α-Sulfenylated Carbonyl Compounds in Organic Synthesis

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Contents

I. Introduction

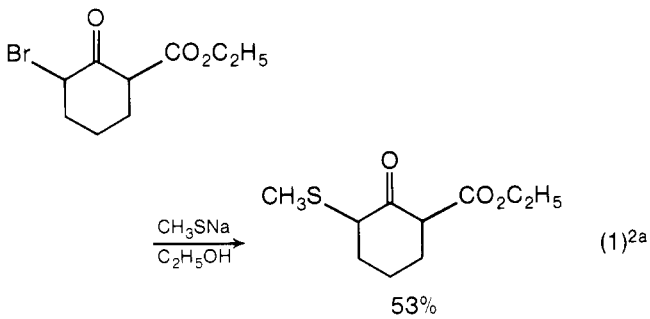
Although organosulfur chemistry can be traced back to the very beginning of organic chemistry, the versatility of sulfur continues to lead to fascinating new chemistry. The existence of so many valence states of sulfur has generated selective and novel ways to effect oxidation, dehydration, and carbon–carbon bond formation. The ability of sulfur to stabilize positive or negative charges on adjacent carbon has been especially important in the development of new ways to form carbon–carbon bonds. These properties continue to evolve new reactions and sequences which facilitate the design of the total synthesis of complex organic molecules.

Recent methods that allow introduction of a sulfur substituent *alpha* to a carbonyl group have shown particular promise. As the desire to increase efficiency and chemoselectivity in organic synthesis grows, this approach becomes increasingly attractive. Adjustment of oxidation level and formation of carbon–carbon bonds are particularly noteworthy. Sulfides, sulfoxides, and sulfones all play a role. In this account, the utility of such intermediates in organic synthetic procedures will be discussed.

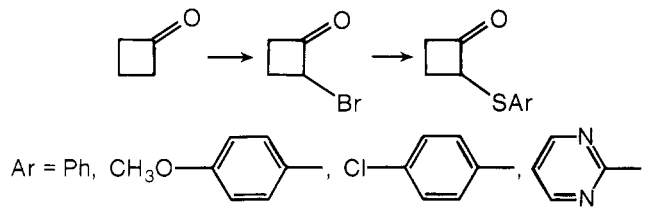
II. Preparation

A. β-Keto Sulfides

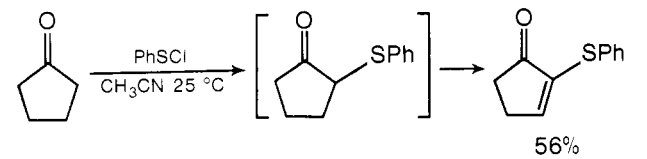
The classic approach to the introduction of sulfur α to a carbonyl groups involves the S_N2 displacement of a halogen by a thiolate (e.g., eq 1).[1] The utility of this approach depends upon the availability of regiodefined α-halo carbonyl compounds. If such compounds are readily available, it served as the best large-scale method. Thus, whereas for substituted cyclobutanones, direct sulfenylation methods are preferred, with cyclobutanone itself bromination displacement was preferred.[3]



(1)[2a]

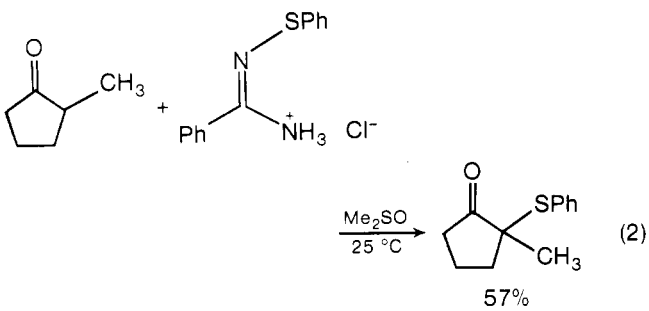


For most more complex cases, direct sulfenylation methods are preferred. The direct reaction of ketones with aryl thiocyanate,[4a] arenesulfenyl acetate,[4b] aryl thiotoluenesulfonates,[4c] and arenesulfenyl chlorides[4d–f] are known; nevertheless, these reactions have not found preparative use. One of the problems stems from the stability of the initial β-keto sulfides to the reaction conditions. For example, treatment of cyclopentanone with benzenesulfenyl chloride led to 2-phenylthiocyclopentenone



without isolation of any of the presumed intermediate 2-phenylthiocyclopentanone.[5]

Sulfenamide derivatives convert ketones to their β-keto sulfides in good yields (eq 2).[6] Furthermore, bissulfenylation can



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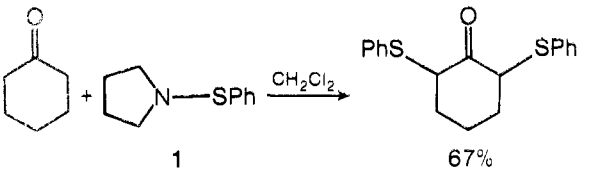
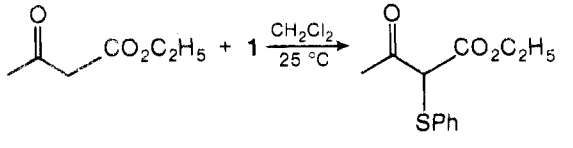


(3)

also be observed (eq 3).[6] The sulfenamides like **1** and thioimides like **2** are particularly good at sulfenylating active methylene compounds like 1,3-diketones, β-keto esters, and malononitriles (cf. eq 4 and 5).



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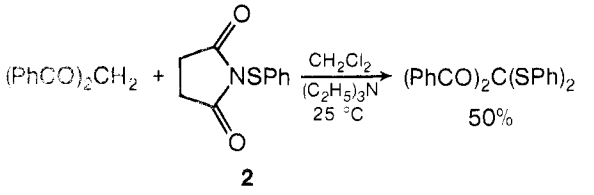
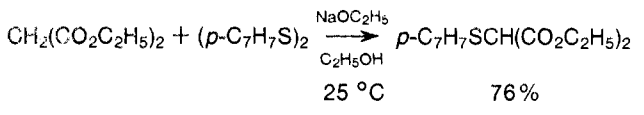
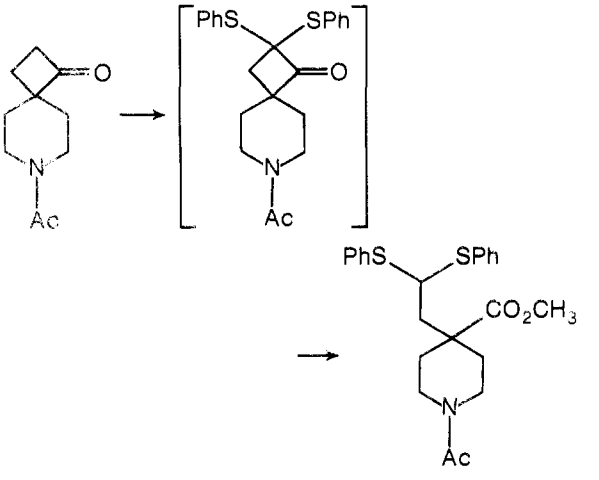


(5)

The commercial availability of disulfides makes them preferred reagents. Their potential for sulfenylating carbonyl partners under reversible conditions for formation of enolates has limited success. Active methylene compounds like diethyl



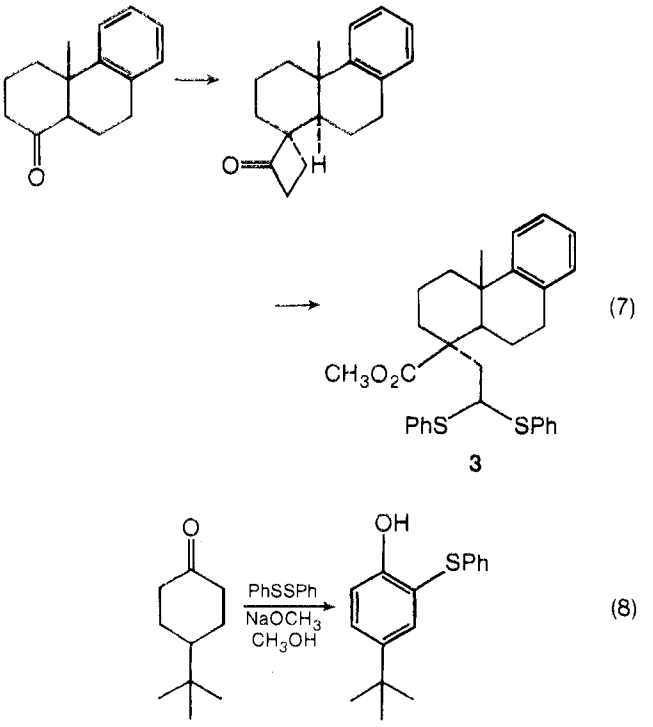
malonate lead to the desired sulfenylated products,[7] but simple ketones generally lead to mixtures of mono- and bissulfenylation products.[8a] With an excess of disulfide cyclobutanones undergo a useful sulfenylation and in situ ring cleavage (eq 6).[8b] This has



(6)

served as a novel way to achieve stereocontrolled geminal alkylation since the initial spiroannelation of the cyclobutanone is highly stereoselective[9] as illustrated in the synthesis of an intermediate toward deoxypodocarpic acid **3** (see eq 7).[10] With cyclohexanones, a sulfenylative dehydrogenation to an *o*-hydroxydiphenyl sulfide is observed in good yields (eq 8) in what appears to be a general reaction.[8a]

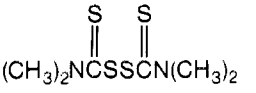
For regiospecific monosulfenylation, formation of the enolate is preferable.[11,12] Direct addition of diphenyl disulfide to solutions



(7)

(8)

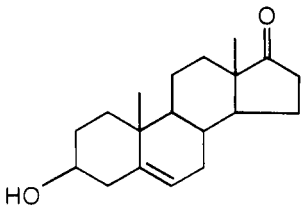
of regiospecifically generated enolates (direct quench) or addition of the enolate solution to a solution of diphenyl disulfide (inverse quench) leads to high yields of the desired products (see Table I). Because of the acidity of the initial product relative to starting ketone, 2 mol of base per mole of ketone is normally employed. Utilizing a more reactive sulfenylating agent, phenyl benzenethiosulfonate (readily available by oxidation of diphenyl disulfide with hydrogen peroxide in acetic acid and an inverse quench), a ketone to base ratio of 1:1 suffices (Table I, entries 2b, 3, 5b, 11, 13). The ratio of the disulfide to enolate varies from 1:1 to 2:1 depending upon the reactivity of the system. With simple ketones whose enolates are fairly reactive, a 1:1 ratio is satisfactory (Table I, entries 2a, 4, 6, 7, and 8); with less reactive enolates a 2:1 ratio is preferred. Other sulfenylating agents like the thiuram disulfide **4** and sulfenyl chlorides also are successful,[12] but dimethyl disulfide does not react under these conditions.[11,12]



4

Increasing the reactivity of the enolate by addition of HMPA is sometimes required (Table I, entries 5, 9, 10, 12, 13, 14, and 15). Under these conditions even dimethyl disulfide sulfenylates ketone enolates (Table I, entries 1a, 6a, and 9a). The regiochemistry of the sulfenylation reflects the regiochemistry of enolate formation (Table I, entries 2, 3, 4, 9, and 15). With 2-methylcyclohexanone maximum regioselectivity required the use of phenyl benzenethiosulfonate. The direct sulfenylation of androst-5-en-3β-ol-17-one (**8**) without protection of the hydroxyl group illustrates the chemoselectivity of the process.[13] Conjugate addition–sulfenylation (eq 9)[18a] and conjugate reduction–sulfenylation[18b] promise to be exciting approaches to regiocontrolled elaboration of enones.

Sulfenylation of aldehydes is best performed via the corresponding metalloenamines (eq 10).[19] Such indirect methods via enamines, metalloenamines, enol silyl ethers, etc., have also been applied to ketones. Reactions of enamines[6,20] and enol silyl ethers[21] generally require more reactive sulfenylating agents such as sulfenyl chlorides or *N*-thioimides (cf. **2**). Metalloenamines are nicely sulfenylated with dissulfides. Use of the hydroxymethylene derivative of ketones and thiosulfonates has



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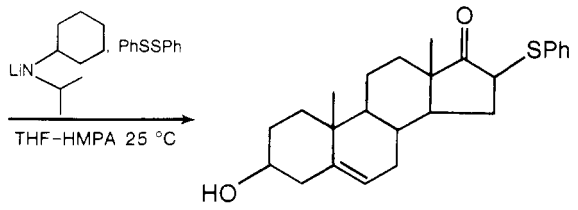
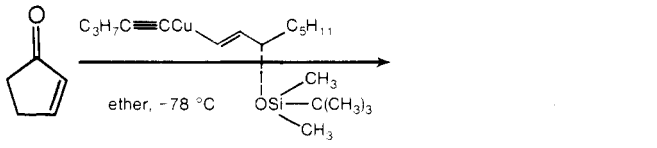
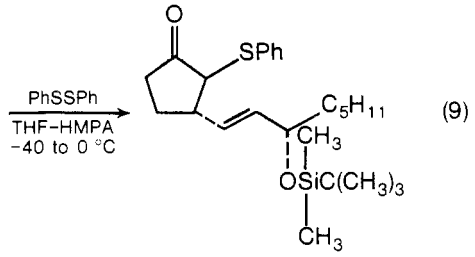


88%

9

K:B:S = 1:2:1





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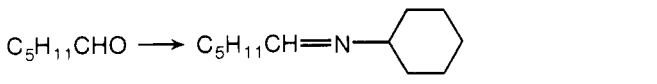
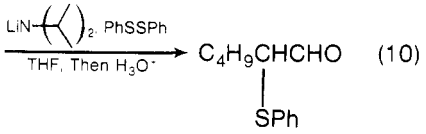
38%





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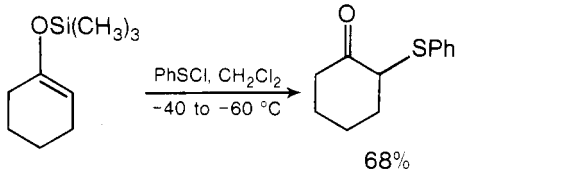
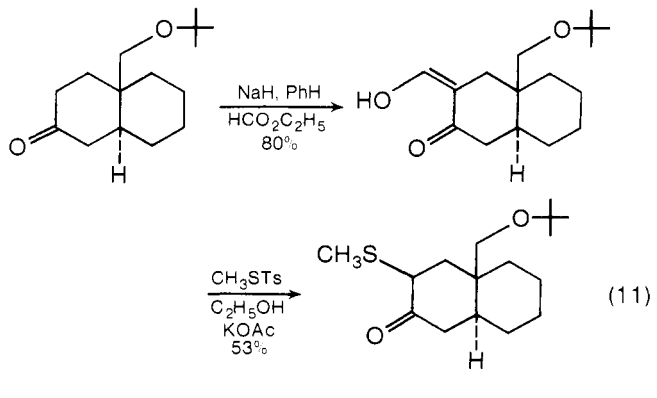


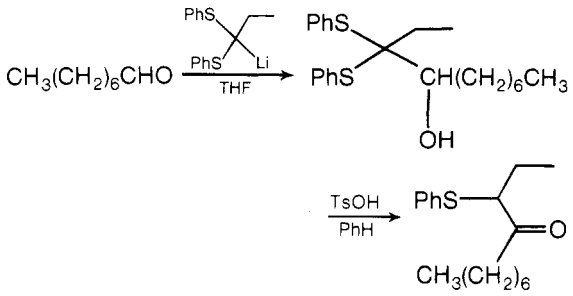
68%

frequently been used[22,23] (eq 11[24]). In these cases, the regiochemistry is determined by the formylation step.



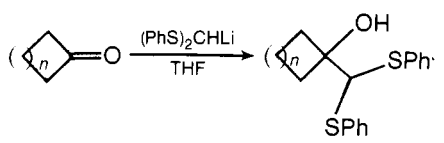
(11)

Elaboration of simple β-keto sulfides forms a major approach to more complex ones (see section III). Several additional indirect methods have also evolved. The adducts of the anion of phenyl thioacetals and aldehydes (eq 12)[25] or ketones (eq 13)[26] rearrange under acid or copper salt catalysis respectively to β-keto sulfides. A novel insertion reaction evolves when adducts like **10** are treated with 2 equiv of *n*-butyllithium or lithium dialkylamides which leads, via a presumed carbene intermediate, to a β-keto sulfide (eq 14).[27]



(12)

58%



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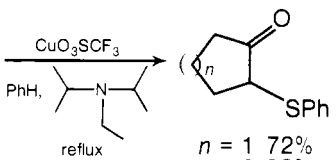
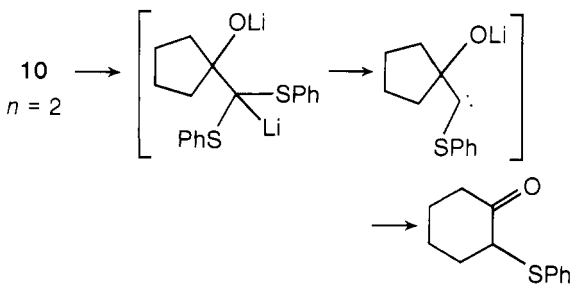


(13)

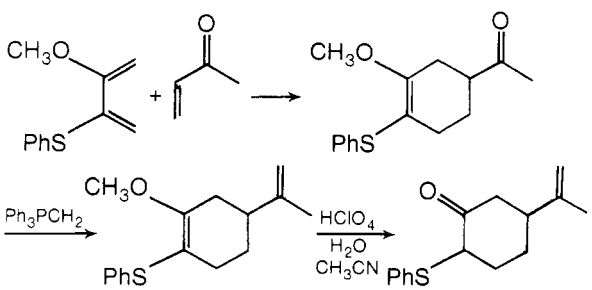
n = 1 72%
2 83%
3 58%



(14)

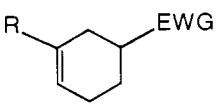
73%

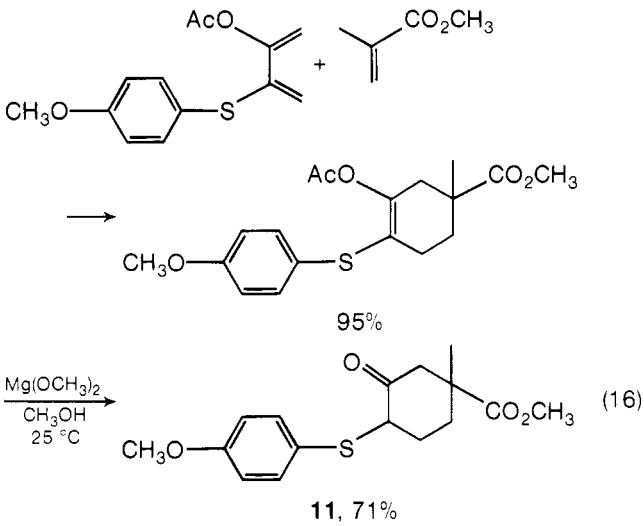
Cycloadditions of 2-methoxy- or 2-acetoxy-3-arylthiobutadienes with dienophiles provide access to masked β-keto sulfides (eq 15[3a] and 16[3b]). A striking feature of this approach is



(15)

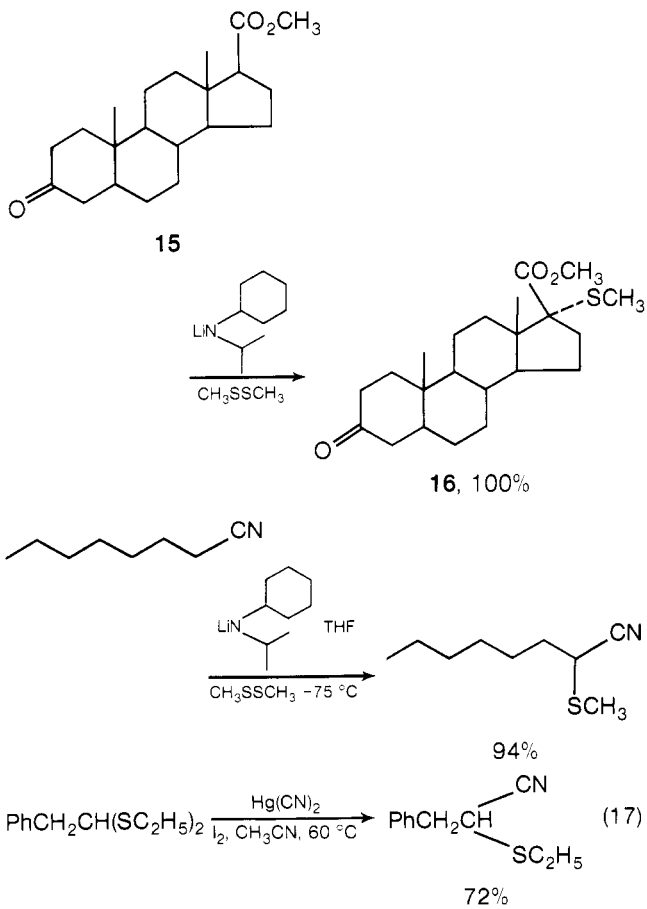
the regiochemical control exercised by sulfur which allows orientation of substituents not available in standard Diels–Alder reactions after desulfurization.



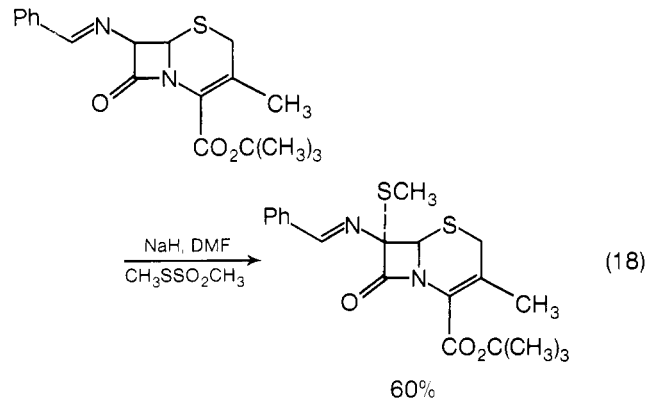


B. Sulfides Related to Carboxylic Acid Derivatives

Carboxylic acid derivatives can be sulfenylated by methods very similar to those employed for ketones and aldehydes. The higher reactivity of the anions derived from carboxylates, esters, and amides normally leads to smooth sulfenylation with disulfides (Table II).[11,12] With acids, most difficulties arise in the ability to generate the dianions required.[28] For this purpose, THF–HMPA is mainly employed. For esters, the stability of the enolate can be limiting. While methyl esters are quite successful in many cases, ethyl esters generally give higher yields. *tert*-Butyl and trimethylsilyl (Table II, entry 7) esters are excellent substrates. The failure of ketone enolates to react with dimethyl disulfide in the absence of HMPA led to a chemospecific sulfenylation of **15** to give **16** via the bis-enolate.[11]

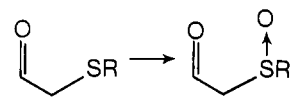


Lactams require inverse addition of the anion to the disulfide to minimize polysulfenylation (Table II, entries 14 and 15).[32] A similar observation was recorded for octanonitrile.[33] An interesting synthesis of sulfenylated nitriles involved replacement of one thioether of a thioacetal or thioketal by cyanide (eq 17).[34] The sulfenylation of cephalosporin derivatives as a route to the commercially important 7-methoxycephalosporins (eq 18) has been reported.[35]

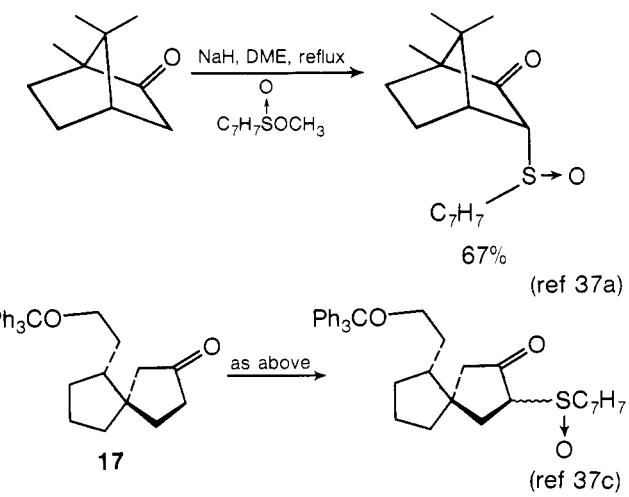


C. β-Keto Sulfoxides and β-Keto Sulfones

The main approach to β-keto sulfoxides involves the oxidation of the sulfides to their sulfoxides.[11] The facility of this transformation is reflected by the plethora of reagents that effect the transformation among which are hydrogen peroxide, *tert*-butyl

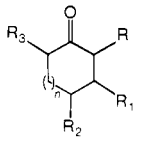
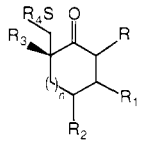
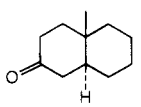
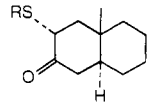
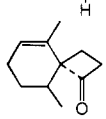
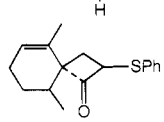
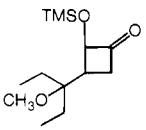
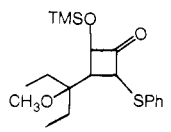
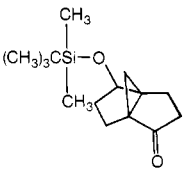
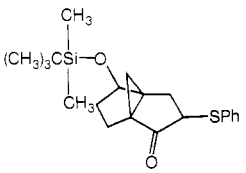
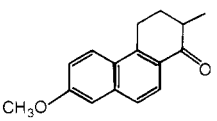
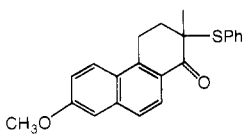
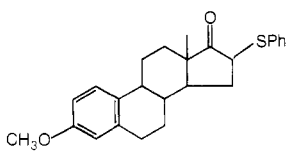
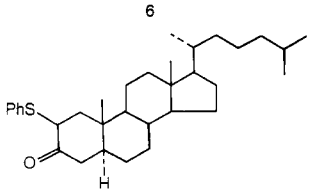
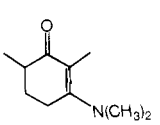
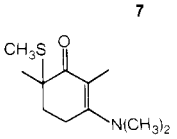


hydroperoxide, ozone, dinitrogen tetroxide, nitric acid, iodosobenzene, sodium metaperiodate, *tert*-butyl hypochlorite, chromic acid, *N*-chlorobenzotriazole, tri-*n*-butylstannic oxide–bromine, other positive halogenating agents, *m*-chloroperbenzoic acid, other peracids, and *N*-methylmorpholine *N*-oxide in the presence of ruthenium catalysts.[36] The direct sulfinylation of ketones offers an attractive approach.[37] In the case of cyclopentanone **17**, this approach offered the only solution to high regioselectivity in functionalizing the unsymmetrical ketone.[37c]



Acylation of sulfoxide stabilized anions such as the sodium or lithium salt of dimethyl sulfoxide with esters (cf. **18** → **19**), acid anhydrides, or acid chlorides provides the β-keto sulfoxides directly.[38] Alternatively, addition of such organolithium species to aldehydes or ketones followed by oxidation[40] or strong base treatment[41] also leads to the β-keto sulfoxides.

TABLE I. Sulfenylation of Ketones

Entry	Ketone	Disulfide	K:B:S[d]	Solvent	Product	% yield	Ref
							
1	n = 1: R = R_1 = R_2 = R_3 = H	(a) CH_3SSCH_3	1:2:2	THF–HMPA	R_4 = CH_3	75	11
		(b) PhSSPh	1:2:2	THF–HMPA	R_4 = Ph	83	11, 12
2	n = 1: R = CH_3; R_1 = R_2 = R_3 = H	(a) PhSSPh	1:1:1	THF	R_4 = Ph[a]	87	11
		(b) $PhSSO_2Ph$	1:1:1	THF	R_4 = Ph[b]	85	11
3	n = 1: R = CH_2Ph; R_1 = R_2 = R_3 = H	$PhSSO_2Ph$	1:1:1	THF	R_4 = Ph	100	13
4	n = 1: R_1 = Ph; R = R_2 = R_3 = H	PhSSPh	1:1:1	THF	R_4 = Ph	62	13
5	n = 1: R_2 = t-C_4H_9; R = R_1 = R_3 = H	(a) PhSSPh	1:2:2	THF–HMPA	R_4 = Ph	78	11
		(b) $PhSSO_2Ph$	1:1:1	THF	R_4 = Ph	96[c]	13
6	n = 1: R = R_3 = CH_3; R_1 = R_2 = H	(a) CH_3SSCH_3	1:1:1	THF–HMPA	R_4 = CH_3	52	11
		(b) PhSSPh	1:1:1	THF	R_4 = Ph	94	11
7	n = 2: R = R_1 = R_2 = R_3 = H	PhSSPh	1:2:1	THF	R_4 = Ph	87	11, 12
8	n = 7: R = R_1 = R_2 = R_3 = H	(a) PhSSPh	1:2:1	THF	R_4 = Ph	93	11, 12
		(b) PhSSPh	1:2:1	THF–HMPA	R_4 = Ph	85	11
9		(a) CH_3SSCH_3	1:2:2	THF–HMPA	 R = CH_3	85	11
		(b) PhSSPh	1:2:2	THF–HMPA	R = Ph	71	11
10		PhSSPh	1:2:2	THF–HMPA		84	14
11		PhSSPh	N.R.[e]	THF		63	16
12		PhSSPh	1:2:2	THF–HMPA	 5	93	15
13		PhSSPh	1:1:1	THF–HMPA		98	13
14	Estrone methyl ether	PhSSPh	1:2:1	THF–HMPA	 6	94	11
15	5α-Cholestanone	PhSSPh	1:1:1	THF–HMPA	 7	81	13
16		CH_3SSCH_3	N.R.[e]	N.R.[e]		N.R.[e]	17

[a] An 80:20 mixture of sulfenylation at C(6) vs. C(2). [b] A > 97: < 3 mixture of sulfenylation at C(6) vs. C(2). [c] Yield of unpurified product. [d] K:B:S = ketone:base:sulfenylating agent. [e] N.R. = not reported.

Table II. Sulfenylation of Carboxylic Acid Derivatives

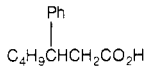
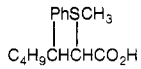
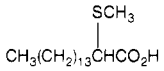
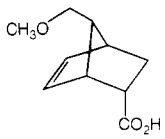
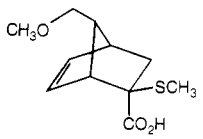
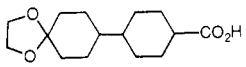
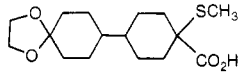
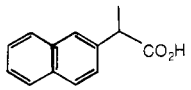
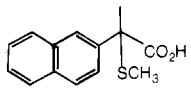
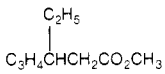
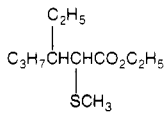
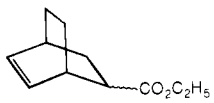
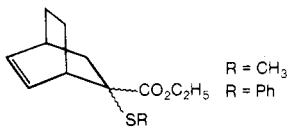
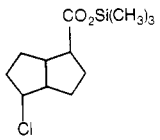
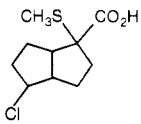
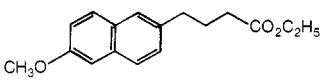
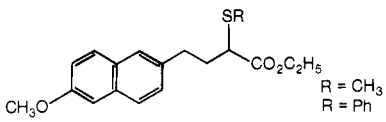
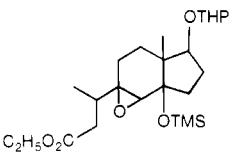
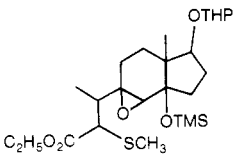
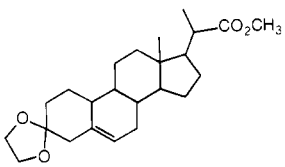
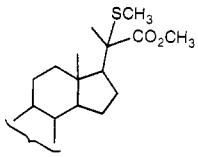
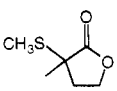
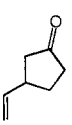
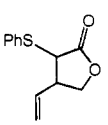
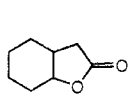
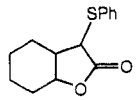
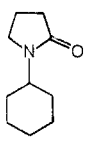
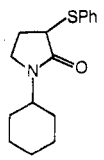
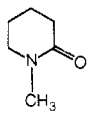
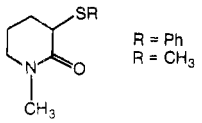
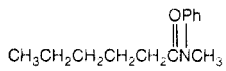
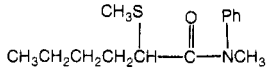
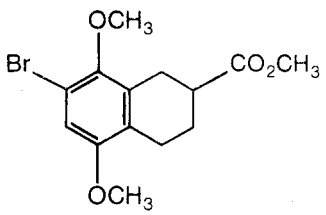
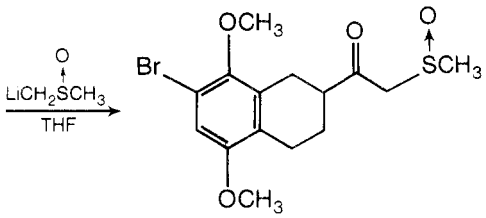
Entry	Substrate	Disulfide	Product	% yield	Ref
			Acids		
1		CH_3SSCH_3		99	28
2	Palmitic acid	CH_3SSCH_3		90	28
3		CH_3SSCH_3	 12	80	28
4		CH_3SSCH_3		98	28
5		CH_3SSCH_3		92	28
			Esters		
5		CH_3SSCH_3		88	11
6		(a) CH_3SSCH_3 (b) PhSSPh	 $R = CH_3$ $R = Ph$ 13	94 91	11 11
7		CH_3SSCH_3		56	29
8		(a) CH_3SSCH_3 (b) PhSSPh	 $R = CH_3$ $R = Ph$	89 87	11 11
9		CH_3SSCH_3		82	11
10		CH_3SSCH_3	 14	98	28
			Lactones		
11		CH_3SSCH_3		79	11
12		PhSSPh		50	30

TABLE II *(continued)*

Entry	Substrate	Disulfide	Product	% yield	Ref
13		PhSSPh		71	31
		Lactams and Amides			
14		PhSSPh		70	32a
15		(a) PhSSPh (b) CH_3SSCH_3	 R = Ph R = CH_3	83 69	32b 32c
16		CH_3SSCH_3		65	32c



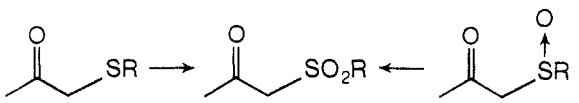
18



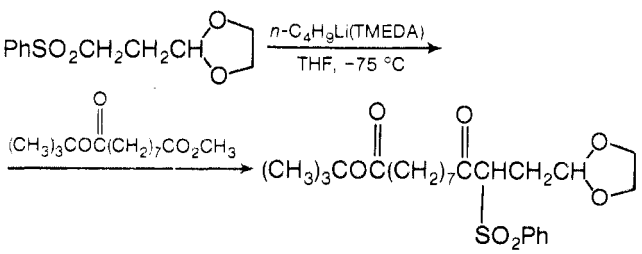
(ref 39)

19, >76%

The β-keto sulfones can also be prepared by oxidation of β-keto sulfides or sulfoxides by many of the same reagents



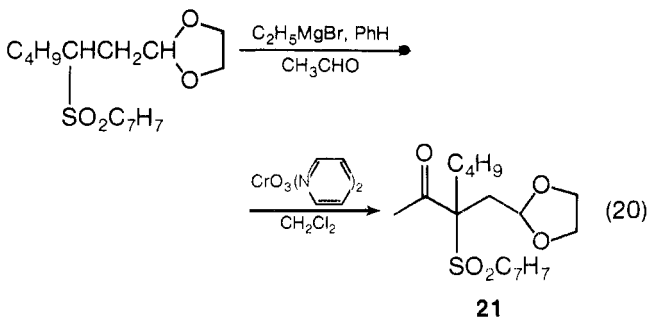
utilized for the oxidation of the sulfide to the sulfoxide. Alternatively the acylation of sulfone stabilized anions (eq 19)[42b] or the



20, 78%

(19)

condensation of such anions with aldehydes followed by oxidation (eq 20)[42c] provides an entry to these systems.[42] Alkylation of sodium benzenesulfinate with α-halocarbonyl compounds directly forms the β-keto sulfone and serves as a valuable



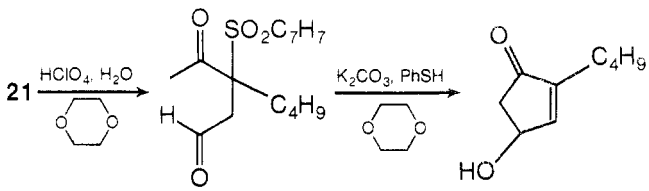
(20)

21

method for forming simple sulfone systems such as methyl benzenesulfonylacetate.[43]

$$PhSO_2Na + ClCH_2CO_2CH_3 \xrightarrow[\text{reflux}]{CH_3OH} PhSO_2CH_2CO_2CH_3 \quad 89\%$$

Unmasking a carbonyl group γ to a sulfone, sulfoxide, or sulfide activates the sulfur substituent toward base-catalyzed eliminations. Such reactions served as a key aspect of cyclopentenone syntheses (eq 21[42c] and 22[44]) and a butenolide synthesis (eq 23[45]).

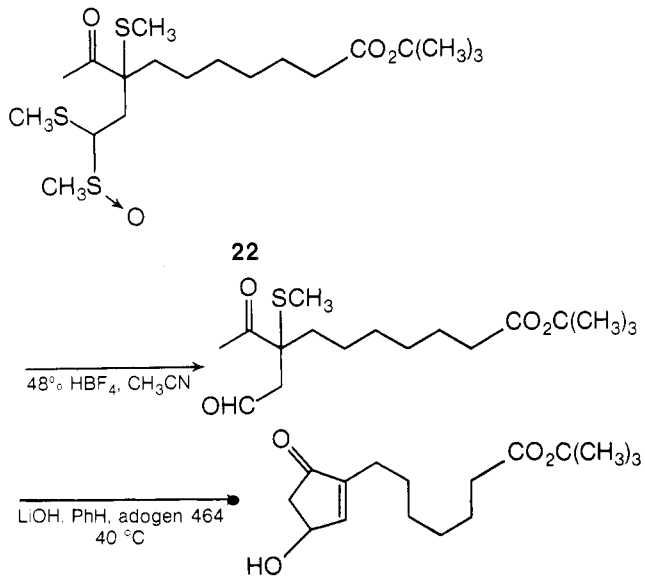


(21)

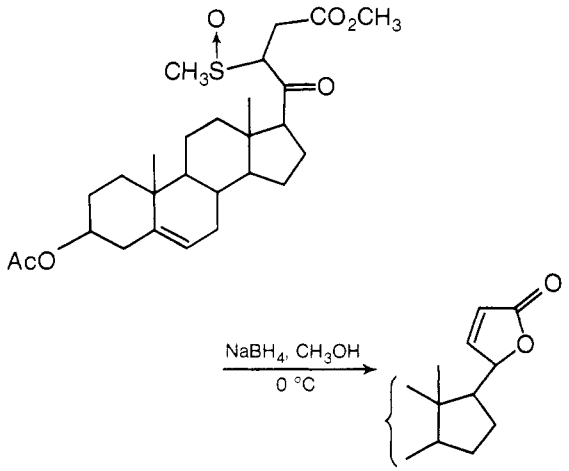
D. Bissulfenylated Carbonyl Compounds

One of the early applications of sulfenylation chemistry derived from the recognition that introduction of two sulfur substituents α to a carbonyl group constitutes a net oxidation of a methylene group to a carbonyl group.[22] Introduction of a dithianyl group by condensing an enamine or a hydroxymethylene derivative of a ketone, e.g., **23**, with trimethylenedithiotosylate (**24**) followed by hydrolysis provided **25** which served as an intermediate in a colchicine synthesis.[26] Marshall used this process to effect a 1,2-carbonyl transposition (eq 24).[47]

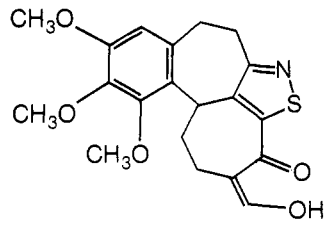
Sulfenylation of β-keto sulfides with sulfenyl chlorides, *N*-alkyl- or arylthioimides, or thiosulfonates proceeds well,[7,13,22,23] whereas such reactions are more capricious with diphenyl disulfide.[11] Mukaiyama used this process combined with or-



(22)



(23)



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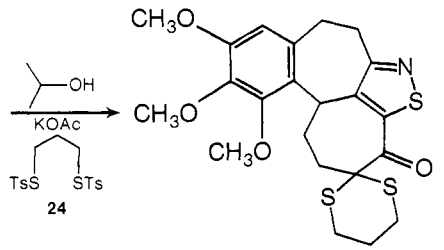

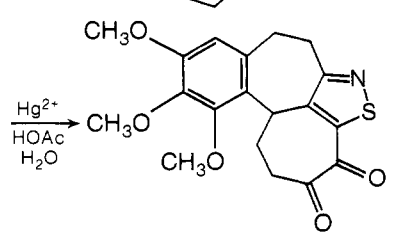

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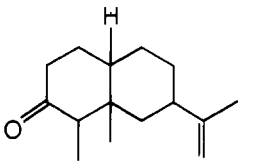
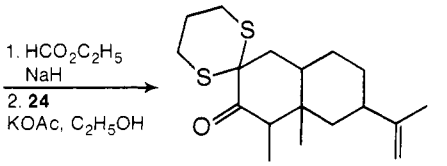
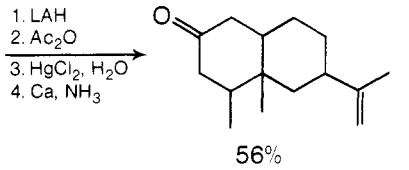
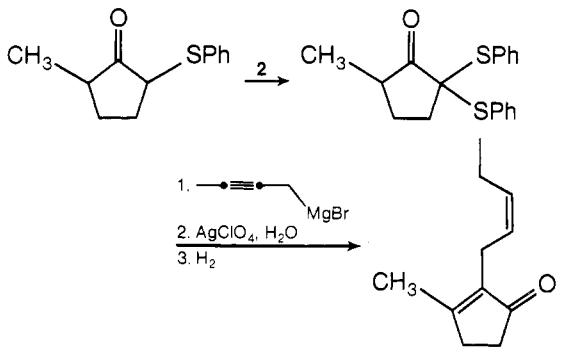






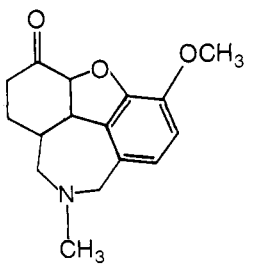
(24)

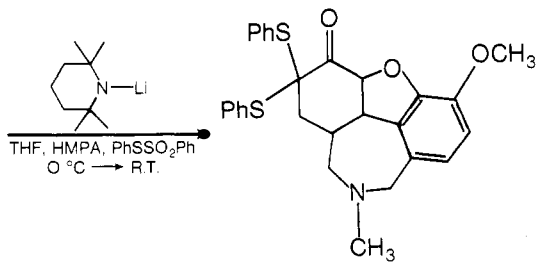
ganometallic addition to effect a 1,2-alkylative carbonyl transposition in a synthesis of *cis*-jasmone (eq 25).[48] Synthetically,



(25)

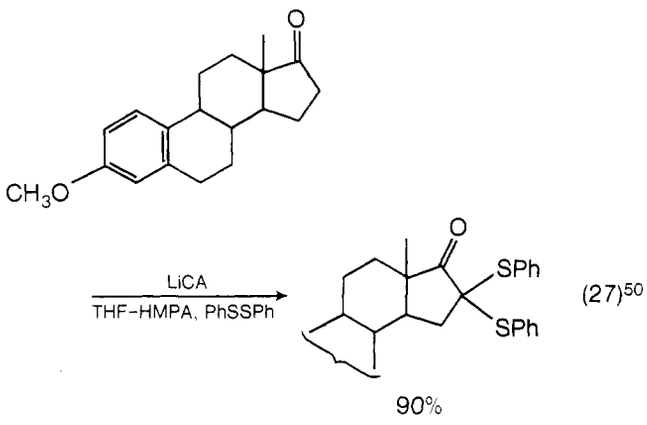
such reactions are most conveniently carried out by direct bissulfenylation of the starting ketone as was done in eq 26 and 27.



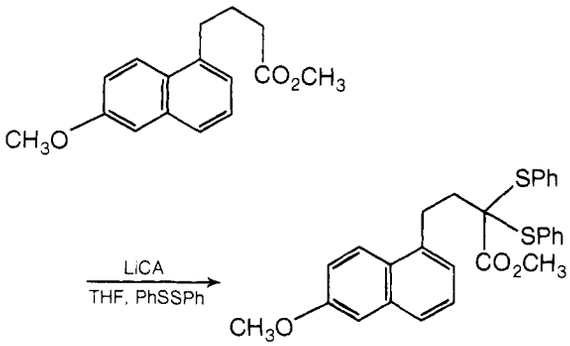


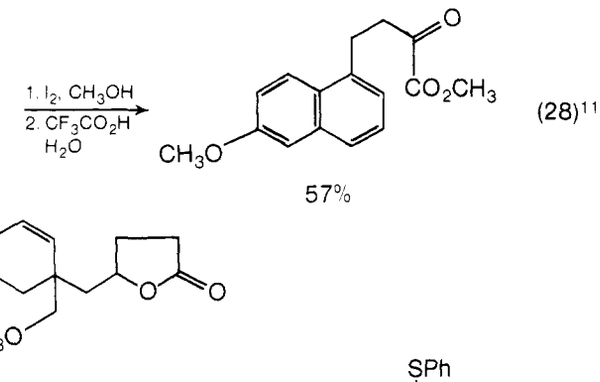
(26)[49]

More reactive carbanions, such as those derived by deprotonation of esters,[11,51] lactones,[52] lactams,[32] imino ethers,[53] or nitriles[33] usually undergo smooth bissulfenylation with diphenyl disulfide as well as the *N*-arylthioimides or thiosulfonates as exemplified in eq 28–30. Hydrolysis of the created thioketal unmasks the α-keto derivative (see eq 28).

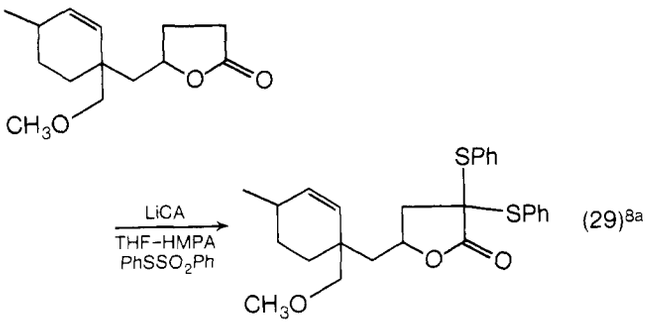


(27)[50]



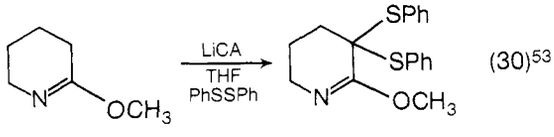


(28)[11]



(29)[8a]

26

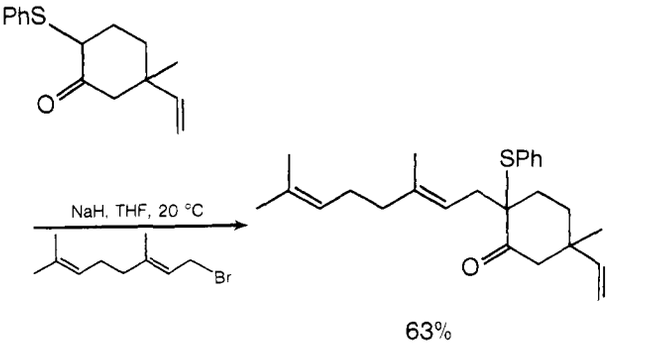


(30)[53]

III. Reactions and Synthetic Conversions

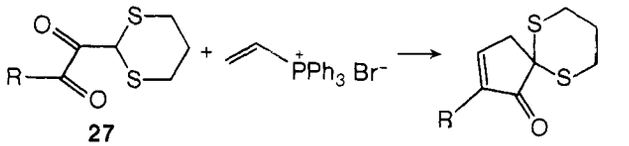
A. Introduction of Alkyl Groups

The presence of a phenylthio group α to a carbonyl group enhances the thermodynamic acidicity of an adjacent proton by ~10^3 over a simple ketone.[19a] Such a fact allows selective alkylation at the carbon bearing sulfur with primary alkyl and allyl halides. Utilizing the corresponding metalloenamines has sometimes been reported.[19a,44] Such sulfur stabilized anions undergo conjugate addition with Michael acceptors. For example, the preparation of **22** involved the addition of the methyl thioketone to 1-methylsulfinyl-1-methylthioethylene (ketenethioacetal monosulfoxide).[44] Use of triphenylvinylphosphonium



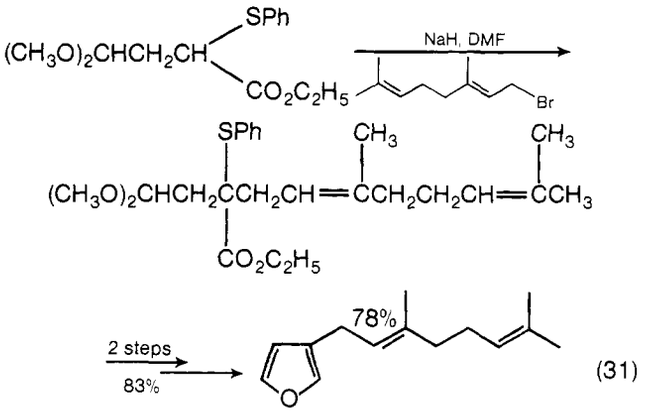
(ref 3a)

bromide with bisthioketal **27** has led to a very useful intermediate for cyclopentanone synthesis.[54]



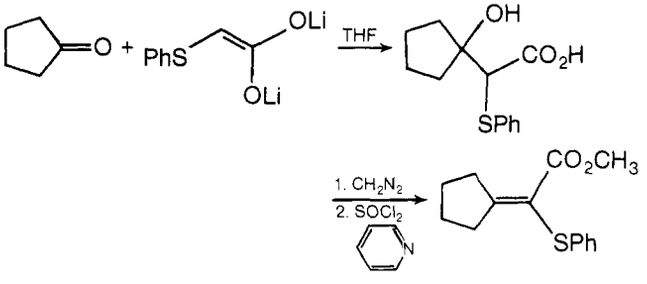
27

The anions of the thiocarboxylic acid derivatives are more reactive. As shown in eq 31, the products of alkylation are quite useful for further elaborations as in the shown furan synthesis.[55a] Alkylation of the β-thioesters,[55] lactones,[31,56] carboxylates,[57]

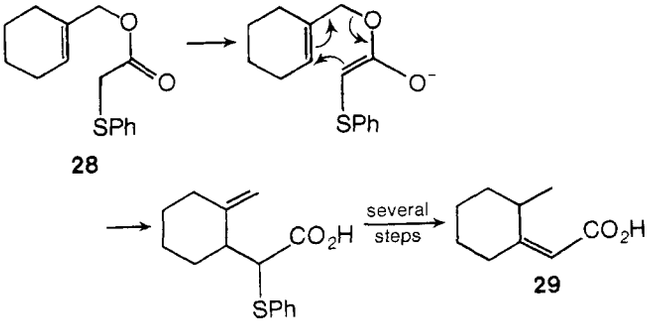


(31)

and nitriles[55c] have all been reported. Such anions also add to carbonyl groups which serve as precursors to α-sulfenylated α,β-unsaturated systems, themselves valuable intermediates.[57b]



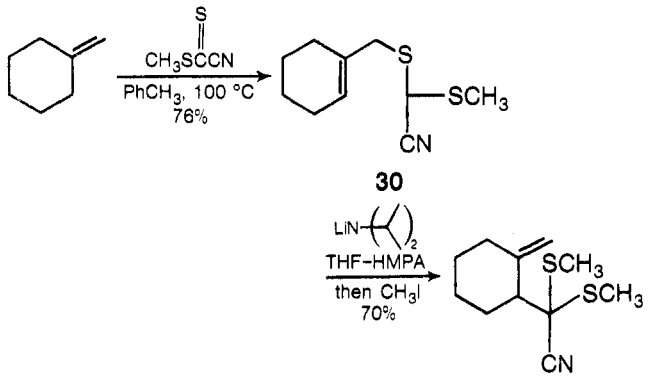
The anions of *S*-allyl carboxylic esters[58] or allyl esters of α-thiocarboxylates[59] undergo smooth sigmatropic rearrangment (cf. **28**) upon deprotonation which serves as an "internal alkyl-



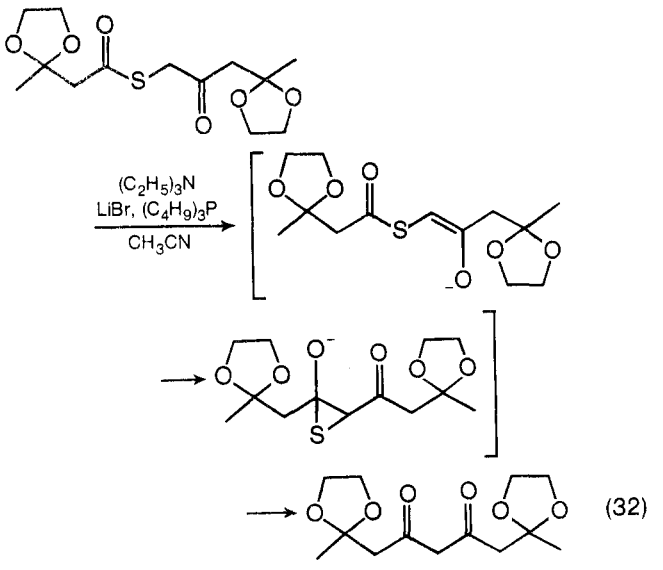
28

29

ation". In the cited case, **29** serves as a model for the A ring of vitamin D. A similar sigmatropic rearrangement of **30** served as a key step in a novel allylic alkylation procedure.[60]

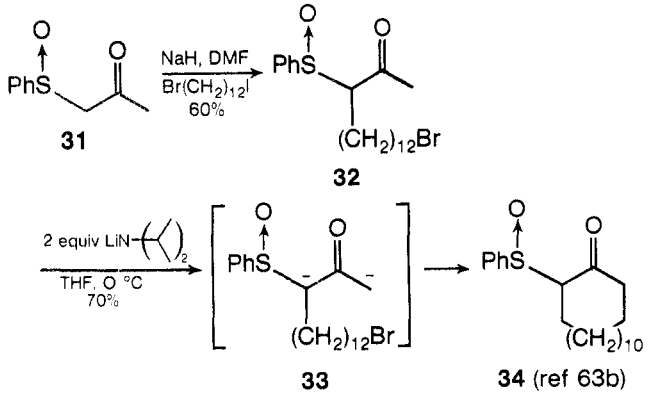


The anions of β-acyl thioketones undergo intramolecular acyl migration and in situ desulfurization in the presence of a thiophile such as a phosphine to give 1,3-dicarbonyl systems (see eq 32).[61] A variant of this process played a key role in the Eschenmoser–Woodward total synthesis of vitamin B_{12}.[62]



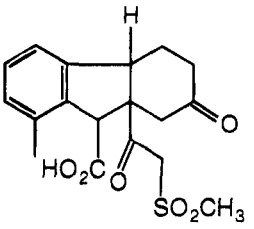
(32)

The anion of β-keto sulfoxides[45,63] and β-keto sulfones[42,64] can also be easily generated with a wide variety of bases. These more stabilized anions react with more reactive alkylating agents such as alkyl iodides, allyl halides, or α-halocarbonyl systems (cf. **31** → **32**). Such anions also undergo conjugate additions.[63a]

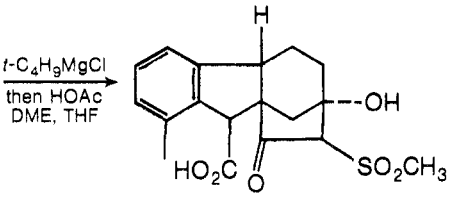


31 **32** **33** **34** (ref 63b)

Anionic stabilization by sulfoxides and sulfones allows the dianions, e.g., **33**, to be formed from β-keto sulfoxides[63b,65] and β-keto sulfones.[66] Alkylation of such anions proceed at the less stabilized carbanionic center; for **33**, the intramolecular alkylation at this center leads to a surprisingly high yield of the 15-membered ring **34** which ultimately led to muscone. The intramolecular addition of a magnesium derivative of a β-keto sulfone, e.g., **35**, to a carbonyl group served as a key cyclization in a synthesis of epiallogibberic acid.[67]

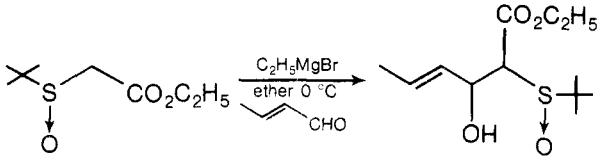


35

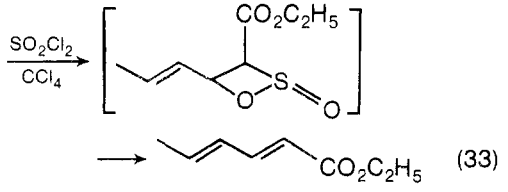


96%

The α-sulfoxides and α-sulfones of carboxylic acid derivatives are more reactive in alkylations and via their magnesium derivatives[68] will add to carbonyl groups of aldehydes and ketones. Taking advantage of sultine formation and their facile elimination of sulfur dioxide, an alternative to the use of stabilized phosphorus ylides and phosphonate anions in the synthesis of α,β-unsaturated carbonyl systems emerged (eq 33).[68b]



74%

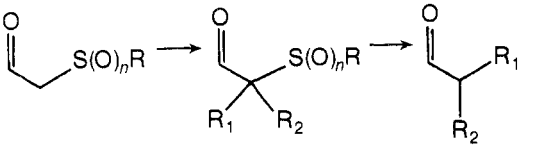


(33)

79%

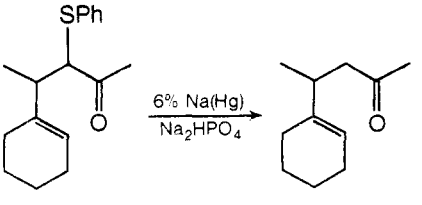
B. Reduction

The ability to reductively remove the sulfur α to a carbonyl group allows these derivatives to serve as convenient activating groups for acylations and alkylations (see eq 34). Of course,



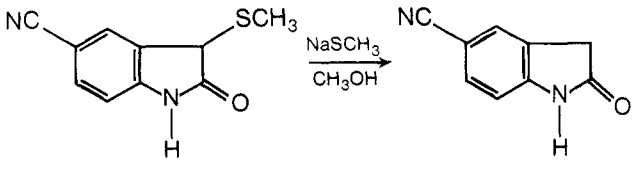
(34)

desulfurization with Raney nickel and related catalysts can be employed for the sulfides and sulfoxides.[69] Many different dissolving metal systems can be employed. For β-keto sulfide **36**,

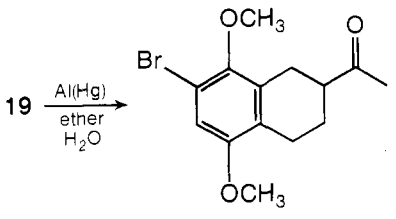


36

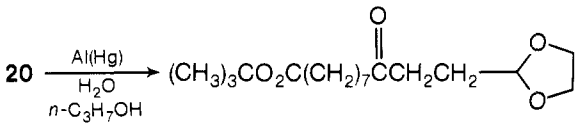
use of 6% Na(Hg) in methanol buffered with disodium acid phosphate[70] or calcium in refluxing liquid ammonia proved best.[71] Use of mercaptide ion in a protonic solvent like alcohol is a very mild approach as illustrated by the oxindole synthesis.[2,72] For the sulfoxides (e.g., **19**[39] and **39**[73]) and sulfones (e.g.,



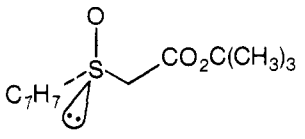
62%



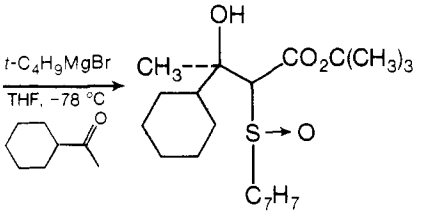
37

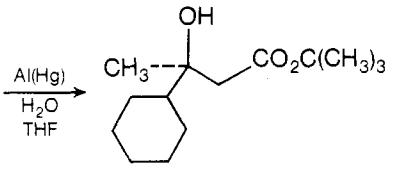


78%



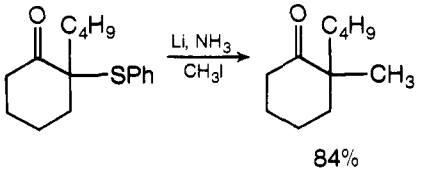
38





95% ee

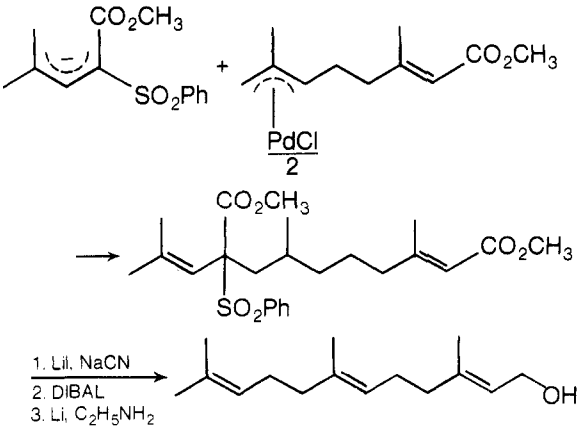
20[42b]), aluminum amalgam produces the desulfurized carbonyl partner in excellent yields. The conversion of **18** (the precursor of **19**) to **37** illustrates the conversion of esters to methyl (or alkyl) ketones. The carbonyl addition of optically pure **38** followed by reduction illustrates the potential of these intermediates in transfering chirality from sulfur to carbon. The fact that such dissolving metal reductions lead initially to enolates creates a regiospecific enolate alkylation procedure as outlined in eq 35.



(35)

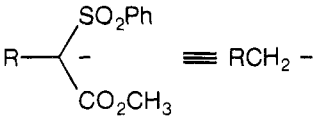
84%

The β-sulfone esters undergo smooth decarboalkoxylation

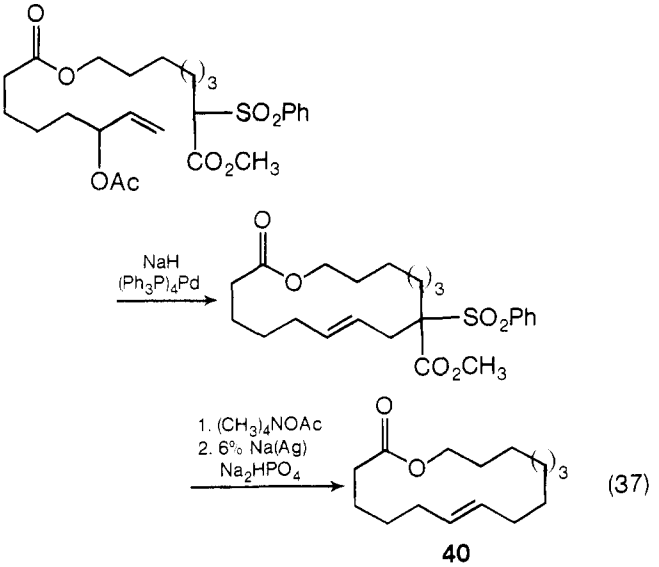


(36)

which when followed by reductive desulfonylation illustrates the use of the sulfone ester as a "soft" carbanion.[74] Equation 36



demonstrates the combination of olefin activation and α-sulfonyl carboxylate alkylation to accomplish a net prenylation of a monoterpene to a sesquiterpene.[74a] Equation 37 provides an

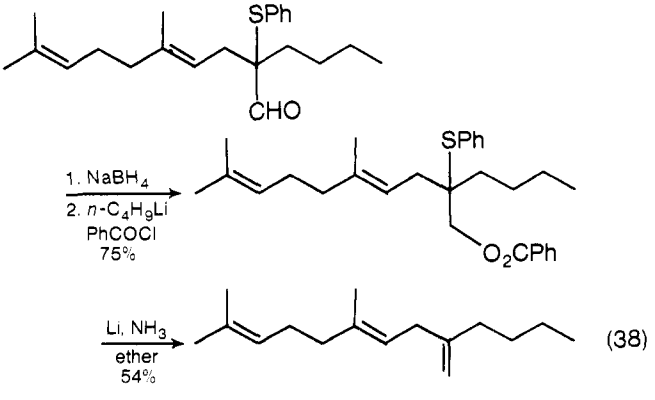


(37)

40

exciting approach to macrocyclization utilizing this same combination in a catalytic palladium process.[74b] The conditions for decarbomethoxylation and desulfonylation illustrated in eq 37 appear to be superior to alternatives. Reduction of **40** forms exaltolide.

Reduction of the carbonyl group (or addition of organometallics) creates a β-hydroxy sulfide, sulfoxide, or sulfone which



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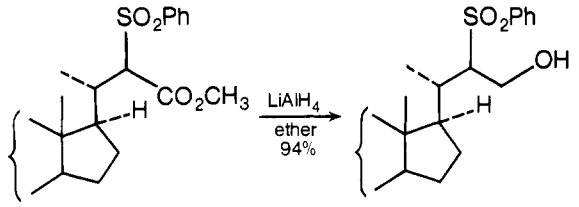

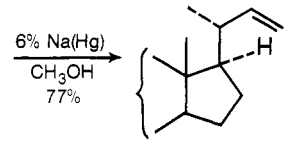

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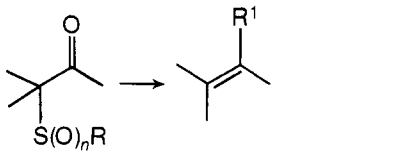

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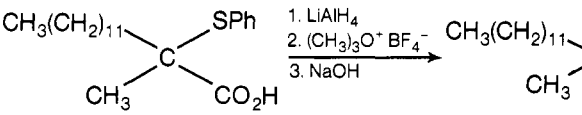
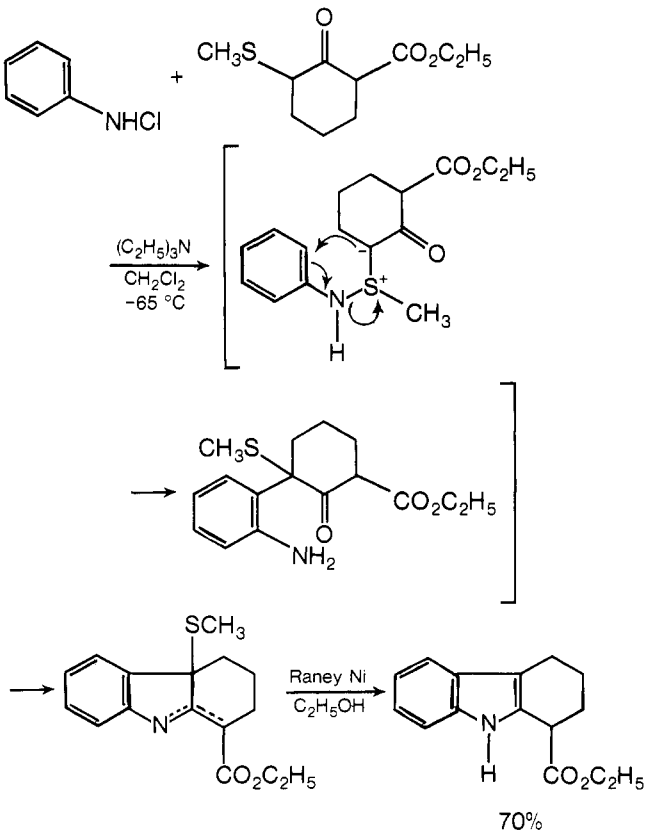


56%

(41)

allows a number of useful synthetic transformations (see section on ring cleavages). For example, such systems are precursors to olefins[75] and have been utilized in a model study toward the antibiotic moenocinol (eq 38)[37a] and in a synthesis of an intermediate toward the insect molting hormone ecdysone (eq 39).[76] Combined with the fact that carbonyl reduction can be replaced by organometallic addition, these sulfur compounds serve as valuable intermediates for regiospecific olefin formation as summarized in eq 40. Epoxides are available from the hydroxy sulfide[77] (eq 41).[57c] Other oxygen heterocycles, as in a butenolide[25b,45] and a furan (eq 31) synthesis, arise by interaction of the hydroxyl groups with remote functional groups.

A very general approach to indoles and related derivatives combines a 2,3-sigmatropic rearrangement with reduction of the intermediate α-methylthioimine as exemplified by the synthesis of 1-carboethoxytetrahydrocarbazole.[2]

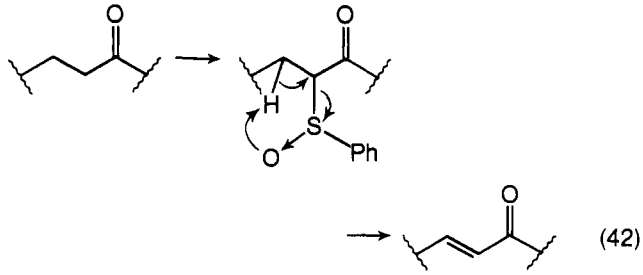


70%

C. Oxidation

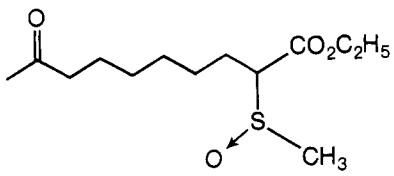
1. Dehydrogenation via Sulfoxide Pyrolysis

The ability to selectively sulfenylate or sulfinylate a carbonyl partner followed by pyrolysis of the α-sulfinylcarbonyl intermediate constitutes a net regiocontrolled dehydrogenation to the synthetically important α,β-unsaturated carbonyl systems as summarized in eq 42.[11] Virtually all the compounds listed in

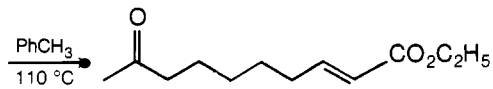


(42)

Tables I and II have been converted to their unsaturated derivatives via this sequence. Thus, α,β-unsaturated ketones,[11] esters,[11] lactones,[11,25b,31,52,57a,78] lactams,[32] and nitriles[33a] have been synthesized by this approach. The temperatures vary as a function of the R group. Normally, the aryl sulfoxides require

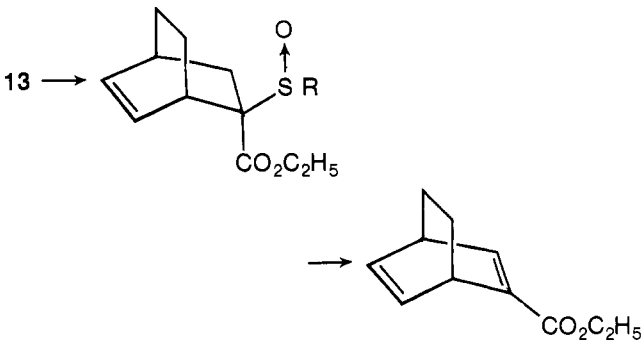


41



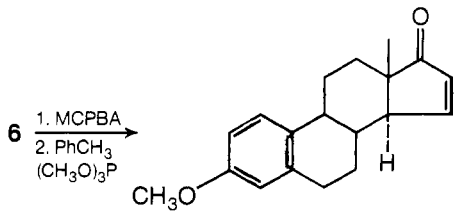
>86%

temperatures of 25–80 °C, whereas the alkyl sulfoxides require temperatures of 110–130 °C. Thus, pyrolysis of **41** required 110 °C to produce the queen's substance with pure *E* stereochemistry.[11] If the higher temperatures of the alkyl sulfoxide elimination becomes a problem, the use of the phenyl sulfoxide elimination generally overcomes it, as in the case of **13** to **42**



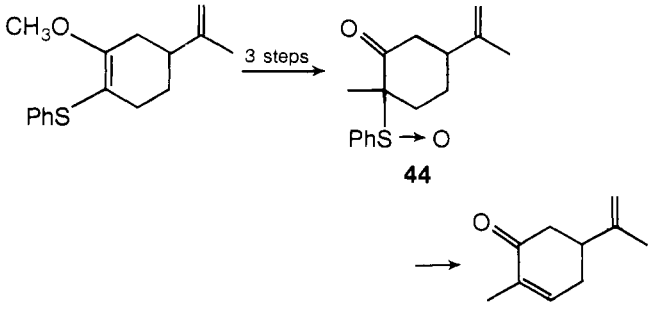
42, 84%

where the methyl sulfoxide led to a retro-Diels–Alder reaction of the initial product to methyl benzoate, but the phenyl sulfoxide led smoothly to **42**.[11] An alkylation–elimination approach that allows elimination at low temperatures has also been described.[79] The conversion of **6** to **43** proceeded more sluggishly than most phenyl sulfoxides and required the presence of a sulfenic acid trap. The related process of selenylation–dehydroselenylation failed in converting estrone methyl ether to **43**.[80]

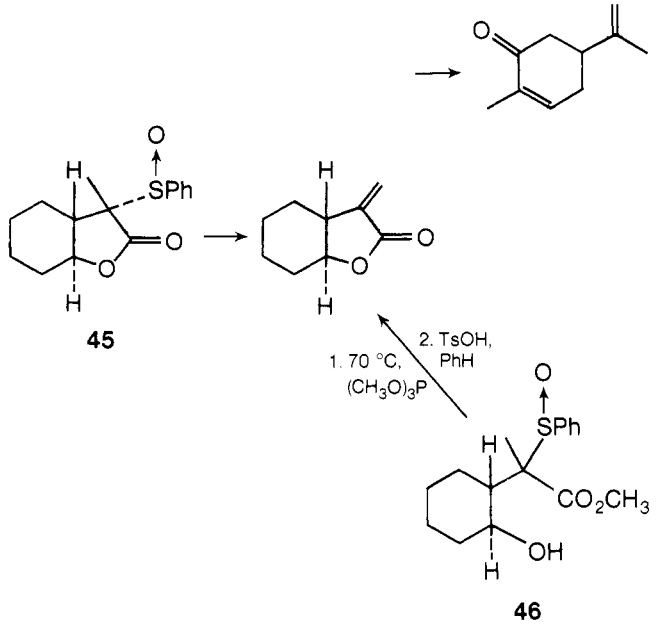


43, 88%

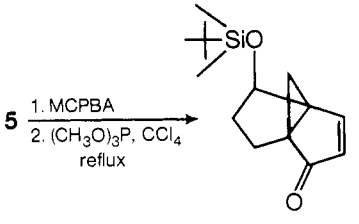
The regiochemistry for hydrogen abstraction in acyclic systems generally follows the order $C{=}CCH_2 \sim C{\equiv}CCH_2 > ArCH_2 \sim CH_3 > >C\text{-}CH_2 \gg >C\text{-}H$; whereas, for cyclic systems, given the restraint that the elimination is cis syn, there is a preference for endocyclic double bond formation. Keto sulfoxide **44** underwent internal elimination to give carvone.[3] On the other hand,



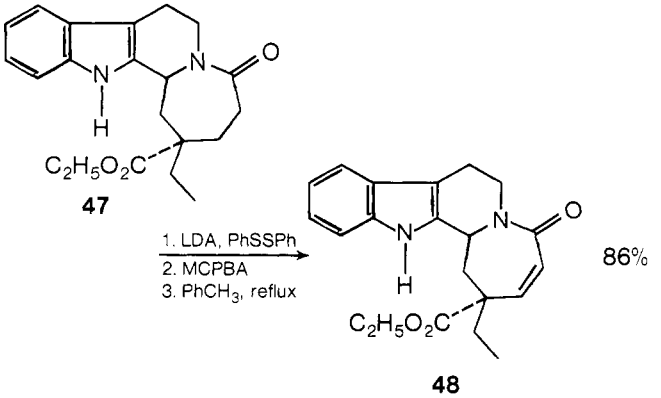
44



45 **46**



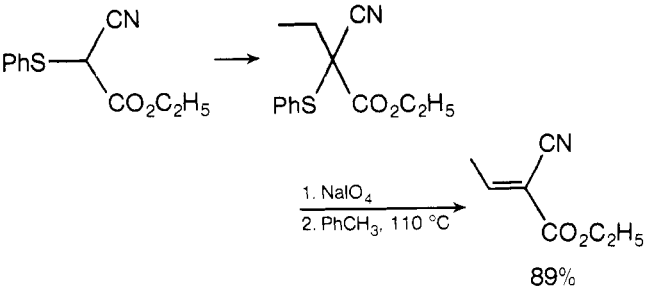
92%



86%

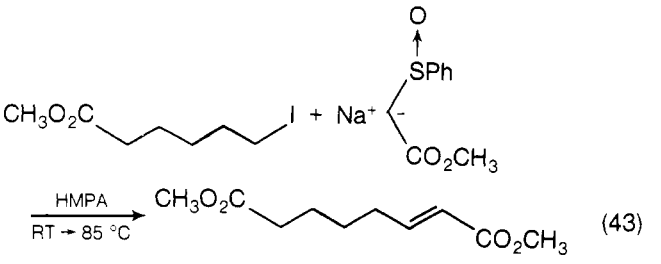
47 **48**

while **45** underwent only exocyclic elimination for geometric reasons, its C(3) epimer generated the endocyclic product (the butenolide) exclusively.[31] The acyclic version **46** only underwent elimination toward the methyl group regardless of stereochemistry at carbon bearing sulfur.[81] The mildness of the method is highlighted by the compatibility with most functional groups, even those which are oxidatively unstable. Its application to highly reactive strained ring systems, e.g., **5**,[15] on one hand, and sensitive intermediates (e.g., **47** → **48**, an intermediate toward tabersonine[82]) directed toward natural products, on the other, confirms the utility of this approach. The availability of alkylidenecyanoacetates via this approach allowed the development of a synthesis of isotopically labeled nicotinamide.[83]



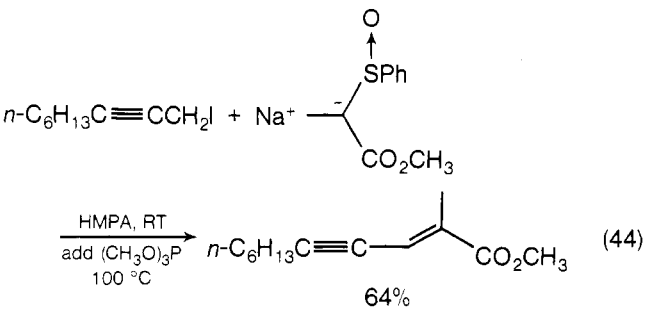
89%

By combining alkylation with in situ dehydrosulfenylation, an alkylative elimination which complements the Wittig and related processes pertains as illustrated in eq 43 and 44.[81,84] Varying



(43)

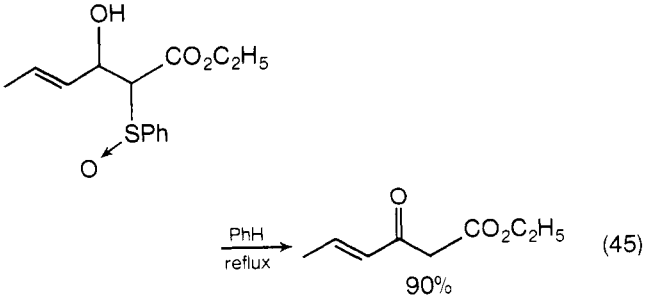
82%



(44)

64%

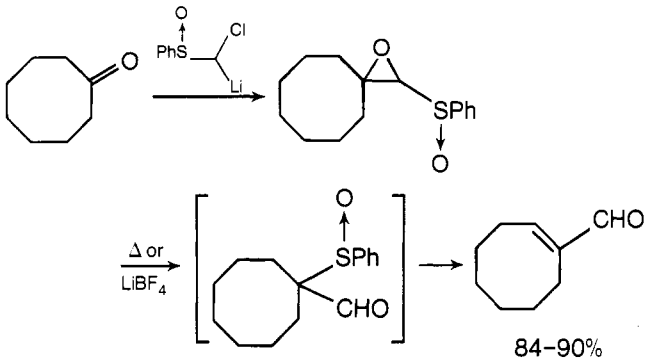
the substitution on the affected carbons can produce novel approaches to other intermediates such as the β-keto ester synthesis outlined in eq 45.[68c]



(45)

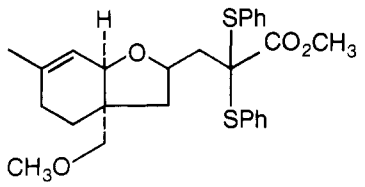
90%

Reaction of the anion of chloromethyl phenyl sulfoxide with carbonyl partners followed by thermolysis[85a] or lithium fluoroborate catalyzed rearrangements and then thermolysis of the epoxide forms a novel approach to one carbon chain extended enals from aldehydes and ketones.

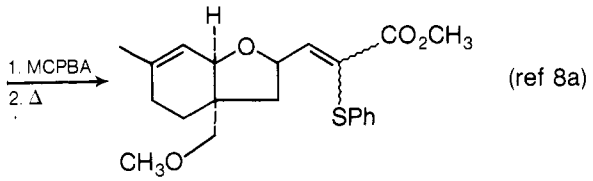


2. α-Keto Carbonyl Compounds and Their Equivalents

As pointed out previously, bisulfenylation constitutes the introduction of a masked carbonyl group (see section II.D). Such compounds can be converted to the enol thioethers of α-keto carbonyl compounds by monooxidation and elimination (e.g., **49** → **50**)—the latter occurring under very mild conditions (even

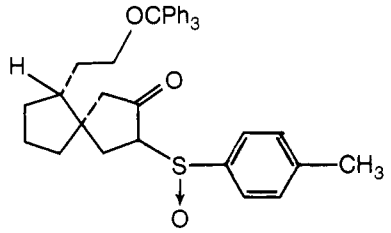


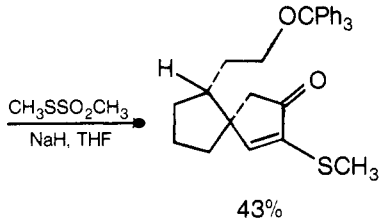
49

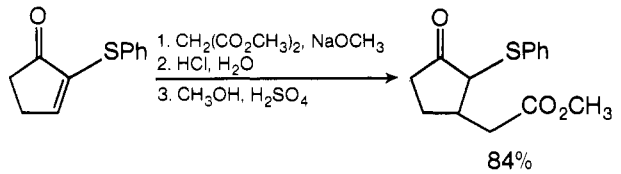


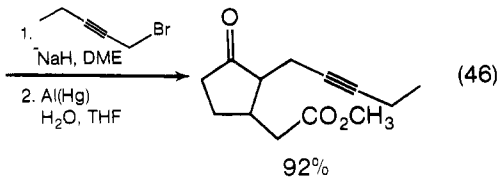
50

room temperature).[8a,52] Sulfenylation of a β-keto sulfoxide is accompanied by elimination to again generate the vinyl sulfide.[37c] Besides being a masked α-keto carbonyl compound,



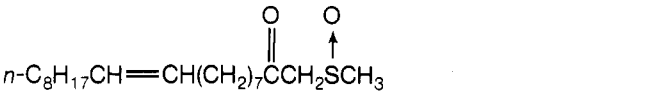


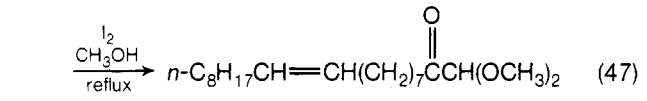


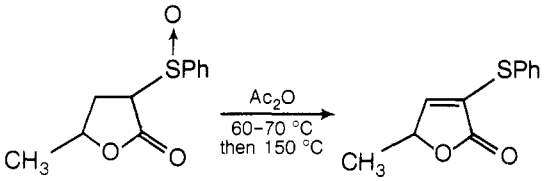


such α-thio-α,β-unsaturated systems are excellent Michael acceptors which have the effect of re-forming the β-keto sulfide in a regiospecific fashion[18,78b,86] as outlined for the synthesis of methyl dehydrojasmonate[5] (eq 46).

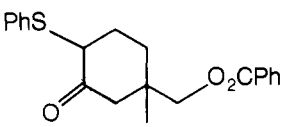
Effecting a Pummerer rearrangement on α-keto sulfoxides provides the 1,2-dicarbonyl systems with aqueous acid[38b] or iodine in methanol (eq 47),[87] whereas, the use of an acid anhydride gives an excellent yield of the enol thioether (eq 48).[78b,88]

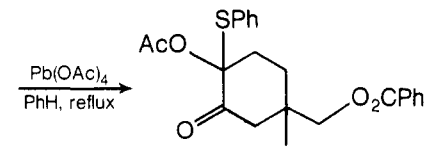


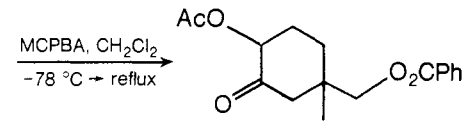




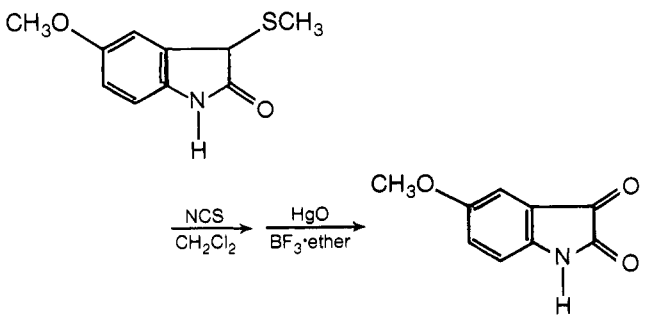
The hemithioacetal, acetal, and enol acetate of an α-keto carbonyl system are available by initial acetoxylation with lead tetraacetate (cf. eq 47).[13,89a] In this regiospecific diosphenol synthesis (eq 49), the sulfoxide elimination proceeds rapidly at







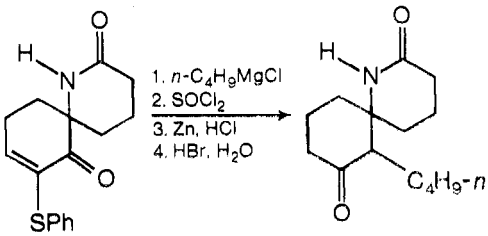
40 °C.[13] An isatin synthesis results by halogenation followed by hydrolysis of a 3-methylthiooxindole.[89b]



3. 1,2-(Alkylative) Carbonyl Transposition

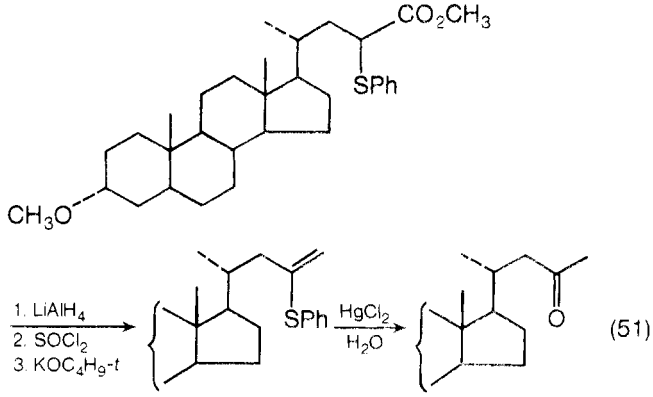
The availability of the newly introduced carbonyl group in a masked form by any of the above methods (see sections II.D and

III.C.2) allows reduction and/or carbonyl addition to the original carbonyl group followed by unmasking the new ketone—a net carbonyl transposition. Such a procedure was employed in a synthesis of lycoramine[49] and perhydrohistrionicotoxin (eq 50).[90]

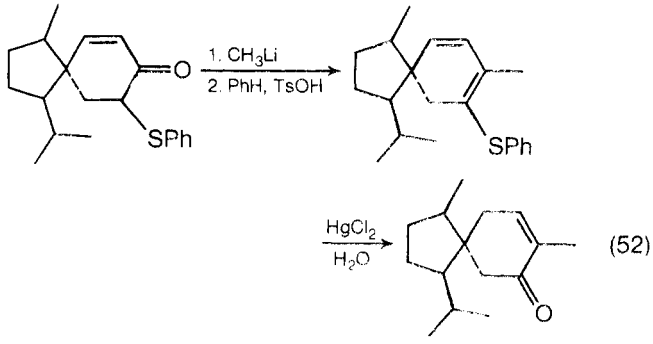


(50)

A more direct approach utilizes the α-thiocarbonyl systems directly and allows carbonyl transpositions of aldehydes, ketones, esters, etc.[91] Equation 51 illustrates the conversion of an ester to a methyl ketone and eq 52 demonstrates the application to an enone which constituted the final stages of the only fully stereocontrolled synthesis of acorenone B.[92]



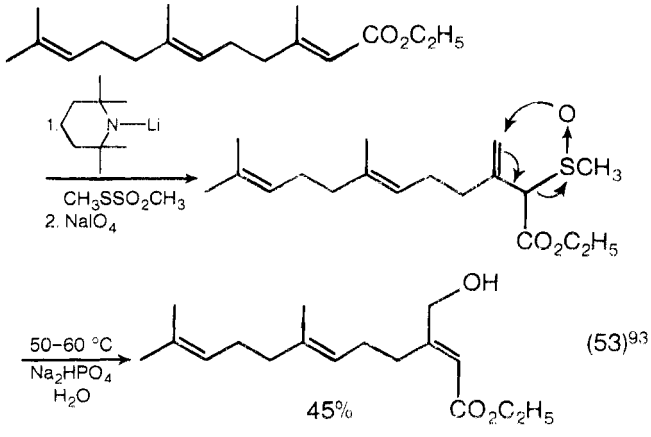
(51)



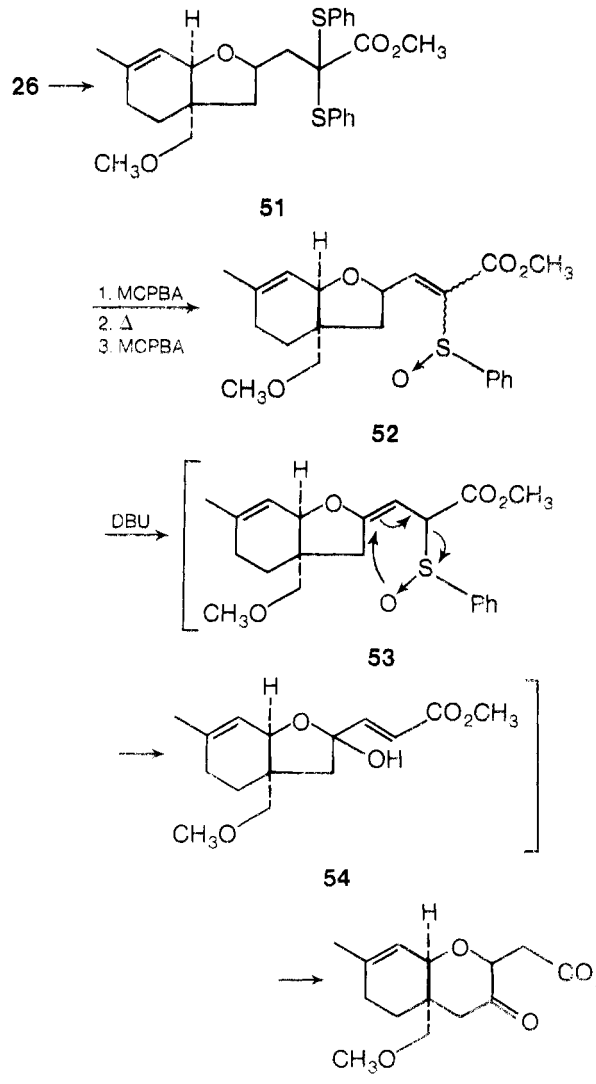
(52)

4. γ-Hydroxylation

The combination of sulfenylation of enoates followed by the [2.3] sigmatropic rearrangement of the corresponding sulfoxide constitutes a net γ-hydroxylation (eq 53).[8a,57b,93] The bissulfenylated compounds offer an opportunity to introduce the double bond and the hydroxyl group. Thus, **51,** available from lactone **26,** produces vinyl sulfoxide **52** after sulfoxide elimination and oxidation.[8a] Equilibration of **52** and the allylic sulfoxide **53** permits in situ rearrangement and desulfenylation to give γ-hydroxylated product **54.** In this case, this product undergoes a 1,2-shift to give the tetrahydropyranone **55** which is a key intermediate toward verrucarol, the sesquiterpene portion of the antitumor agent verrucarin.

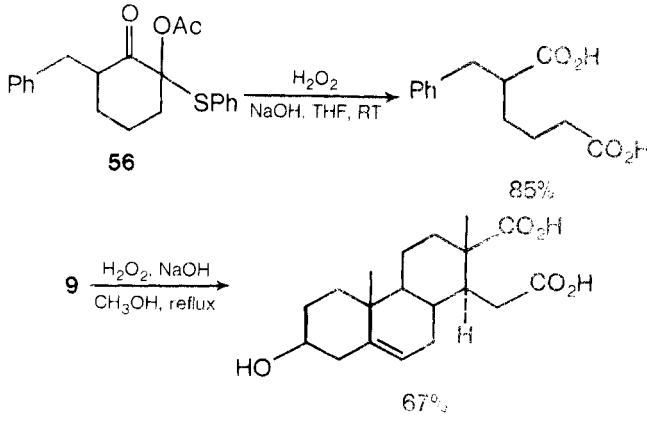


(53)[93]



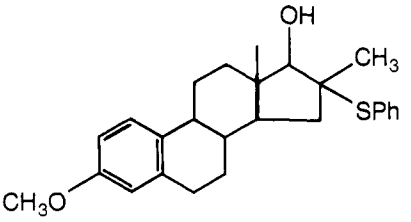
D. C–C Bond Cleavage Applied to Rings

The availability of the equivalent of a 1,2-dicarbonyl compound offers the opportunity to effect mild cleavage of C–C bonds. The

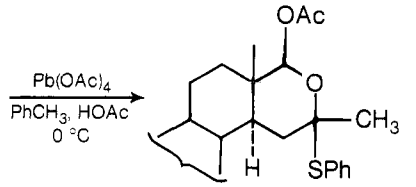


acetoxylated β-keto sulfides such as **56** cleave at room temperature with basic hydrogen peroxide.[13] Alternatively, the β-keto sulfides suffer direct cleavage with basic hydrogen peroxide at somewhat higher temperatures presumably via in situ formation of the 1,2-diketone.[13] The compatibility of the sensitive homoallylic alcohol portion of **9** to this overall process illustrates the chemoselectivity of the method.

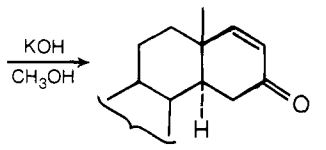
The hydroxy sulfides undergo C–C bond fission of four- and five-membered rings.[14] The availability of **57** from esterone methyl ether and the conversion of **58** to cyclohexenone **59** constitutes a ring expansion–carbonyl transposition sequence. A modified version utilizes a reagent generated by mixing lead tetraacetate and pyridine and appears to give better yields.[94] This



57

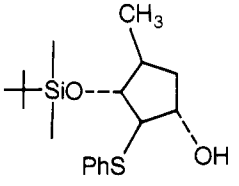


58
91%

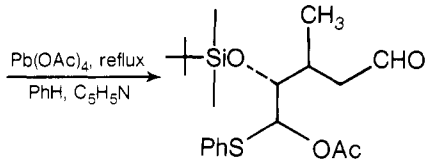


(ref 14),

59
70%



60

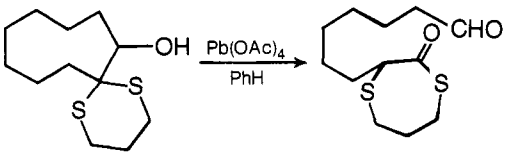


(ref 94)

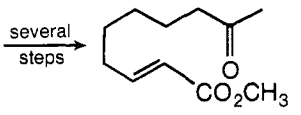
61
100%

ring cleavage (as in **60** → **61**) produces the equivalent of a dialdehyde where a chemodifferentiation of the two ends is maintained.

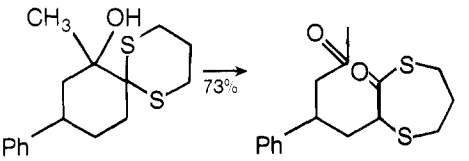
For six-membered rings or larger, cleavage required conversion to a dithionyl alcohol such as **62** and **63**.[95] Fragmentation is accompanied by sulfur migration to C(3) (see eq 54) to give a 1,4-dithiacycloheptan-2-one, an α-sulfenylated thioester. The utility of the thioester as an activated ester is illustrated by the mild alcoholysis of **64** which ultimately led to a synthesis of the queen's substance **66** of honey bees[95a] and the chemoselective cuprate coupling followed by sulfoxide elimination of **65**.[95b] This



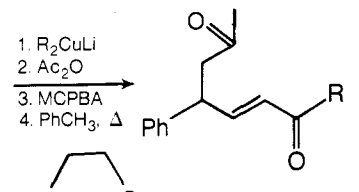
62 **64**
66%

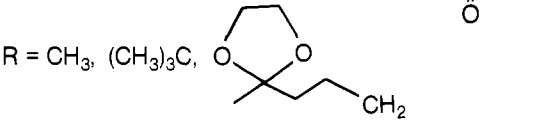


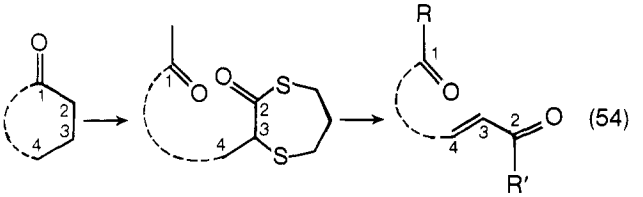
66



63 **65**



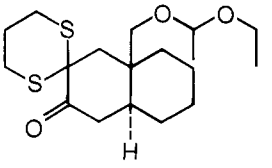


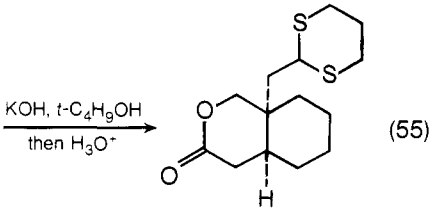


(54)

ring cleavage process which we have termed oxidative seco rearrangement allows selective modification of the oxidation level at C(1), C(2), and/or C(3) and/or C(4) with chemodifferentiation of the two ends as summarized in eq 54.

Bissulfenylated ketones undergo nucleophilically triggered cleavages as illustrated in a model study for the synthesis of vernolepin (eq 55).[96] An alternative which involves a second-



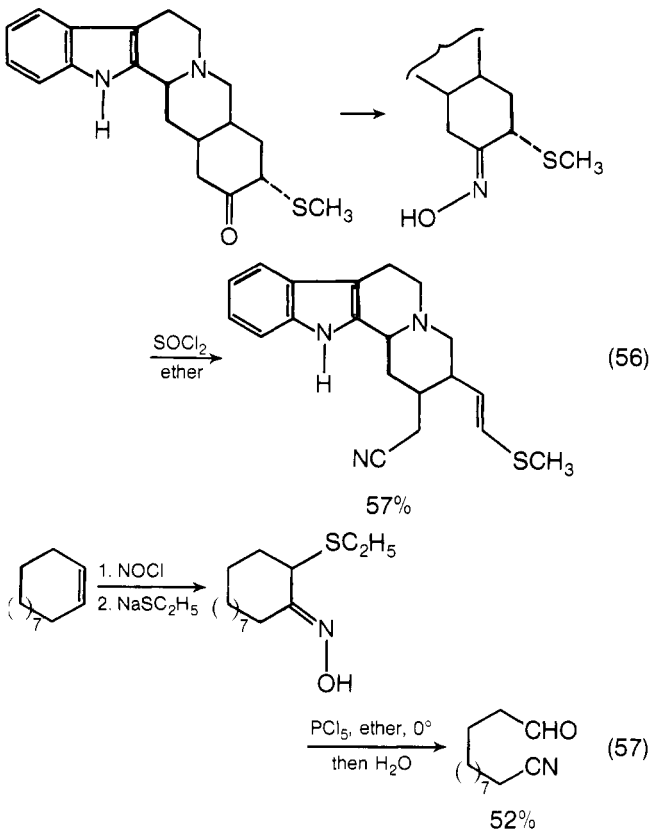


(55)

order Beckmann reaction of the oximes of α-thioketones has served in several natural products syntheses (e.g., eq 56).[23,97] The availability of the requisite α-thiooximes from olefins (eq 57) makes this reaction an intriguing approach to olefin cleavage.[97b,c]

E. Oxidative Decarboxylation

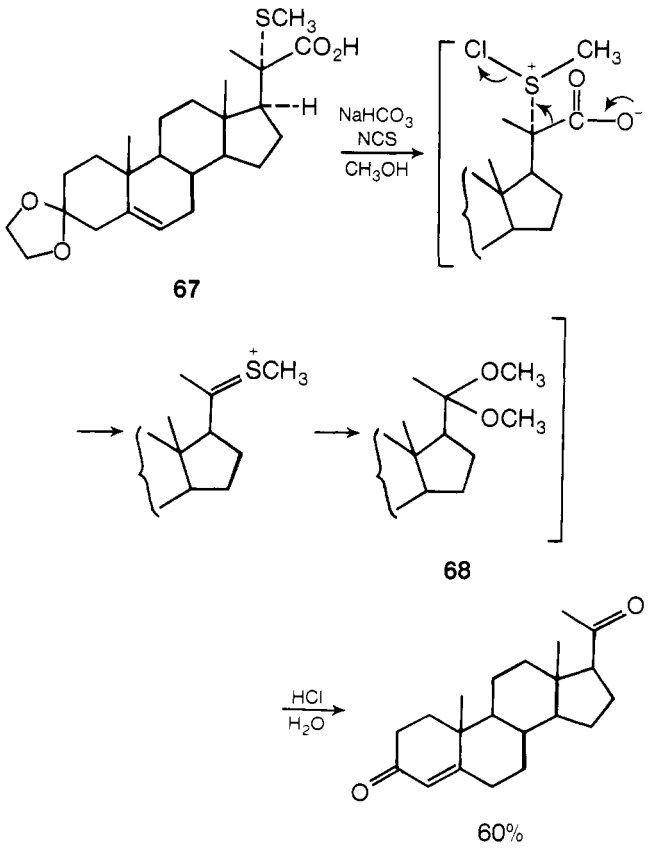
The α-thiocarboxylic acids undergo facile decarboxylation upon treatment with mild oxidizing agents such as positive halogen species, sodium metaperiodate, or lead tetraacetate.[28] For example, carboxylic acid **67**, available by hydrolysis of the



(56)

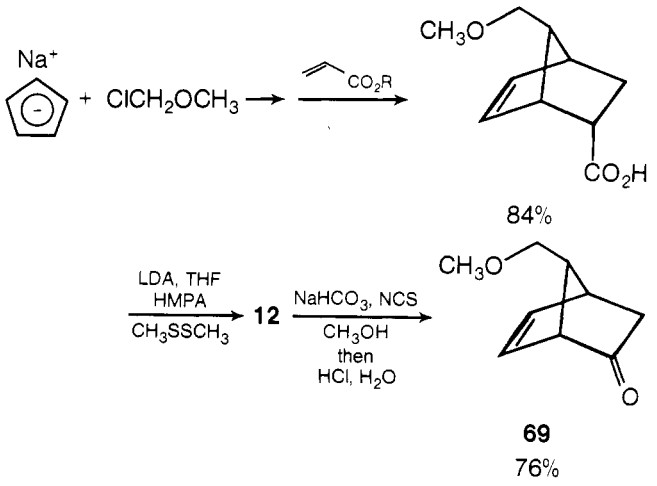
(57)

ester **14** (Table II), led to the acetal **68** presumably through an intermediate thionium ion as depicted. Hydrolysis of **68** produces progesterone. Thus, the degradation of the carboxylic acid to

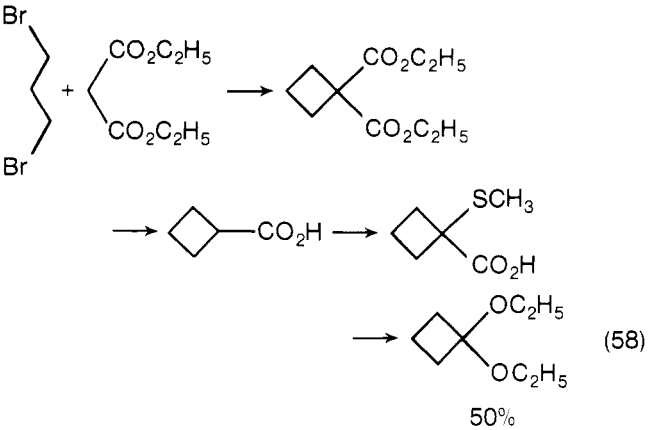


the norketone via sulfenylation–oxidative decarboxylation allows isolation of a protected ketone (as its ketal) or the ketone itself. For oxidative decarboxylation of α-methylenecarboxylic acids, such as palmitic acid (via **11**, Table II), powdered sodium metaperiodate in methanol is required to avoid oxidation at the carbon bearing sulfur prior to decarboxylation.

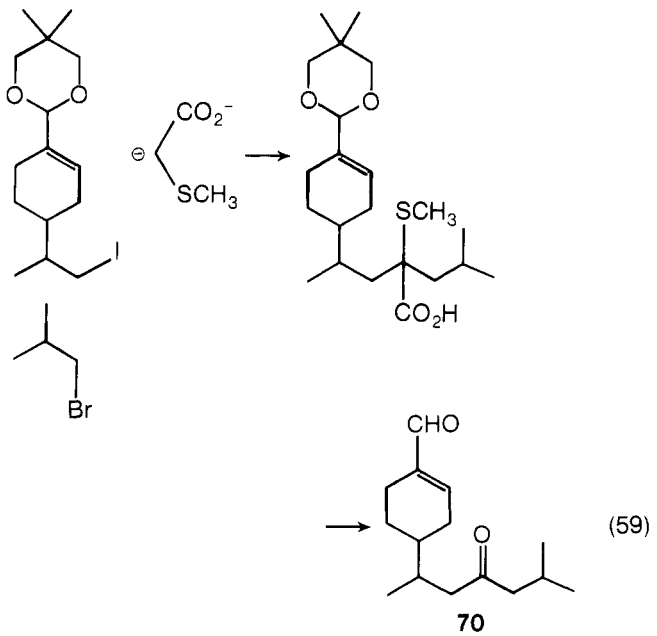
The use of acrylic acid or α-methylthioacrylic acid[98] as a ketene synthon in cycloadditions is feasible and illustrated by the synthesis of the Corey prostaglandin intermediate **69**.[28]



Malonic esters (eq 58) and methylthioacetic acid (eq 59) serve as synthons for a carbonyl dianion. Ketone **70** served as an intermediate toward juvabione.

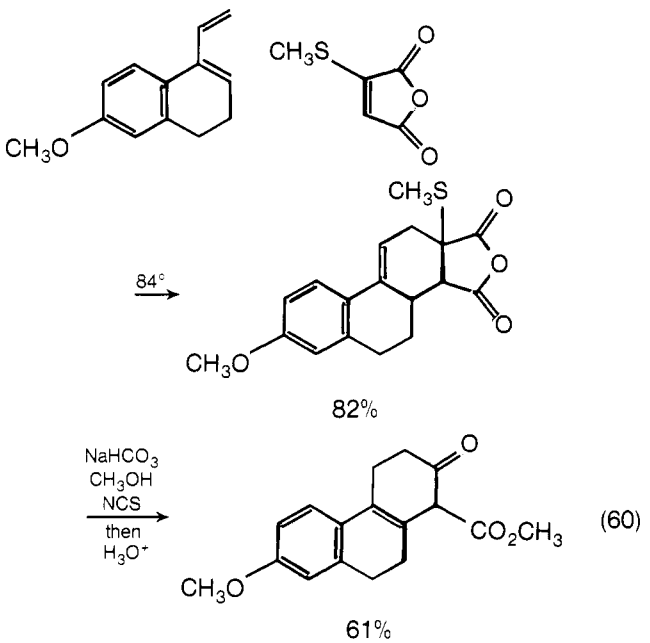


(58)



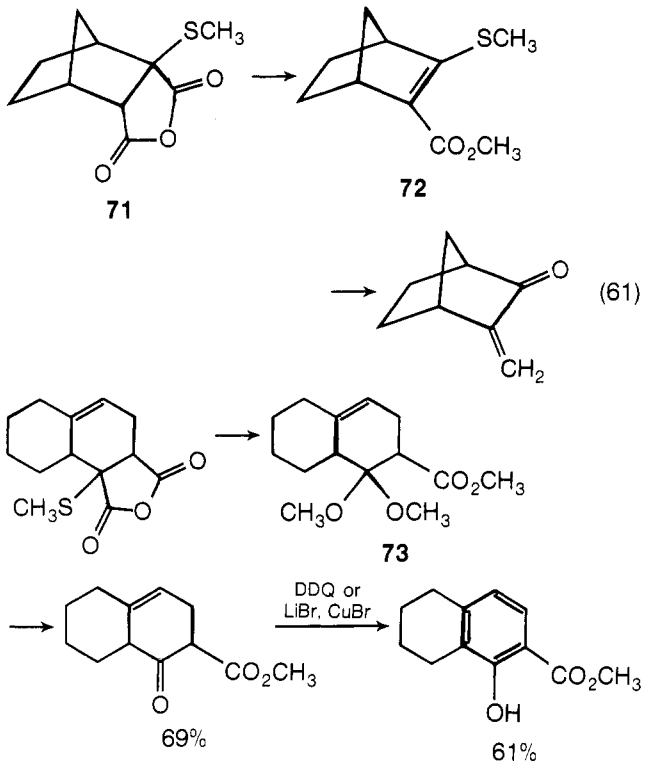
(59)

α-Methylthiomaleic anhydride, readily available from acetylenedicarboxylic acid and methanethiol, serves as a source of carbomethoxyketene (eq 60) and methyleneketene (eq 61) in cycloadditions.[99] It can also serve as a source of salicylic



(60)

esters (eq 62). The regiochemistry of the cycloaddition in eq 60 contrasts with that for methylmaleic anhydride with the same diene and shows the regiocontrol exercised by sulfur in the dienophile as well as the diene. In bicyclic systems like **71,** the product of oxidative decarboxylation prior to hydrolysis is the enol thioether, e.g., **72,** which can be converted to the β-keto ester or as shown reduced before unmasking the ketone. For all other cases, the initial product is the ketal ester such as **73**



(61)

(62)

in eq 62 which can be isolated in 84% yield.

The thermodynamically less stable vinyl sulfides are nicely

SCHEME I. Structural Elaborations

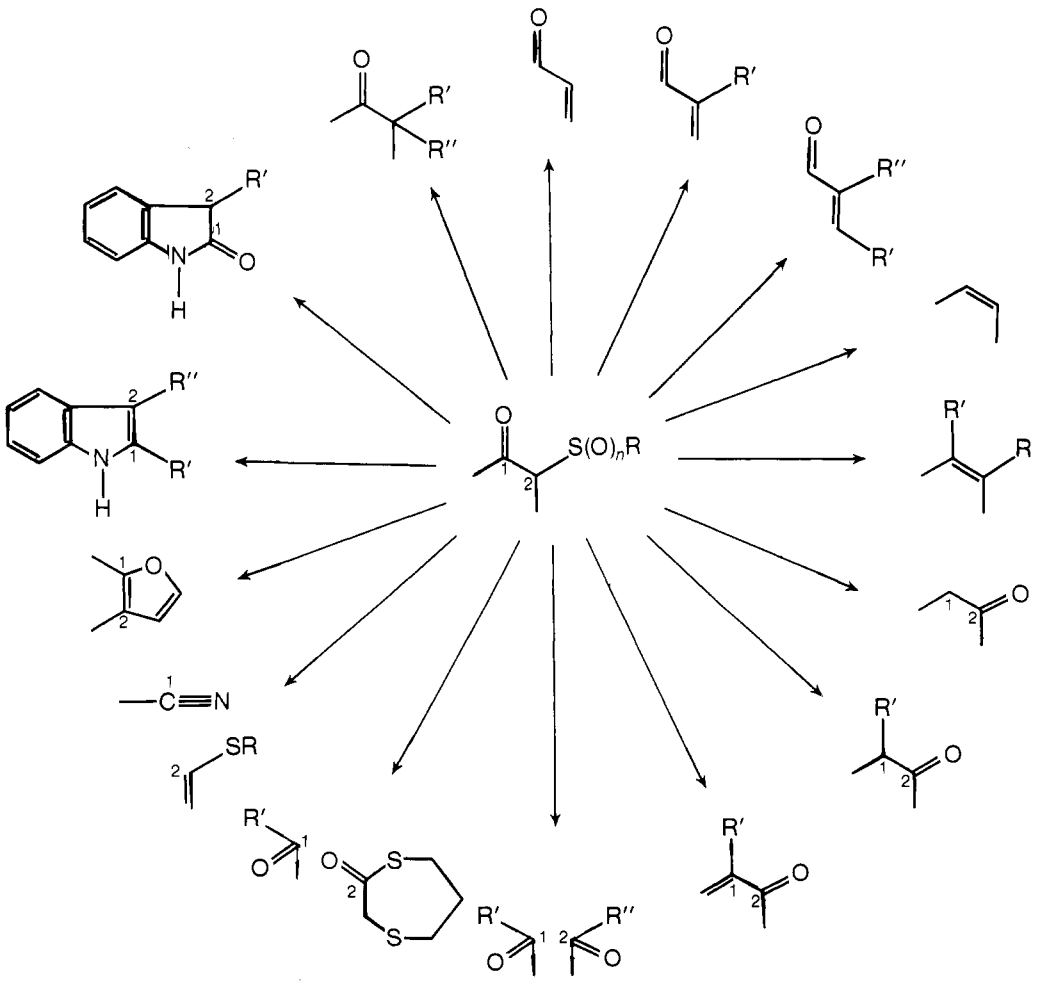
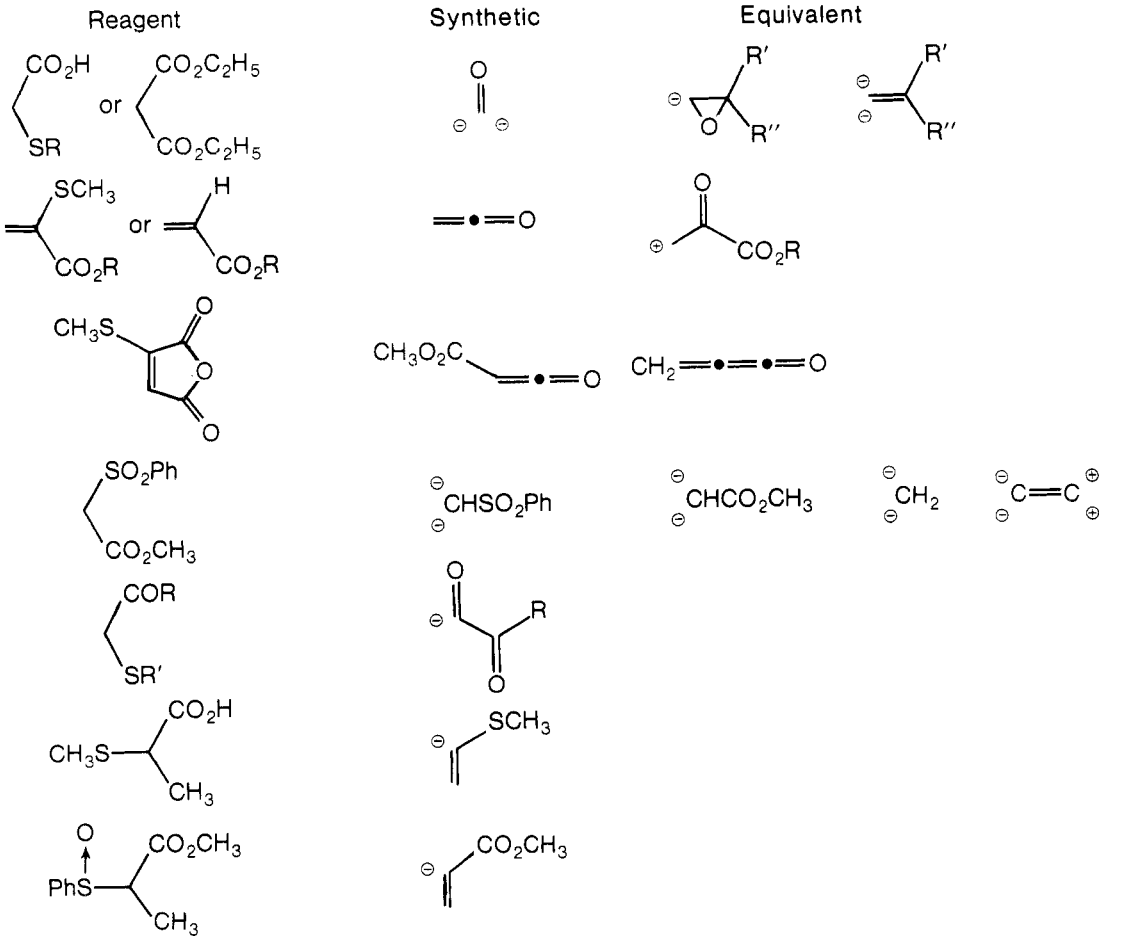
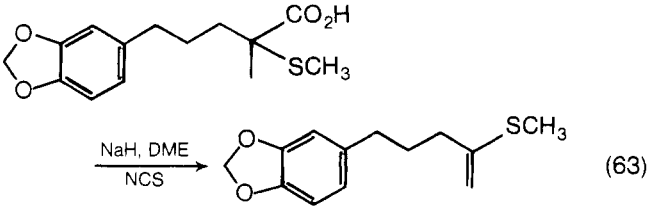


CHART I. Synthons



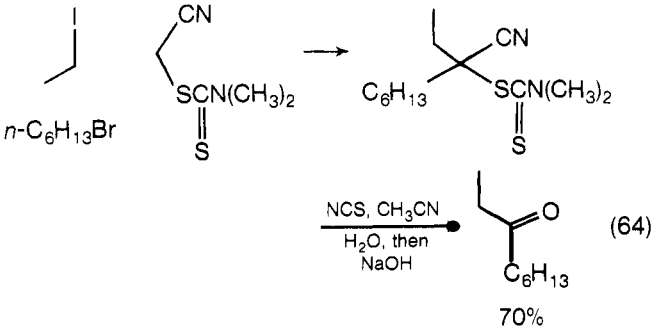
available via oxidative decarboxylation in the absence of a participatory solvent (eq 63).[100]



(63)

85%

The oxidative decyanation degradation of nitriles into the norketones via the cyanohydrin has been developed by Wat and utilized to convert *N,N*-dimethyldithiocarbamoylacetonitrile into a carbonyl dianion equivalent (eq 64).[101]



(64)

70%

IV. Conclusions

The flexibility of sulfur on carbon adjacent to a carbonyl group allows great diversity in structural modification and elaboration as outlined in Scheme I. In addition, it allows the development of synthons as basic building blocks, as summarized in Chart I. Although sulfur chemistry has been an active field for a century, its versatility creates a potential so vast that we have yet discovered but a small portion. The last few years have seen a major assault and the benefits have been immense. Further efforts will surely be exciting and richly rewarding.

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