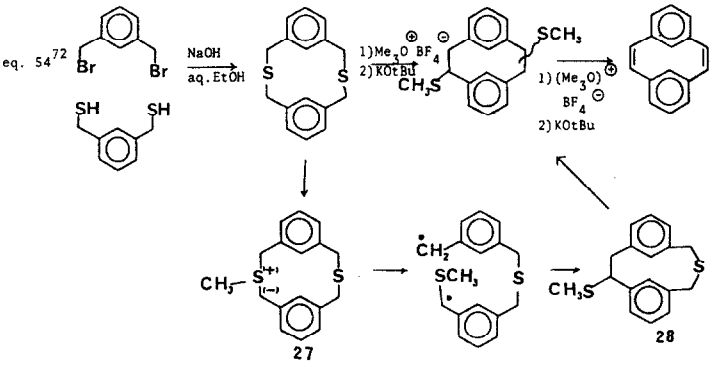
The Stevens sulfur extrusion method has also been used to prepare para-cyclophanes (eqn 55). Depending on bridging ring size, the intermediate ylide **29** may rearrange by the Stevens pathway to **30**, and/or a competing Sommelet–Hauser rearrangement (2,3-shift) to form **31**.[74]

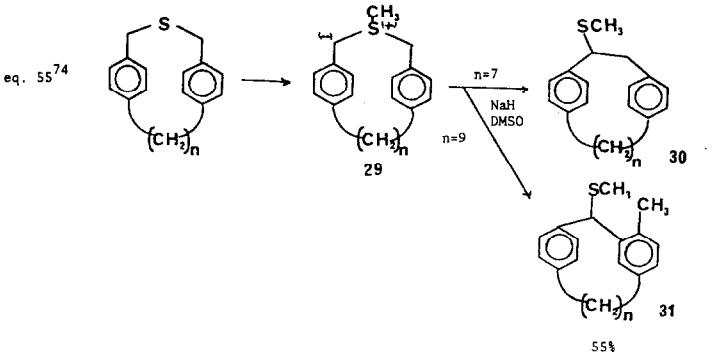
Acceptable yields in the Stevens sulfur extrusion require the presence of a radical stabilizing substituent at the migrating carbon. In virtually all examples of efficient rearrangement involving large rings, this limitation is only satisfied by α-aryl substituents. Sulfur ylides lacking radical stabilizing groups at the α-carbon usually find other intramolecular pathways.[75,76]

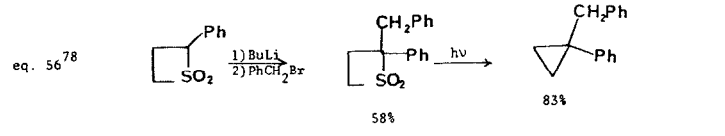
Cyclophanes have been prepared by thermal[77a] or photochemical[77b] SO_2 extrusion from benzylic sulfone precursors. The extrusion of sulfur from a cyclic benzylic sulfide is also known.[77c] Similar photochemical SO_2 extrusion can be used to convert thietane S,S-dioxides into cyclopropanes (eqn 56).[78]

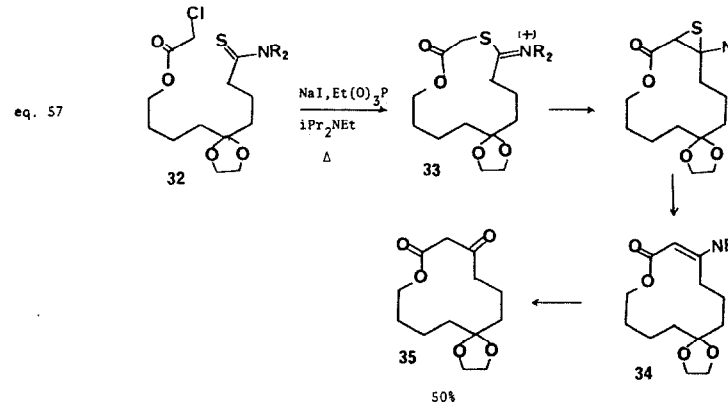
An interesting method for sulfur extrusion has appeared recently[79] using a cyclic analog of the Eschenmoser sulfide contraction technique.[80] In an application to lactone synthesis, (eqn 57), the thioamide **32** is treated with NaI, triethyl phosphite, and diisopropylethylamine under high dilution conditions. A cyclic thioimidate salt **33** is formed *in situ*, and sulfur extrusion occurs via an unstable episulfide intermediate to form the enamino lactone **34**. Hydrolysis of the enamine affords the β-keto lactone **35**, 50%. Lactones of several other ring sizes have been made by similar procedures.[79]

Several other α,α'-sulfur extrusions of primarily mechanistic interest are described. These include thermal or anionic generation of episulfide derivatives,[81] photolysis of S-ylides,[82] Stevens rearrangement of S-ylides,[83] and fragmentation of thietanonium salts by butyllithium via a sulfurane intermediate.[84]









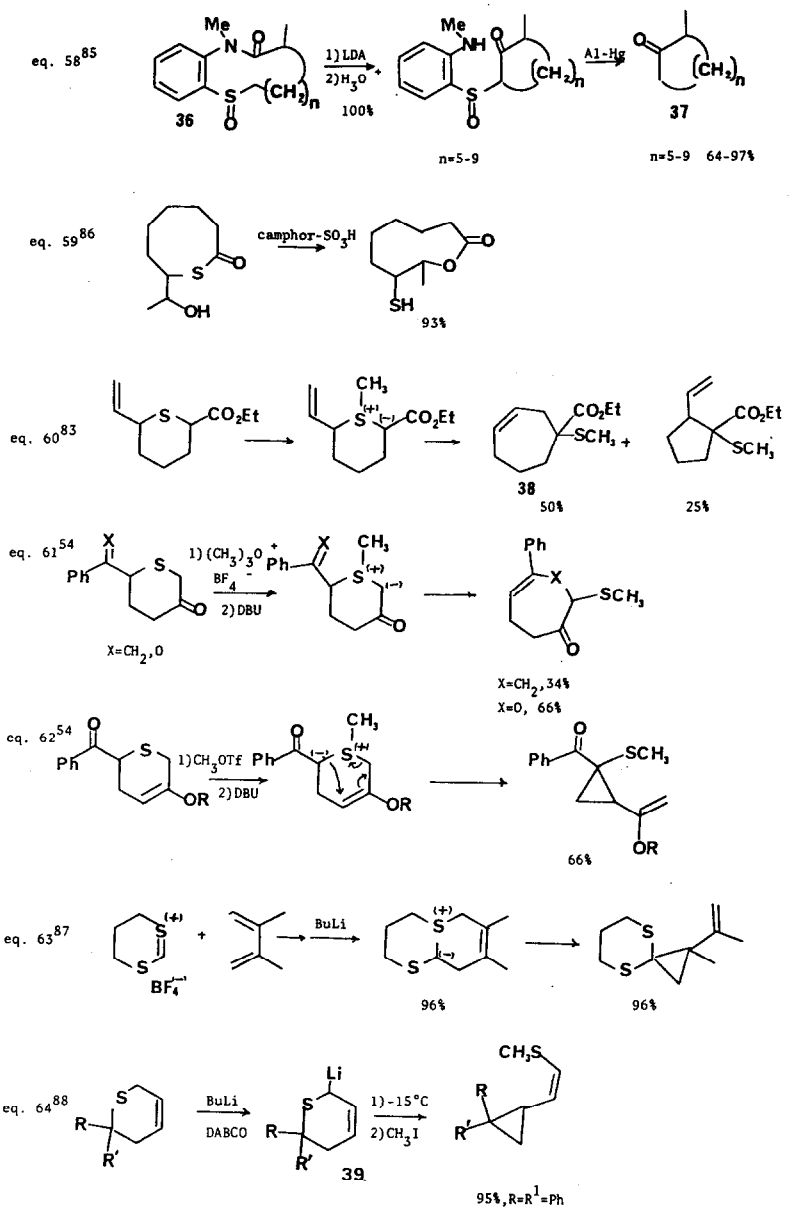
Miscellaneous sulfur bridging reactions; bonding between C_α and a ring substituent

Most examples in this diverse group have interesting potential rather than demonstrated general utility. The bridging reactions remove sulfur from a sulfide ring by cyclic, intramolecular analogs of well-known acyclic sulfur transformations. For example, an internal anionic acylation (eqn 58) of sulfoxide lactam **36** via a bicyclic intermediate affords a carbocyclic product. After desulfurization of the keto sulfoxide with Al–Hg, the 2-methyl cycloalkanones **37** are obtained.[85]

A somewhat different bicyclic intermediate is involved in the lactone synthesis of eqn (59). Acyl transfer from a hydroxyalkyl-substituted thiolactone proceeds to the thermodynamically more stable mercapto lactone.[86]

The replacement of a ring C–S bond by a bridging group can also be achieved using rearrangements which occur via bicyclic transition states (eqns 60–63). All these examples are based on 2,3-sigmatropic

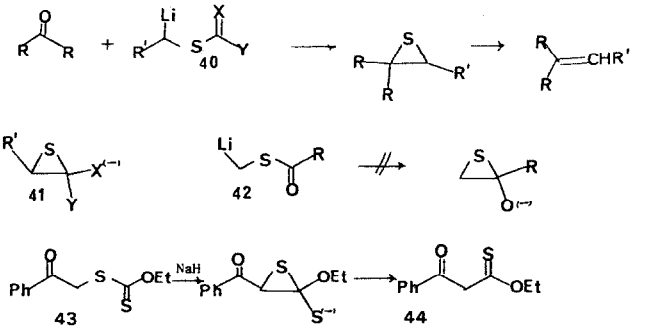
shift of sulfur ylide intermediates. Low yields of 7-membered ring products in eqn (61) are due to the presence of two ylide diastereomers, one of which is unreactive in the 2,3-shift. In the example of eqn (60), the yield of carbocycle **38** is limited by a competing Stevens rearrangement.[83] An 8-membered ring analog of eqn (60) gives a product of Stevens rearrangement in low yield, but no 2,3-shift product has been found.[83] Cyclopropane derivatives can also be obtained using the 2,3-shift method for sulfur bridging (eqns 62,[54] 63[87]). A unique cationic analog of dithioester Diels–Alder addition is employed to prepare the starting sulfonium salt in eqn (63).[87] One mechanistically unrelated example of cyclopropane preparation is included (eqn 64) due to the high yield. The mechanism of this reaction is not known exactly, but a fragmentation-recombination process is indicated by the observation that anion **39** rearranges at $-15°$ if one or both substituents R or R′ = phenyl but not if R = R′ = H.[88]



Conversion of cyclic sulfides into sulfur-free alkenes

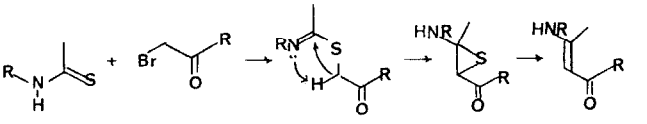
Alkenes from thiirane derivatives. Most examples of the thiirane → olefin conversion are performed without actually isolating the three-membered ring. One example is the Ramberg–Backlund rearrangement where loss of SO_2 is uaually faster than episulfone formation. Other examples include anionic

cyclizations such as the previously discussed condensations of the type:



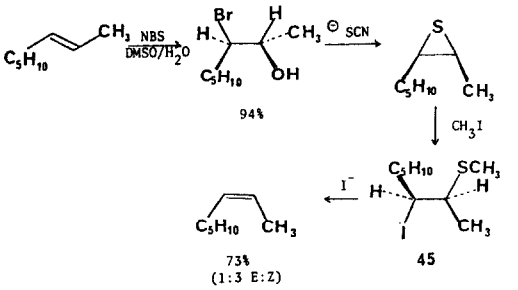
It is interesting that **40** and several related anions condense with carbonyl compounds without competition from intramolecular episulfide formation, **40**→**41**. Even the more reactive dipole-stabilized carbanion **42** prefers to decompose by mechanisms not involving an episulfide.[89] However, the closely related **43** is believed to afford **44** via the episulfide pathway upon treatment with sodium hydride.[90] Also, the Eschenmoser sulfide contraction of thioimidate salts occurs readily by a very similar process (eqn 65)[80] (see also eqn 57).

eq. 65[80]



Episulfides (or the closely related episelenides) are useful as intermediates in an alkene inversion scheme. The sequence of bromohydrin formation and KSCN treatment (eqn 66) affords the episulfide of inverted geometry with respect to the starting alkene. Conversion to inverted alkene occurs upon reaction with methyl iodide, presumably by iodide-induced E2-elimination via iodo sulfide **45**. Other common reagents for thiirane desulfurization to alkenes include trivalent phosphorus compounds,[8,9] alkylithium reagents,[72] zinc/acetic acid,[93] etc. The diversity of desulfurization methods is understandable in view of the number of episulfide derivatives which decompose readily to alkenes: episulfones, episulfoxides,[94] sulfuranes (episulfide + RLi),[92] ylides (episulfide + RCH = N_2/Cu),[95] and sulfilimines (episulfide + oxaziridine).[96]

eq. 66[91]

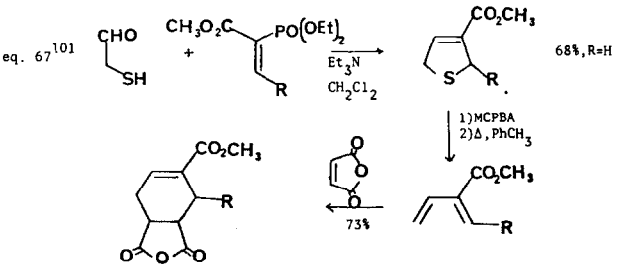


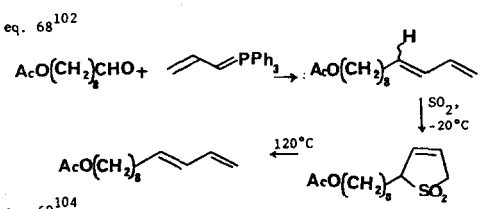
Alkenes from thiolane derivatives

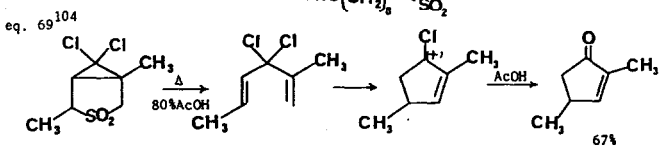
The most important reaction in this group is the concerted thermal (*ca.* 150°) decomposition of 2,5-dihydrothiophene S-dioxides (3-sulfolenes) into conjugated dienes and SO_2.[97] The decomposition may also be induced by $LiAlH_4$[98] or by photolysis,[99] and similar decomposition is observed with the sulfoxide analogs.[99b,100]

Some interesting examples of diene synthesis are illustrated in eqns (67) and (68). The first example (eqn 67) uses the intramolecular Wadsworth-Emmons approach to prepare the 5-membered ring. In eqn (68), the formation and decomposition of a 3-sulfolene is used to convert a cis, trans diene mixture into the pure trans diene, the sex phereomone of the female red bollworm moth. Either diene can give only

one and the same 3-sulfolene, and disrotatory cycloreversion with the alkyl group turning away from the ring results exclusively in the E isomer. Similar SO_2 extrusion is observed with carbene adducts of 3-sulfolenes, resulting in 1,4-dienes.[103] An interesting application of this process employs dichloro carbene adducts of 3-sulfolenes as precursors of cyclopentenones under acidic conditions (eqn 69).[104]

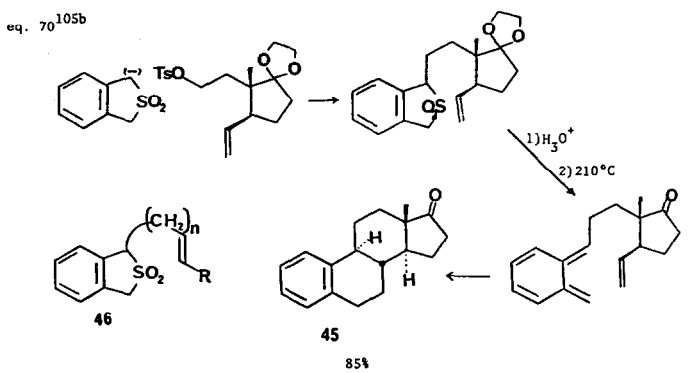


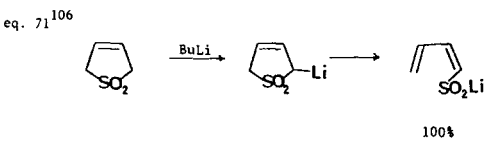




Recent work has focused on the use of 3,4-benzosulfolenes as precursors of o-quinodimethanes, reactive intermediates which are of interest for theoretical and synthetic reasons.[105] An application to synthesis of an estratrienone derivative (eqn 70) employs the alkylation of a benzosulfolene anion to connect steroid ring D, functionalized with a simple vinyl group as the dienophile. Upon thermolysis (210°), an intermediate o-quinomethane affords the steroid ring system (**45**, 85%).[105b] Several tricyclic molecules have been prepared by a similar technique using alkylated 3,4-benzosulfolenes of general structure **46**.[105] Analogous alkylation of the parent 3-sulfolene anion is not successful due to electrocyclic ring opening (eqn 71).[106]

If 3,4-benzosulfolenes are heated in the absence of dienophiles, it is possible to isolate benzocyclobutenes or their transformation products.[107] In one special case, the o-quinomethane from appears to be more stable (radialene).[108]





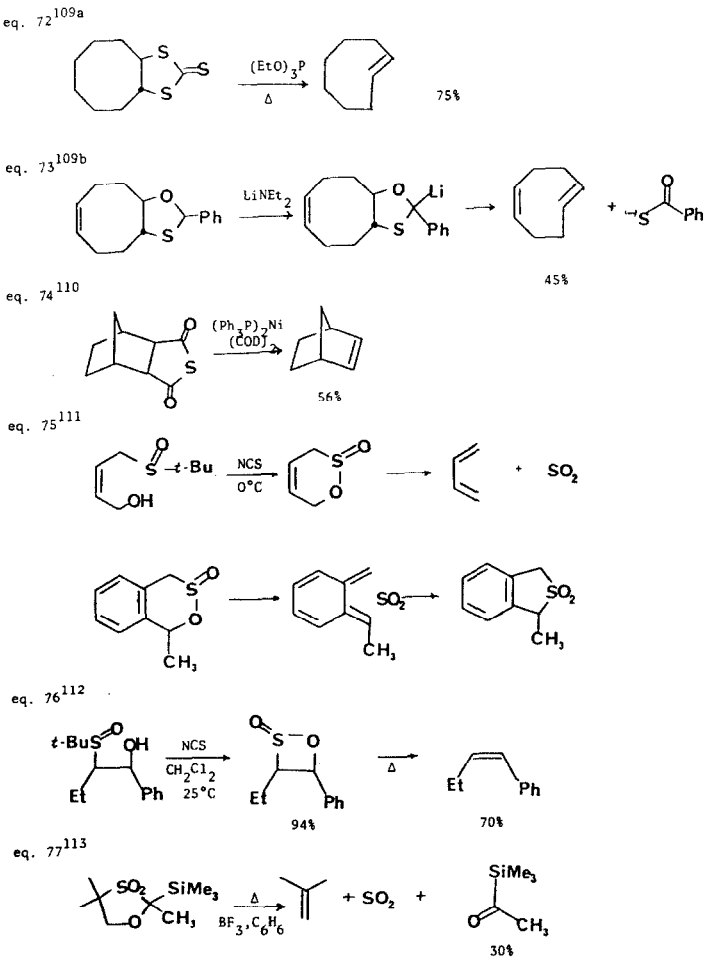
Miscellaneous alkene-forming cycloreversion reactions involving sulfur heterocycles

Typical reactions in this group are mechanistically interesting, but their synthetic utility has not been explored extensively. Useful alkene syntheses have been demonstrated from trithiocarbonates (eqn 72, heating with trialkylphosphites),[109a] from 2-phenyl-1,3-oxathiolanes by anionic cycloreversion (eqn 73)[109b] and from thiolanhydride, (eqn 74), heating with $Ni(Ph_3P)_2(COD)_2$.[110]

Miscellaneous cycloreversions of O,S-heterocycles are summarized in eqn (75)–(77). Related alkene-forming reactions of 1,3-dithiolanes will be discussed in the next section because their applications focus on the preparation of unusual sulfur fragments.

Sulfur-containing products by cycloreversion. As already mentioned, 2-lithio-2-phenyl-1,3-oxathiolanes decompose to alkenes and $Li^+C_6H_5COS^-$. Similar reactions occur with 2-aryl or 2-alkylthio-1,3-dithiolanes.[113,114] In the former case (eqn 78), NaH/DMF conditions are used for the cycloreversion step, resulting in modest yields of dithiobenzoate anion.

More effective anion-stabilizing groups at dithiolane C-2 tend to slow down the cycloreversion process. The ester enolate **47** is stable at −78° and can be trapped by acylation (eqn 79). Decomposition of **47** does occur at 20°, but a complex mixture is obtained. On the other hand, the analogous



2-acyl-1,3-dithiolanium ylides **48** undergo cycloreversion at 0° to afford α-oxo dithioesters.[55] Due to the high reactivity of the latter, the reaction is performed in the presence of 1,3-dienes which trap the thiocarbonyl product by [2 + 4]cycloaddition (eqn 79).

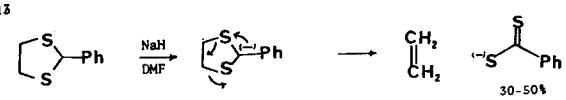
Treatment of simple 2-alkyl-1,3-dithiolanes with butyllithium results in an interesting variation of the cycloreversion process. Products are formed via the 4-lithio derivative (eqn 80), rather than from the intuitively expected 2-lithio-2 alkyl-1,3-dithiolane, and the initial reaction affords a thioaldehyde. Addition of butyllithium results in a mercaptan as the major product. Starting with 2,2-dialkyl-1,3-dithiolanes, the butyllithium-induced cycloreversion leads to a thioketone. Rapid reduction by butyl-

lithium (rather than addition) takes place, and a simple conversion of thioketals into secondary mercaptans is the result.[115]

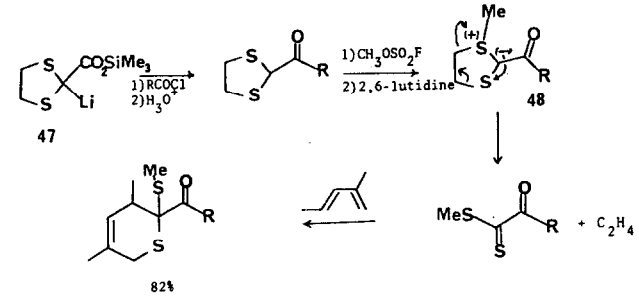
Several cycloreversions of unknown synthetic potential are summarized in eqns (81)–(84). Ylide intermediates are generated by thermal [3 + 2]cycloaddition in eqns (81) and (82).[116,117] An alternative [3 + 2]cycloreversion then takes place, resulting in ethylene and a stable sulfur heterocycle. There is good precedent for the trithiocarbonate cycloaddition of eqn (81) in the conversion of dithiocarboxylates into 5-membered ring products upon reactions with electron deficient alkynes.[118] Cycloreversion of thiolanium ylides generated from thiolanium salt with base is also known,[76] analogous to the last step in eqn (82).

In eqn (83), the base-induced version of cycloreversion is used to generate thioynolate **49**. This unusual molecule is trapped by reaction with amines to give thioamides via a thioketene intermediate.

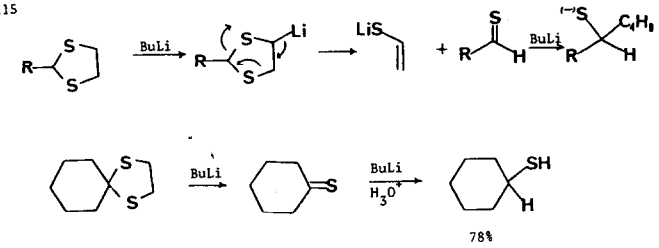
eq. 78[113]



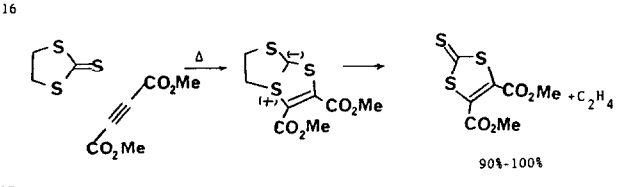
eq. 79[55]



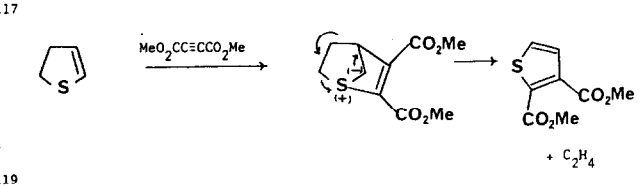
eq. 80[115]



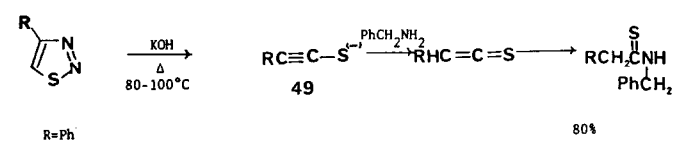
eq. 81[116]



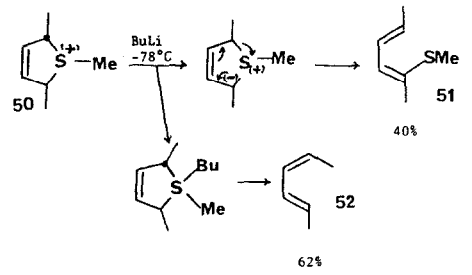
eq. 82[117]



eq. 83[119]



eq. 84[120a]



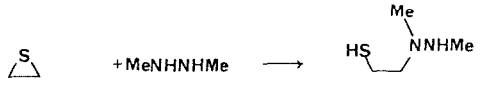
Two different concerted decomposition pathways are observed when **50** (eqn 84) is treated with butyllithium. Formation of **51** occurs via α-deprotonation and electrocyclic ylide rearrangement, while **52** is derived from the sulfurane.[120a] A benzo analog of **50** behaves similarly, resulting in generation of o-quinomethane intermediates.[120b]

Cyclic sulfides as alkylating agents

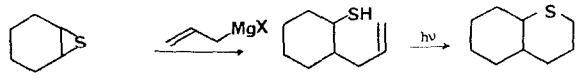
Nucleophilic attack at the α-carbon of strained cyclic sulfides or cyclic sulfonium salts can be used to prepare sulfur-substituted acyclic molecules. Thiiranes are sufficiently reactive toward heteroatom or carbon nucleophiles to afford products of ring cleavage without prior S-alkylation. Numerous examples of thiirane cleavage by amines are known, as illustrated for preparation of a 2-mercaptoethyl hydrazine (eqn 85[121]). Oxygen nucleophiles also cleave thiiranes.[122] Since the resulting thiols may react further with the thiirane, careful experimentation is necessary to avoid polymerization.

Carbon nucleophiles may attack thiiranes at sulfur or at carbon. Sulfur attack is observed with alkyllithium reagents and results in alkenes as mentioned earlier. On the other hand, Grignard reagents react primarily at carbon at give mercaptan products. Use of an unsaturated Grignard reagent allows preparation of cyclic sulfides via the free radical cyclization of an unsaturated mercaptan intermediate (eqn 86).[123] The dianion of ethyl acetoacetate also attacks thiiranes at the α-carbon.[124] In this case, the initially formed mercaptan cyclizes to give a 5-membered thioenol ether which can be aromatized to the thiophen (eqn 87).

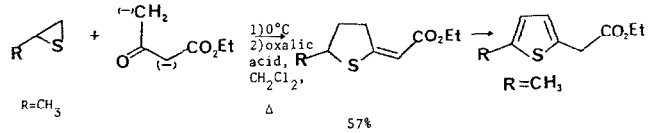
eq. 85[121]



eq. 86[123]

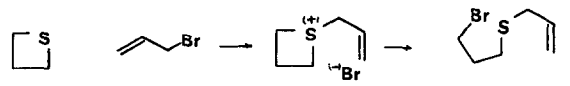


eq. 87[124b]

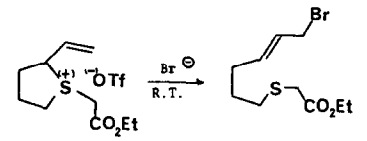


In larger rings, sulfonium salts may be used as alkylating agents. Thietanonium salts are highly reactive in this regard, and can only be isolated in the absence of nucleophiles.[125] Thus, treatment of thietane with allyl bromide affords an acyclic sulfide rather than a thietanonium bromide (eqn 88). In general, sulfonium halides derived from saturated thianes or thiolanes are stable, but small changes in substitution or reaction conditions may cause formation of the acyclic haloalkyl sulfide (eqn 89). A remarkable application of a bicyclic sulfonium salt for carbon bond formation has been reported in a biotin related synthesis (eqn 90).[126]

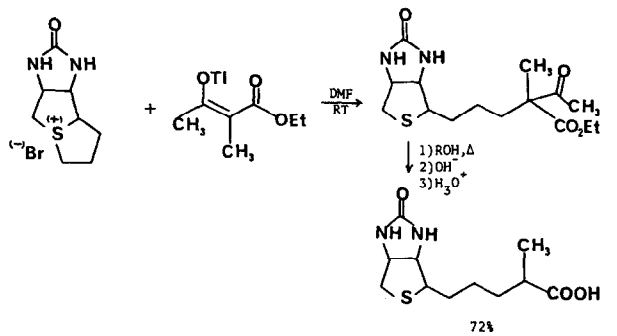
eq. 88[62]



eq. 89[62]



eq. 90[126]



Sulfur-containing rings from cyclic sulfide precursors

Natural products. With the exception of penicillin and cephalosporin derivatives, few naturally occurring sulfur heterocycles have been prepared by methods which rely upon the synthetic versatility of sulfur rings. More often, the sulfur is introduced near the end of a synthetic sequence. Examples from biotin synthesis where sulfur plays a more important role have already been noted (eqns 18 and 90). Another important application is described in eqn (91) where the biotin side chain is introduced by a stereoselective sulfoxide anion alkylation. Carbon bond formation takes place from the endo face of the exo-sulfoxide **53**. This remarkable selectivity (exo-bonding should be less hindered) was anticipated from other alkylation reactions involving 6-membered cyclic sulfoxide anions, but the mechanistic details are not clear.[127]

Cyclic thioacetals serve an important function in the synthesis of 3,6-epidithiapiperazine-2,5-diones such as gliotoxin and sporidesmin A (eqn 92).[128] In this case, two mercapto groups are protected through several synthetic steps by the acetal. Then, an unusual oxidative transformation is used to introduce the sensitive disulfide linkage of the natural products. The thioacetal is first converted into a monosulfoxide (**54**, assumes a single regioisomer for simplicity). Treatment with perchloric acid converts **54** into gliotoxin **56**, a reaction which may be rationalized via intial cleavage to a sulfenic acid derivative **55**.

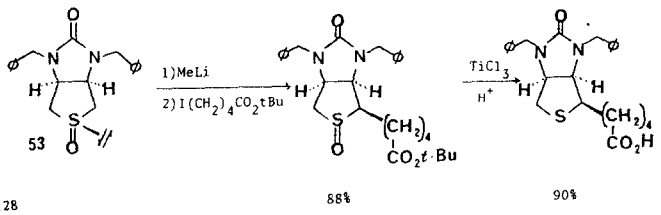
Miscellaneous S-heterocycles. The acid catalyzed rearrangement of 1,3-dithiolane 1-oxides takes an alternative course compared to the related gliotoxin example if the parent carbonyl compound is an enolizable ketone. Cleavage to a sulfenic acid followed cyclization affords a dihydro-1,4-dithiin derivative (eqn 93).[129] Similar reactions are observed in other heterocyclic systems,[130] as well as in the penicillin–cephalosporin conversion.

Other reactions which allow the synthesis of unusual cyclic sulfides have already been summarized under the category of 2,3-sigmatropic ring expansions (eqns 43–49). Related rearrangements of mechanistic interest allow a net ring contraction (eqn 94)[131] or a net 4-carbon ring expansion of unsaturated thioketals (eqn 95).[132]

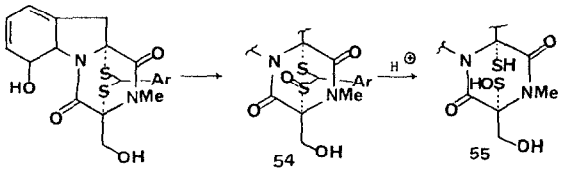
Applications in natural product synthesis with reductive desulfurization. Conversion of cyclic C–S bonds into C–H bonds is possible with a variety of nickel reagents (e.g. Raney Ni, eqn 96;[133] nickel boride,[134] eqn 97;[135] bis(1,5-cyclooctadiene)nickel + $LiAlH_4$, eqn 98).[136] Dissolving metal reduction can be used to cleave activated C–S bonds (eqn 99)[137] or to induce 1,2-reductive elimination if a β-leaving group is available (eqn 100). These simple examples illustrate representative methods for conversion of cyclic sulfides into sulfur-free reduction products.

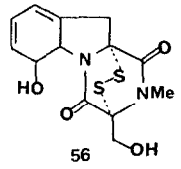
In the context of natural product synthesis, cyclic sulfides have been used primarily to solve problems of geometry or regiochemistry. For example, Ra–Ni desulfurization of a bicyclic thiolane (eqn 101) affords a substituted cyclohexane derivative of defined stereochemistry.[139] Control of trisubstituted

eq. 91[127]

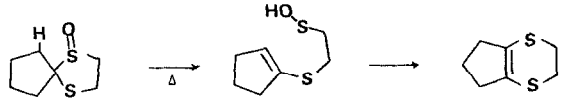


eq. 92[128]

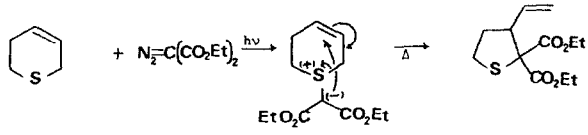




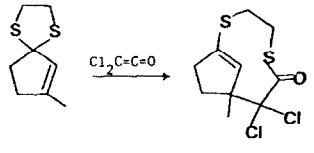
eq. 93[129]



eq. 94[131]



eq. 95[132]

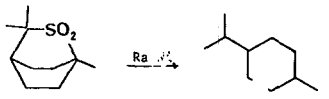


olefin geometry is achieved in the interesting juvenile hormone approach, illustrated by eqn (102). In this series of experiments, a cyclic allylic sulfide anion is used to link repeating alkene units. Cleavage of an allylic C–S bond by Li/$EtNH_2$ followed by reductive desulfurization of the remaining C–S bonds with Ra–Ni gives the juvenile hormone precursor **57**.[140]

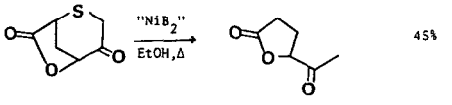
An application of ring expansion techniques for synthesis of a naturally occurring decanolide is described in eqn (103).[141] A 9-membered cyclic sulfide is assembled from acyclic materials by intramolecular S-alkylation and 2,3-sigmatropic shift. After conversion to the thiolactone **58**, S–O acyl transfer occurs to give the decanolide ring system. Reductive desulfurization of the thiol **59** with Bu_3SnH completes the synthesis of phoracantholide J. A similar ring expansion sequence via a bicyclic ylide intermediate (eqn 104) affords a sulfur-bridged cycloundecenone **60**, a model compound for cytochalasin D synthesis.[142] The 11-membered ring corresponds to the natural product in location of the trans olefin, acetoxy, and carbonyl substituents.

The most impressive application of cyclic sulfides in natural product synthesis to date is in the Woodward erythromycin route (eqn 105).[143] Here, the sulfur intermediates satisfy key strategic and

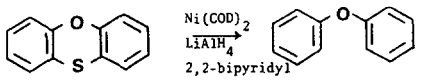
eq. 96[133]



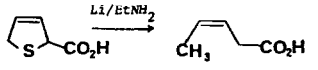
eq. 97[135]



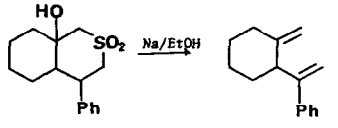
eq. 98[136]



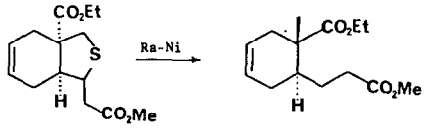
eq. 99[137]



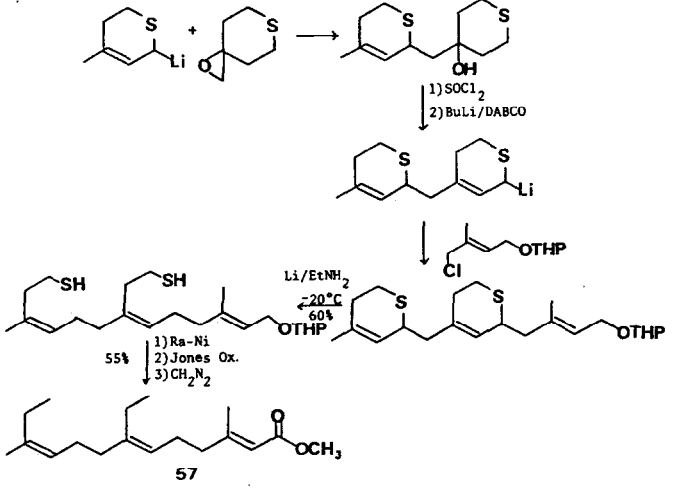
eq. 100[138]



eq. 101[139]



eq. 102[140a]



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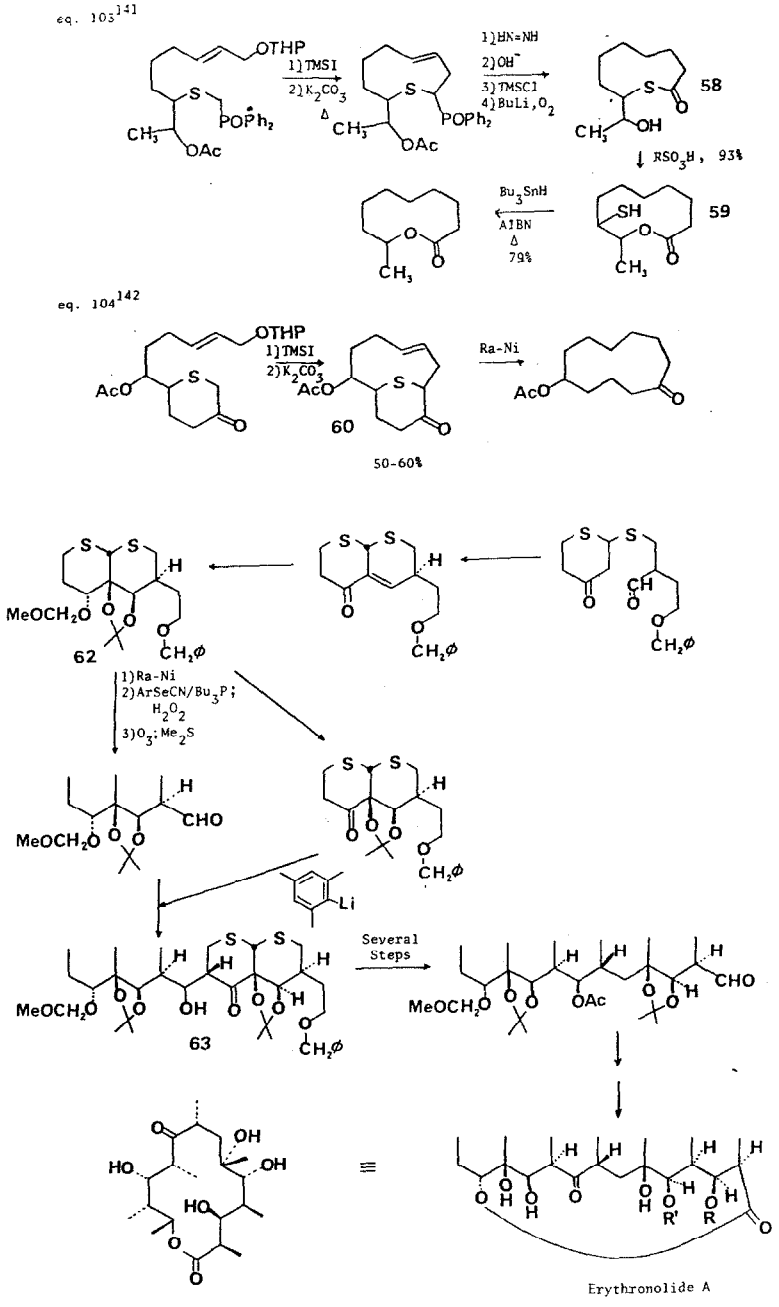
stereochemical requirements. Most noteworthy is the use of intermediate **62** for conversion to two different segments of the erythronolide ring. Desulfurization of **63** with Ra–Ni sets the stage for cyclization to the macrolide.



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