have delineated the ultraviolet–visible absorption and emission spectra of these species. One might hope also to obtain direct ultraviolet spectroscopic measurements of the various rate constants of the cascade mechanism (Scheme II) by flash photolysis techniques. Direct tests for the intervention of a bisected singlet intermediate and for internal heavy atom effects on the intersystem crossing rate, as well as the preparation of "high spin" compounds containing four or more unpaired electrons, are projects under active study. It seems likely that many of the techniques used here could be applied to the investigation of other biradical species.

(57) Cf. N. J. Turro, M. Mirbach, N. Harrit, J. A. Berson, and M. S. Platz, *J. Am. Chem. Soc.*, in press.

Our studies have been generously supported by the National Science Foundation, the National Institute of General Medical Sciences, and the Hoffmann-La Roche Foundation. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. I am greatly indebted to the many members of our research group who contributed their skill and insight. We thank Professors J. M. McBride and N. J. Turro and their collaborators for joining and guiding us in some of the projects and Professors W. T. Borden, P. Dowd, and W. Schoeller for stimulating exchanges of information.

Some Aspects of Organosulfur-Mediated Synthetic Methods

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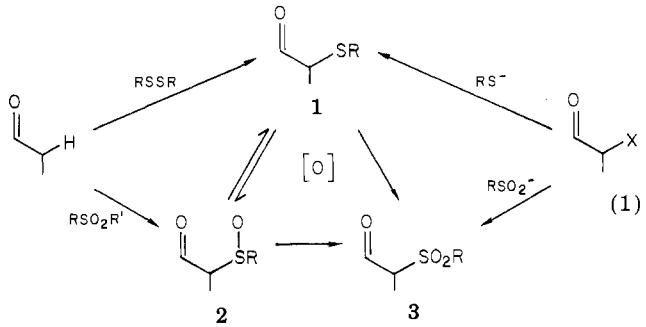
Organosulfur chemistry continues to play a major role in chemical research. While past trends emphasized sulfur compounds for their intrinsic interest, recent efforts are increasingly focusing on the incorporation of sulfur as a temporary control element in an organic molecule. Such sulfur substituents can direct formation of C–C bonds and adjust the oxidation level of carbon. The tremendous flexibility offered by sulfur as a result of its ability to stabilize a reactive carbon species such as a cation, radical, anion, carbene, etc. provides an almost unique opportunity in devising new reactions and reagents. Especially valuable is the juxtaposition of a sulfur substituent α to a carbonyl group. Recently developed reactions and reagents incorporating such a structural feature and their application in synthesis will be considered in this Account.

The utility of sulfur as a chemical control element stems in part from the ease with which it can be introduced into organic molecules (see eq 1).[1-5] Not only

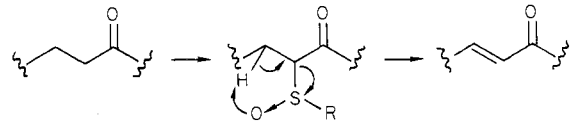


can the sulfur substituents be introduced directly into carbonyl compounds by replacement of C–H or C–X (X = halogen) bonds but also new reagents (vide infra) offer the opportunity to incorporate this structural unit into a starting material for carbon–carbon bond formation. In addition to being able to synthesize the sulfoxides and sulfones directly, they are also available by controlled oxidation of the sulfides. Generally, for any given substrate, the sulfide **1**, sulfoxide **2**, or sulfone **3** is readily available, and each has its own application.

Barry M. Trost joined the faculty at the University of Wisconsin, where he is now the Evan P. and Marion Helfaer Professor of Chemistry, following receipt of the Ph.D. from Massachusetts Institute of Technology in 1965. He was born in Philadelphia, and studied at the University of Pennsylvania for his undergraduate degree. Development of new reactions and reagents and the applications of these new methods to the total synthesis of natural products form a major part of his research program. He was recipient of the ACS Award in Pure Chemistry in 1977.

Dehydrogenation via Sulfoxide Pyrolysis

The selective sulfenylation or sulfinylation of carbonyl compounds followed by thermolytic extrusion of a sulfenic acid constitutes an exceptionally mild and



general route for converting a saturated compound to its α,β-unsaturated derivative.[2] The temperatures vary as a function of R. For R = aryl (e.g., **4**), a temperature of 25–80 °C is normal, whereas for R = alkyl (e.g. **5**), a temperature of 110–130 °C is common. The mildness of the conditions is demonstrated by the success with **4** and the exceedingly broad variety of functional groups compatible with the reaction. The formation of only the queen's substance of bees (**6**) from **5** illustrates the pure *E* configuration obtained with disubstituted olefins.

(1) For a review, see B. M. Trost, *Chem. Rev.*, **78**, in press.
(2) B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976); B. M. Trost and T. N. Salzmann, *ibid.*, **95**, 6840 (1973).
(3) D. Seebach and M. Teschner, *Chem. Ber.*, **109**, 1601 (1976); *Tetrahedron Lett.*, 5113 (1973).
(4) (a) R. M. Coates and H. D. Pigott, *Synthesis*, 319 (1975); (b) H. J. Monteiro and J. P. De Souza, *Tetrahedron Lett.*, 921 (1975); (c) B. M. Trost and L. H. Latimer, *J. Org. Chem.*, **43**, 1031 (1978).
(5) R. Otto and A. Rossing, *Chem. Ber.*, **23**, 756 (1890); F. Asinger, M. Thiel, and I. Kalzendorf, *Justus Liebigs Ann. Chem.*, **610**, 25 (1957); F. Asinger, W. Schafer, and H. Triem, *Monatsch. Chem.*, **97**, 1510 (1966); W. E. Truce and R. Knospe, *J. Am. Chem. Soc.*, **77**, 5063 (1955).
(6) B. M. Trost and B. E. Williams, unpublished observations; B. E. Williams, Ph.D. Thesis, University of Wisconsin, 1977.

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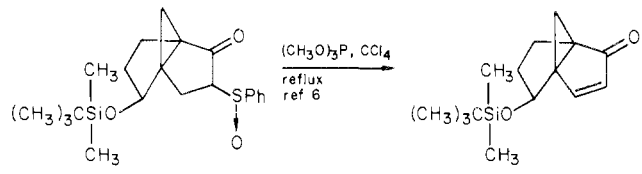

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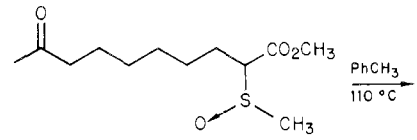

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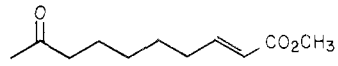

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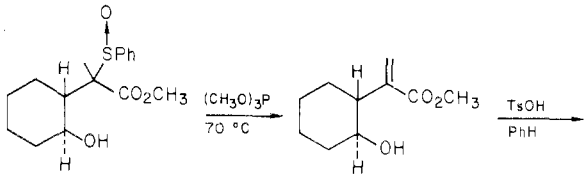
The regiochemistry for hydrogen abstraction in acyclic systems generally follows the order $C{=}C{-}CH_2 \sim C{\equiv}C{-}CH_2 > ArCH_2 \sim CH_3 > {>}C{-}CH_2 \gg {>}C{-}H$. The α-methylene lactone **8** was the exclusive product from **7**.[8] For cyclic systems, a preference for



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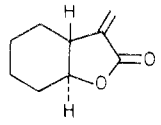

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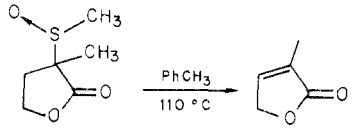
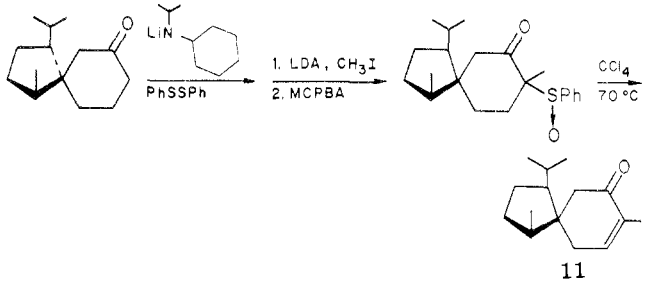


9 10

endocyclic vs. exocyclic elimination is observed within the constraint of the elimination being a cis,syn process. The butenolide **10** is the main product (87%) seen from **9**.[2,9]

The fact that such sulfur intermediates allow regiospecific alkylation as a result of the strong acidifying influence of the sulfur[10] allows combination of the elimination with alkylation. The synthesis of acorenone (**11**) employed such a sequence.[11]

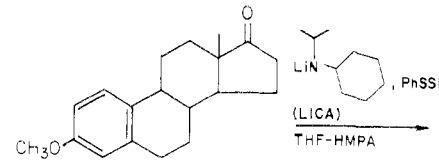


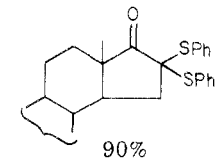
11

(7) B. M. Trost and T. N. Salzmann, *J. Org. Chem.*, **40**, 148 (1975). Also see T. Kumamoto, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 866 (1972).
(8) B. M. Trost and K. K. Leung, *Tetrahedron Lett.*, 4197 (1975).
(9) Also see P. A. Grieco and J. J. Reap, *Tetrahedron Lett.*, 1097 (1974).
(10) (a) R. M. Coates, H. D. Pigott, and J. Ollinger, *Tetrahedron Lett.*, 3955 (1974); (b) cf. ref 3; (c) A. Jonczyk, M. Lukwikow, and M. Makosza, *Rocz. Chem.*, **51**, 175 (1977).

1,2-Dicarbonyl Synthesis and Equivalents

Introduction of a second sulfur substituent in **1**, **2**, or **3** should in principle create a second carbonyl group in a protected form α to an existing carbonyl group. Indeed, the direct bissulfenylation gives the monothioketal of the dicarbonyl compound directly (eq 2).[2,7]





(2)

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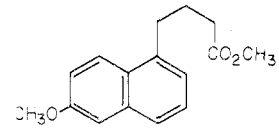

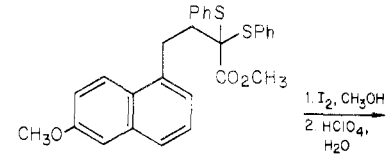

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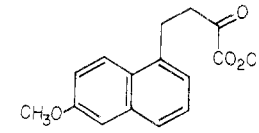

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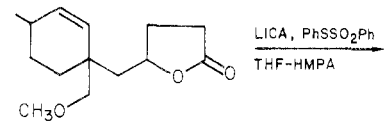
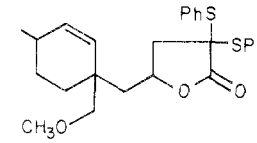
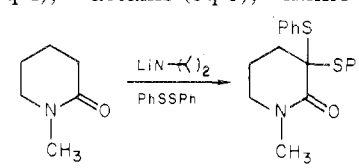




(4)

While diphenyl disulfide works well, phenyl benzenethiosulfonate (readily available by oxidation of diphenyl disulfide) is frequently preferred since it minimizes complications due to desulfenylation of the desired product. Such a reaction proceeds with esters (eq 3),[2,7] lactones (eq 4),[13] lactams (eq 5),[14] imino ethers,[15] and

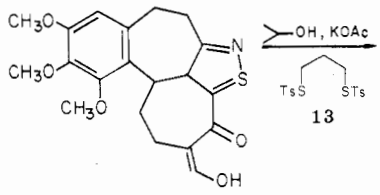


(5)

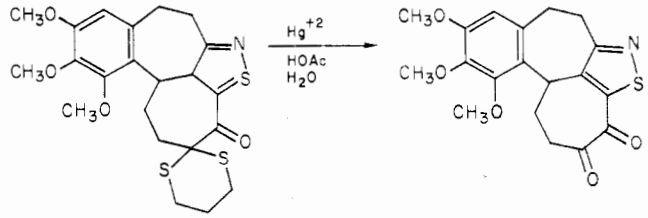
76%

(11) W. Oppolzer, K. K. Mahalanabis, and K. Bättig, *Helv. Chim. Acta*, **60**, 2388 (1977).
(12) B. M. Trost and K. Hiroi, unpublished work.
(13) J. Rigby, Ph.D. Thesis, University of Wisconsin, 1977.
(14) (a) A. Guzman, J. M. Muchowski, and J. Saldana, *Chem. Ind. (London)*, 357 (1977); (b) P. G. Gassman and R. J. Balchunis, *J. Org. Chem.*, **42**, 3236 (1977); (c) P. A. Zoretic and P. Soja, *ibid.*, **41**, 3587 (1976).

nitriles.[16] For the last three classes of compounds, the extraordinarily high propensity for bissulfenylation makes it difficult to obtain the monosulfenylated product directly. In one of the first applications of bissulfenylation for synthesis of an α-dicarbonyl system, a dithianyl group was created by condensing an enamine or a hydroxymethylene derivative of a ketone,[17] e.g., **12**, with trimethylenedithiotosylate (**13**) to give **14**, an intermediate in a colchicine synthesis.[18]

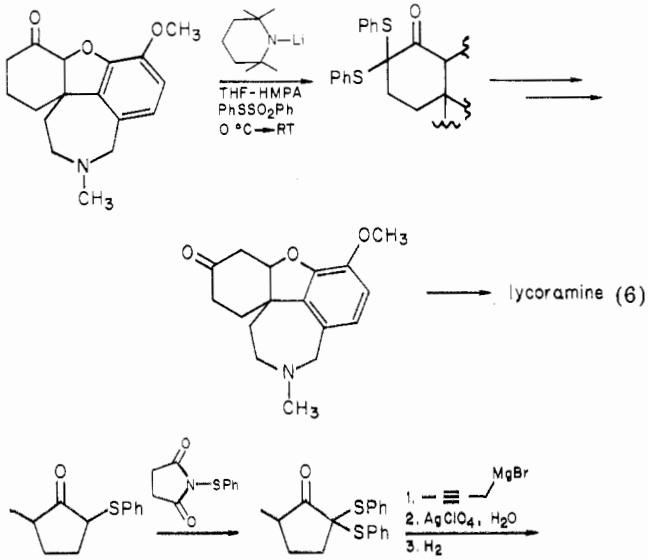


12 **13**



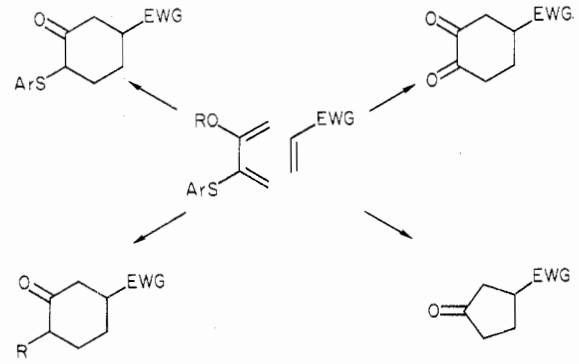
14

1,2-Carbonyl transpositions based upon such methodology have found applications as illustrated by the synthesis of lycoramine (eq 6)[19] and *cis*-jasmone (eq 7).[20]

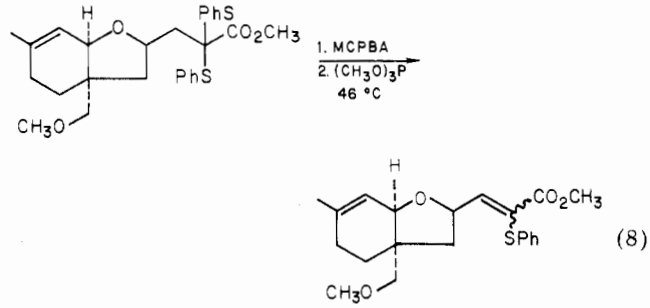


(15) B. M. Trost and R. A. Kunz, *J. Org. Chem.*, **39**, 2475 (1974).
(16) D. N. Brattesani and C. H. Heathcock, *Tetrahedron Lett.*, 2279 (1974).
(17) R. B. Woodward, I. J. Pachter, and M. L. Scheinbaum, *J. Org. Chem.*, **36**, 1137 (1971).
(18) R. B. Woodward, *Harvey Lect.*, **59**, 31 (1965).
(19) A. G. Schultz, Y. K. Lee, and M. H. Berger, *J. Am. Chem. Soc.*, **99**, 8065 (1977).
(20) T. Mukaiyama, S. Kobayashi, K. Kamro, and H. Takei, *Chem. Lett.*, 237 (1972).

Chart I
Structural Variations Available from Dienes 46



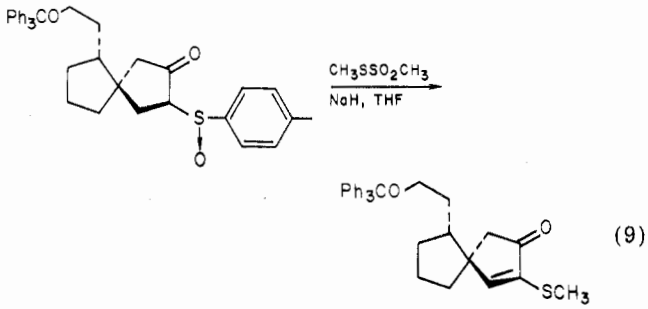
Conversion of the bissulfenylated compound to its monosulfoxide followed by elimination (e.g., eq 8)—the



(8)

48%

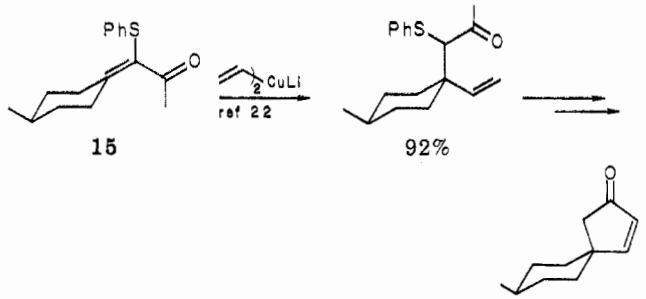
latter occurring under very mild conditions (even room temperature)—generates the monoenol thioether of the α-diketone.[13,21] Sulfenylation of a β-keto sulfoxide is accompanied by elimination to again generate the vinyl sulfide (eq 9).[4c] Such α-sulfenylated α,β-unsaturated



(9)

43%

ketones are activated Michael acceptors, as illustrated for **15** (an intermediate for formation of spiro[4.5]de-

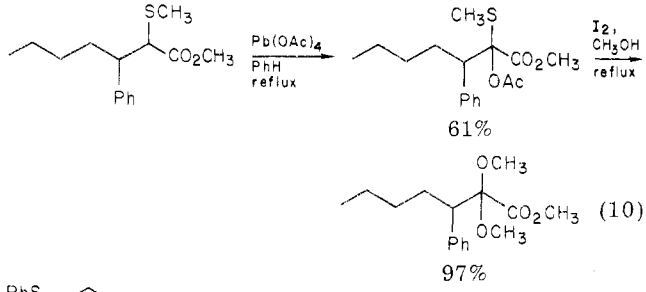


15 92%

cane skeleton), and have the advantage of regiospecifically creating a β-keto sulfide.[21-23]

(21) Also see M. Watanabe, K. Shirai, and T. Kunemoto, *Chem. Lett.*, 855 (1975).
(22) H. C. Arndt, Ph.D. Thesis, University of Wisconsin, 1976.

Acetoxylation also is the equivalent of creating a 1,2-dicarbonyl system (see eq 10 and 11).[24] Oxidation



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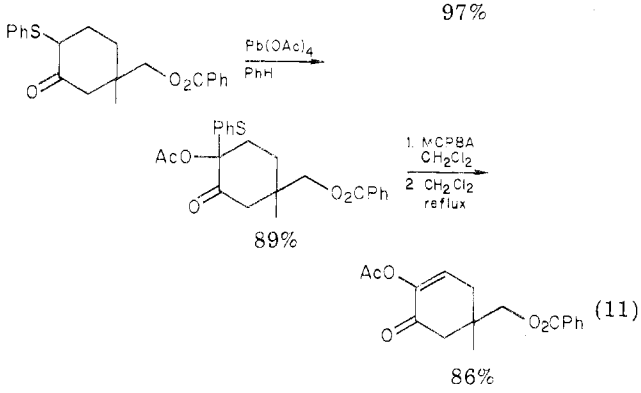
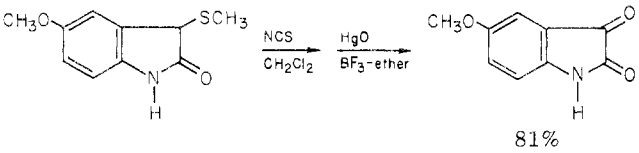
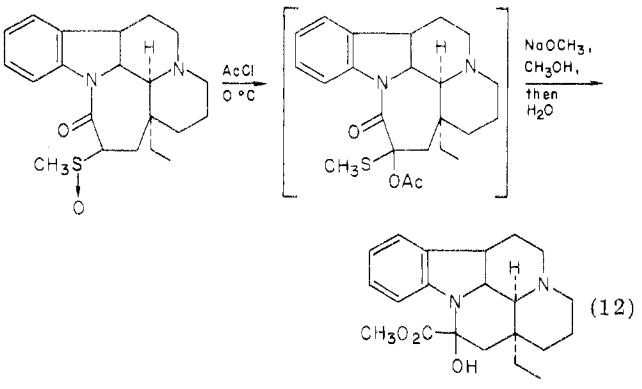


(11)

to the acetoxy sulfoxide which undergoes particularly facile thermolysis (~50 °C) to the olefin constitutes a regiospecific diosphenol synthesis.[25,55a] Other oxidizing agents accomplish a similar net effect, as illustrated by an isatin synthesis from a 3-methylthiooxindole.[26]



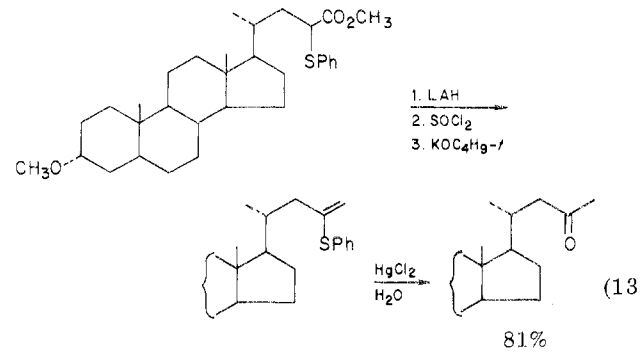
Pummerer reactions of β-keto sulfoxides also effect introduction of carbonyl groups in protected forms and were employed in an elegant synthesis of vincamine (eq 12).[27,28]



(12)

1,2-(Alkylative) Carbonyl Transpositions

While the monoprotected form of the α-dicarbonyl system allows for a carbonyl transposition, the α-thiocarbonyl compounds are excellent intermediates for this type of transformation.[29] Equations 13 and 14



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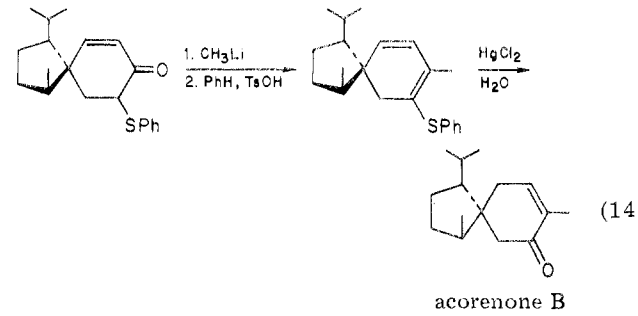


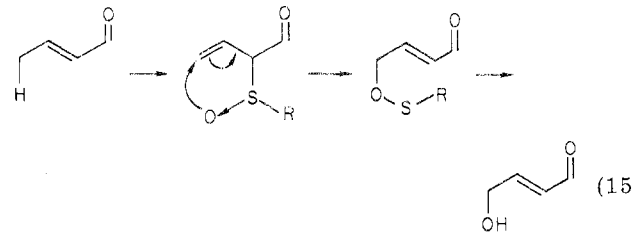
(14)

acorenone B

illustrate the application to both an ester[29] and a ketone,[30] the latter forming a key sequence in the only completely stereocontrolled synthesis of acorenone B. Such methodology is applicable to all types of carbonyl systems, i.e., aldehydes, ketones, esters, etc.

γ-Hydroxylation

The combination of sulfenylation followed by [2.3]sigmatropic rearrangement (eq 15) provides a net



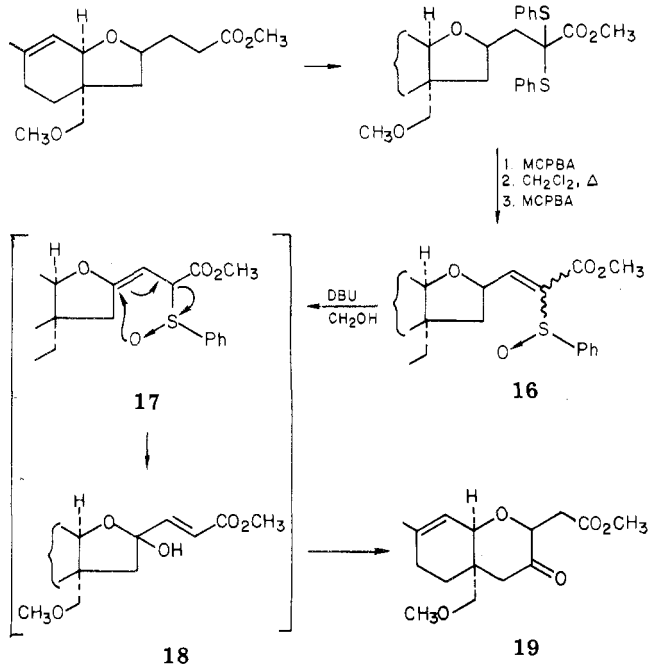
(15)

γ-hydroxylation of an α,β-unsaturated carbonyl system.[13,31] The bissulfenylated compounds offer an opportunity to combine introduction of the double bond with γ-hydroxylation starting from a saturated carbonyl system. The vinyl sulfoxide **16**, available as shown, equilibrates with the allyl sulfoxide **17** which suffers 2,3-sigmatropic rearrangement and in situ desulfenylation to the γ-hydroxyenoate **18**.[13] In this case, **18** undergoes rearrangement to the thermodynamically more stable **19** which is a key intermediate in the projected synthesis of verrucarol, the sesquiterpene portion of the antitumor agent verrucarin.

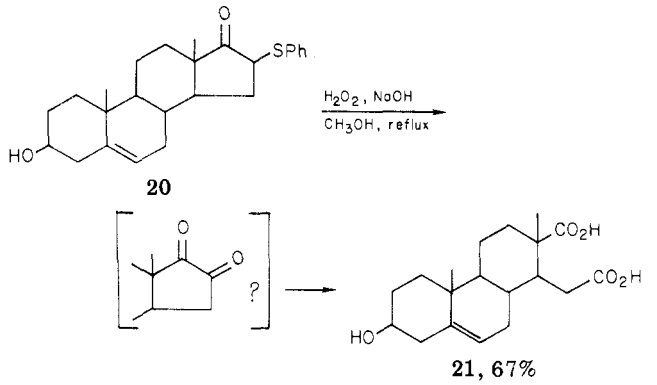
Ring Cleavage

The β-keto sulfides suffer direct ring cleavage upon treatment with basic hydrogen peroxide at slightly

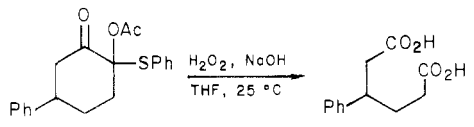
(23) Also see R. J. Cregge, J. L. Hermann, and R. H. Schlessinger, *Tetrahedron Lett.*, 2603 (1973); S. Kurozumi, T. Toru, T. Tanaka, M. Kobayashi, S. Muira, and S. Ishimoto, *ibid.*, 4091 (1976).
(24) B. M. Trost and G. S. Massiot, *J. Am. Chem. Soc.*, **99**, 4405 (1977).
(25) W. C. Vladuchick, Ph.D. Thesis, University of Wisconsin, 1978.
(26) P. G. Gassman, B. W. Cue, Jr., and T. Y. Luh, *J. Org. Chem.*, **42**, 1344 (1977).
(27) J. L. Hermann, R. J. Cregge, J. E. Richman, C. L. Semmelhack, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **96**, 3702 (1974).
(28) Also see J. E. Thompson, *J. Org. Chem.*, **32**, 3947 (1967); H. J. Monterro and A. L. Gernal, *Synthesis*, 437 (1975).
(29) B. M. Trost, K. Hiroi and S. Kurozumi, *J. Am. Chem. Soc.*, **97**, 438 (1975).
(30) B. M. Trost, K. Hiroi, and N. Holy, *J. Am. Chem. Soc.*, **97**, 5873 (1975).
(31) P. R. Ortiz de Montellano and C. K. Hsu, *Tetrahedron Lett.*, 4215 (1976).



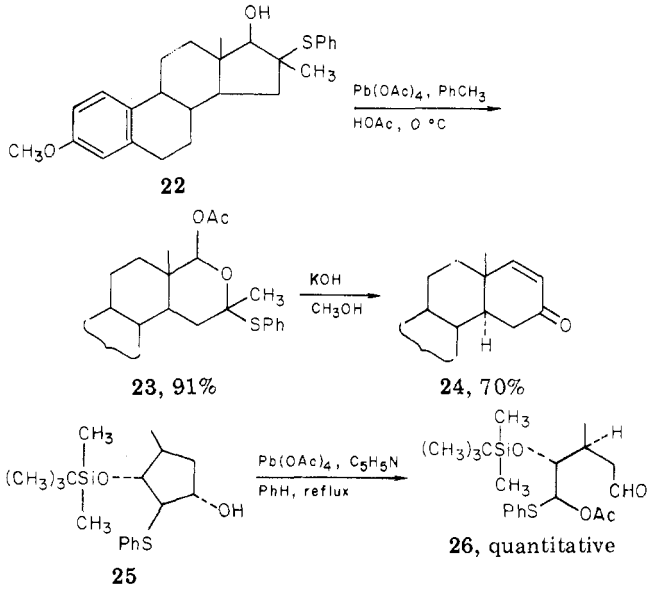
elevated temperatures.[24] The chemoselectivity is illustrated in this example (**20** → **21**) in which the



sensitive homoallylic alcohol need not be protected. Presumably the α-dicarbonyl compounds are intermediates which undergo rapid cleavage to the diacids. The availability of such proposed intermediates under exceptionally mild conditions from the acetoxylated β-keto sulfides allows the latter to be utilized in such reactions under milder conditions.[24]

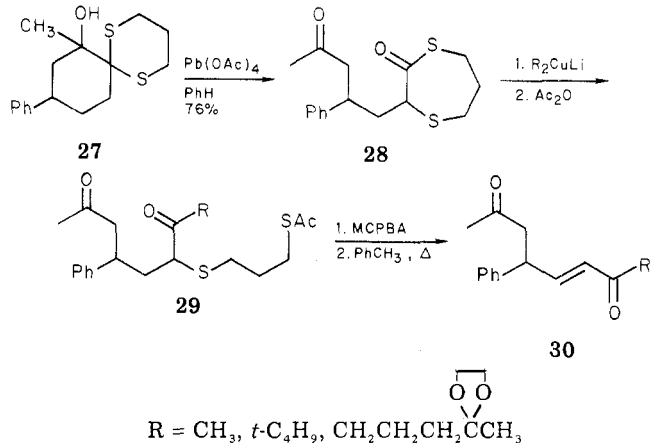


The hydroxy sulfides, available from the keto sulfides by simple reduction with metal hydrides, suffer C–C bond fission with lead tetraacetate.[32] While strained rings (four- and strained five-membered rings as in **22**) cleave under exceptionally mild conditions, the generality is greatly enhanced by the use of pyridine at elevated temperatures as in **25**.[33] The latter conditions allow the reaction to be extended to six-membered or larger rings. A key feature of this ring cleavage is the chemodifferentiation between the termini of the acyclic unit as in **26**. Considering the conversion of **23** to **24**,



the overall process (**22** to **24**) becomes a ring expansion with a 1,3-carbonyl migration. This reaction has recently been utilized in a synthesis of α-cadinol.[34]

An alternative approach for six-membered and larger rings utilizes the β-hydroxydithianes, e.g., **27**, which

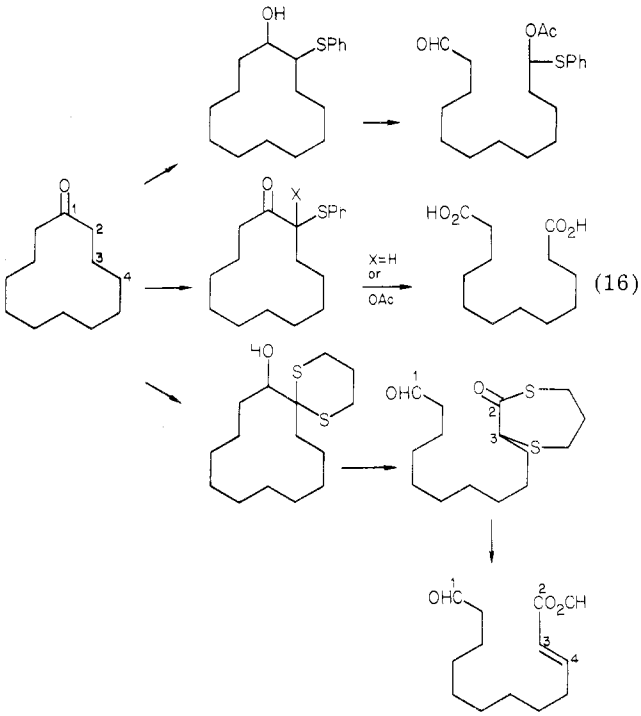


undergo ring cleavage accompanied by sulfur migration to generate an unusual heterocycle, an α-sulfenylated thiolactone, **28**—a process we have termed oxidative seco rearrangement.[35] Taking advantage of the fact that **28** is a thioester allows chemospecific cuprate coupling to generate the ketone **29** and of the fact that it is also an α-sulfenylated carbonyl compound allows facile introduction of the conjugated double bond (e.g., **29** → **30**).

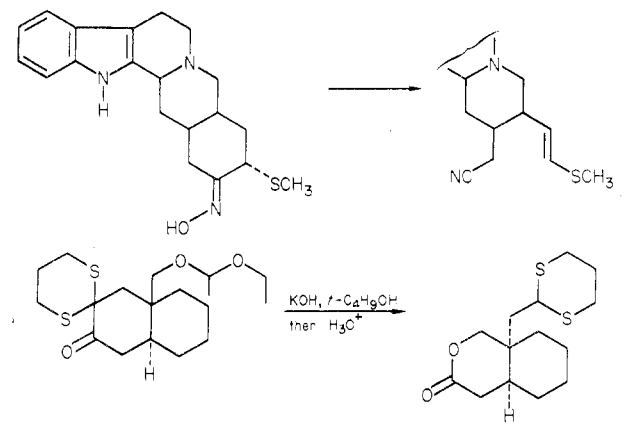
As summarized in eq 16 for the case of cyclododecanone, the chemodifferentiated dialdehyde, aldehyde ester, or diacid is available. The oxidative seco rearrangement is particularly striking since it allows selective modification of the oxidation level of C(1) and C(2), C(1) through C(3), or C(1) through C(4).

Other sulfenylated carbonyl compounds also allow ring cleavage such as the second-order Beckmann reaction of the oximes of α-thioketones[36] and the nu-

(32) B. M. Trost and K. Hiroi, *J. Am. Chem. Soc.*, **97**, 6911 (1975).
(33) B. M. Trost and P. J. McDougal, unpublished observations.
(34) D. Caine and A. S. Frobese, *Tetrahedron Lett.*, 3107 (1977).
(35) B. M. Trost and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4313 (1976); B. M. Trost and L. Jungheim, unpublished observations.
(36) R. L. Autry and P. W. Scullard, *J. Am. Chem. Soc.*, **90**, 4917, 4924 (1968).

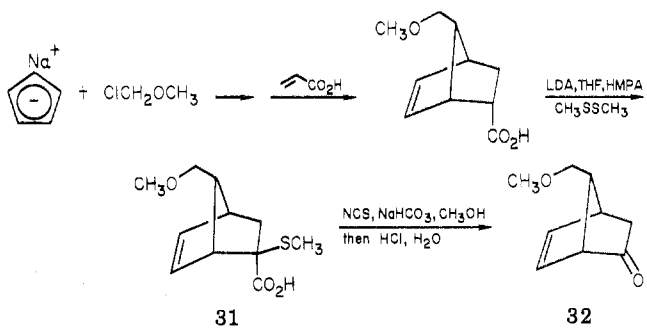


cleophilically induced cleavage of α-dithianyl ketones.[37]



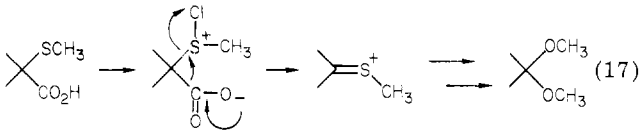
Oxidative Decarboxylation

Treatment of α-thiocarboxylic acids with mild oxidizing agents such as positive halogen species, sodium metaperiodate, or lead tetraacetate initiates loss of carbon dioxide.[38,39] Thus, the prostaglandin intermediate **32** is available upon subjecting the acid **31** to

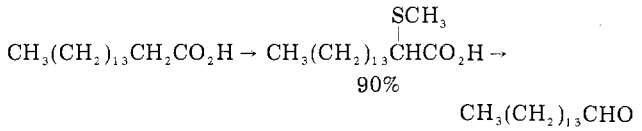


31 **32**

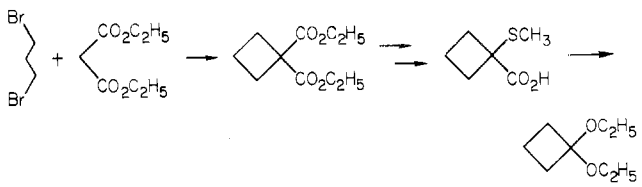
NCS in methanol solvent. The reaction presumably involves the formation of a thionium ion which is trapped by the alcohol solvent to ultimately give a ketal as shown in eq 17. Such ketals can be easily isolated



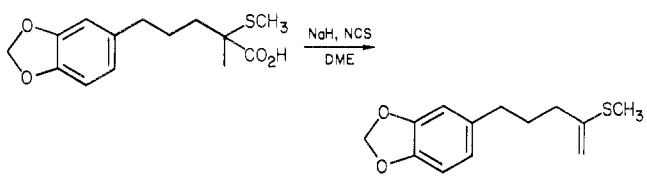
or hydrolyzed during workup to the ketone. This method of degrading a carboxylic acid to its norketone can be applied to fatty acids such as palmitic acid employing powdered sodium metaperiodate in methanol to avoid oxidation at the carbon bearing sulfur prior to decarboxylation.[39,40]



By this approach, enolates of carboxylic acids become synthons for acyl anions. Thus, acrylic acid is a ketene synthon as illustrated in the synthesis of **32**. The anions from malonates are synthons for carbonyl dianions as represented by the synthesis of the ketal of cyclobutanone.[39,40]



In the absence of a participatory solvent, the intermediate thionium ion undergoes deprotonation to the vinyl sulfide.[41] Only the thermodynamically less stable enol thioether was observed.

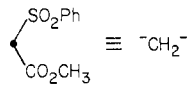


Conjunctive Reagents[42] 42

The flexibility that the S—C—C=O unit has for elaboration allows the creation of a number of basic building blocks for constructing complex molecules in which such a grouping is present as such or in a masked form. By using this approach, steps are obviously saved and a synthesis becomes more convergent. For example, α-methylthioacrylic acid is a more direct ketene synthon in cycloadditions than acrylic acid followed by a later sulfenylation.

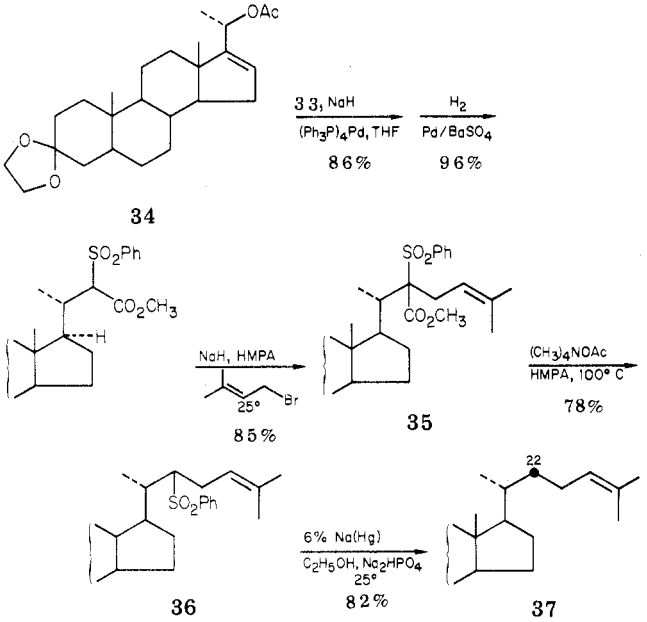
Taking advantage of the acidifying influence of sulfur and its ease of removal allows the use of methyl benzenesulfonylacetate (**33**) as an equivalent for methylene dianion.[43] Thus, a steroid side chain was introduced using this conjunctive reagent in which two allylic al-

(37) J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, **39**, 1814 (1974); **40**, 534 (1975). For in situ bissulfenylation and ring cleavage of cyclobutanones, see B. M. Trost and J. Rigby, *ibid.*, 41, 3217 (1976).
(38) B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, **97**, 3528 (1975).
(39) B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, **99**, 3101 (1977).
(40) B. M. Trost and Y. Tamaru, *Tetrahedron Lett.*, 3797 (1975).
(41) B. M. Trost, M. Crimmin, and D. Butler, *J. Org. Chem.*, in press.
(42) The term conjunctive reagents is introduced to focus on those "reagents" which are simple building blocks that are incorporated in whole or in part into a more complex system and to differentiate them from reagents that operate on but are not normally incorporated into a substrate. Thus, methyl vinyl ketone would be a conjunctive reagent and chromic acid would be a simple reagent.
(43) For a review of sulfone chemistry see P. D. Magnus, *Tetrahedron*, 2019 (1977).

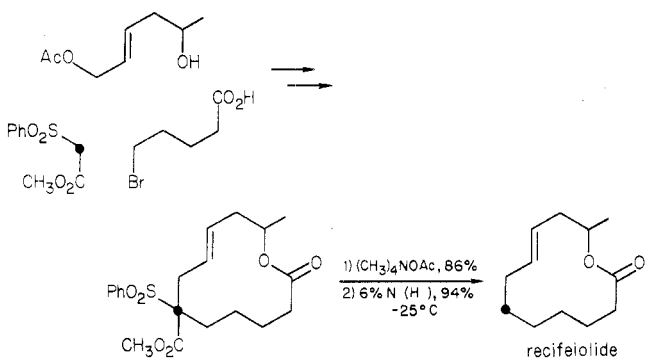


33

kylations (**34** → **35**) replaced the two C–H bonds with



C–C bonds.[44,45] Decarbomethoxylation of **35** proceeds smoothly using a dealkylative decarboxylation technique to give **36**. Smooth desulfonylation of **36** with buffered sodium amalgam produces **37** in which C(22) is the conjunctive point.[46] The ease with which these latter two steps proceed has made this conjunctive reagent a key one in our macrolide syntheses,[47] as illustrated in the recifeiolide synthesis.[48] The steric

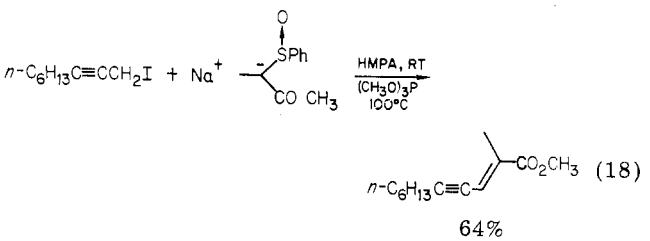


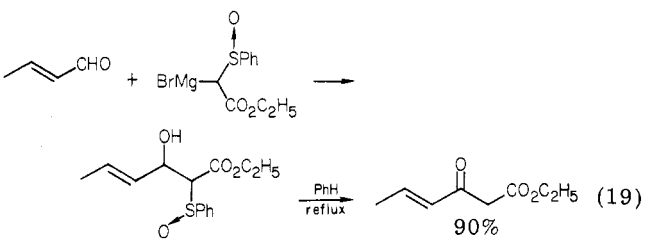
hindrance provided by the sulfone and its high anion-stabilizing ability normally mean that reactive alkylating agents like primary or allyl halides (as well as π-allylpalladium complexes) are required.[49]

The fact that β-hydroxy sulfones (as well as β-hydroxy sulfides) undergo smooth elimination to olefins[50] makes **33** the equivalent of a vinyl anion. The introduction of a vinyl group at C(20) of **38** gave **39**

which served as an intermediate toward the stereocontrolled generation of the side chain of the insect molting hormone, ecdysone.[51]

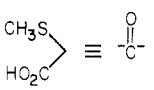
Methyl or ethyl α-benzenesulfinylcarboxylates are olefination conjunctive reagents that complement the Wittig and related reagents.[8,52] Alkylation with alkyl halides and in situ thermolysis lead directly to conjugated carbonyl compounds (eq 18); moreover, a facile





β-keto ester synthesis pertains by adding the magnesium salt to an aldehyde followed by thermolysis (eq 19).[53]

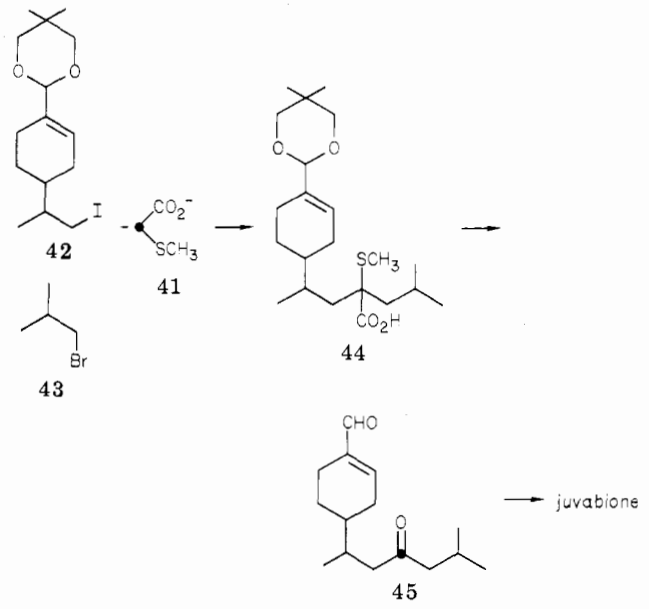
Methylthioacetic acid (**40**) is a carbonyl dianion equivalent.



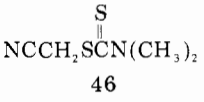
40

The presence of the thio substituent allows particularly facile dianion (**41**) formation to generate a fairly good nucleophile.[39,40] For example, in a synthesis of the insect hormone mimic, juvabione, **41** was sequentially alkylated with **42** and **43** to give **44**. Subjection of the latter to the usual conditions of oxidative decarbox-

(44) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **100**, 3435 (1978).
(45) Also see B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **98**, 630 (1976).
(46) B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, *Tetrahedron Lett.*, 3477 (1976).
(47) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **99**, 8116 (1977).
(48) B. M. Trost and T. R. Verhoeven, *Tetrahedron Lett.*, 2275 (1978).
(49) For related studies see M. Julia and P. Badet, *Bull. Soc. Chim. Fr.*, 1363 (1975); K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1397 (1975); G. K. Cooper and L. J. Dolby, *ibid.*, 4675 (1976).
(50) M. Julia and J. M. Paris, *Tetrahedron Lett.*, 4833 (1973).
(51) B. M. Trost and Y. Matsumura, *J. Org. Chem.*, 42, 2036 (1977).
(52) B. M. Trost, W. P. Conway, P. E. Strege, and T. J. Dietsche, *J. Am. Chem. Soc.*, **96**, 7165 (1974); B. M. Trost and A. J. Bridges, *J. Org. Chem.*, **40**, 2014 (1975).
(53) J. Nokami, N. Kunieda, and M. Kinoshita, *Tetrahedron Lett.*, 2841 (1975). Also see N. Kunieda, J. Nokami, and M. Kinoshita, *ibid.*, 3997 (1974); J. Nokami, N. Kunieda, and M. Kinoshita, *ibid.*, 2179 (1975).



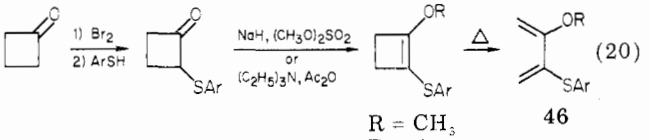
ylation followed by hydrolysis gave the desired keto aldehyde **45**, after which oxidative esterification gave juvabione. *N*,*N*-Dimethyldithiocarbamoylacetonitrile (**46**) has been used in similar fashion in which oxidative decyanation unmasks the ketone.[54]



46

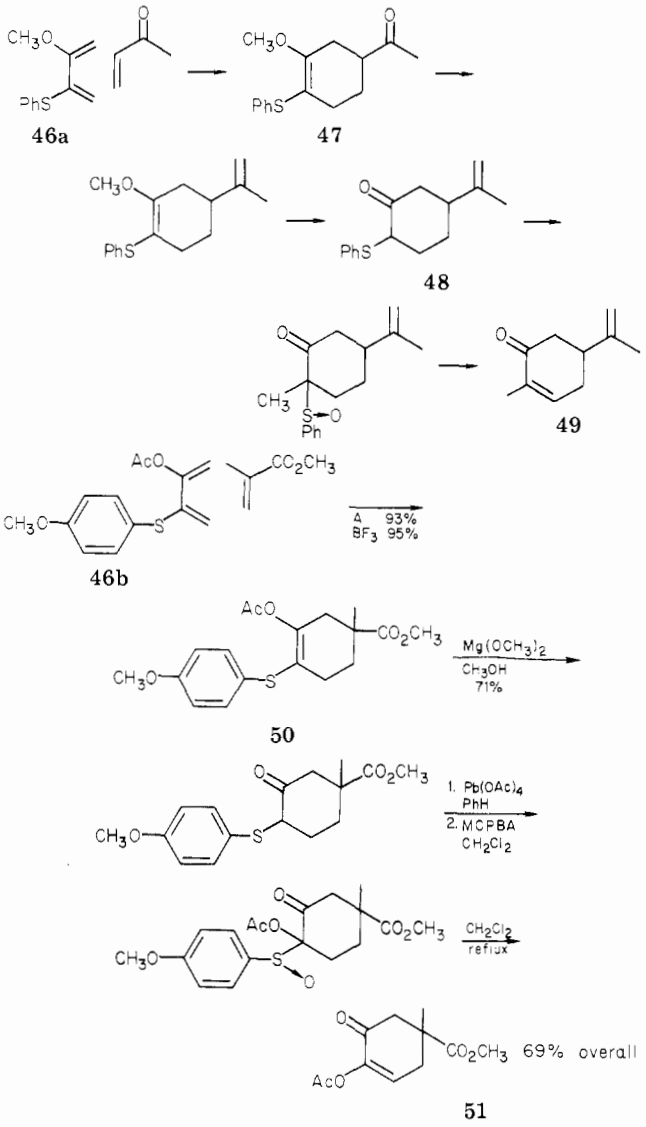
The development of conjunctive reagents that can be partners in cycloaddition reactions form a particularly exciting class. In such reactions, not only will the versatility of the sulfenylated product provide utility, but the ability of sulfur to exercise high regiochemical control can be particularly fruitful. Attention focused on incorporating such substitution in the partners of the Diels–Alder reaction.

The requisite dienes were readily available from cyclobutanone (eq 20).[55,56] Thermal cycloaddition of

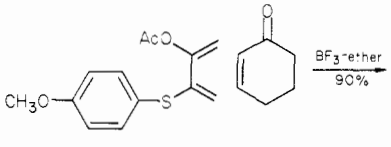


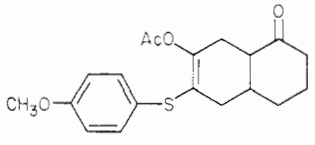
(20)

these compounds (**46**) provides adducts whose regiochemistry is dominated by sulfur and in which the β-keto sulfide is present in a protected form (see **47**). Thus, subjection of the adduct **47** to the Wittig reaction followed by hydrolysis provides the β-keto sulfide **48**. Taking advantage of the acidifying influence of the sulfur and the sulfoxide pyrolysis, **48** was easily methylated and eliminated to give (±)-carvone **49**. The alternative diene **46b** exhibits a higher selectivity for sulfur control compared to **46a**. Thus, in the reaction with methyl methacrylate, **46a** gave a >5:1 ratio of the two regioisomers in which sulfur dominated (i.e., S and ester in a 1,4 relationship). With **46b**, the thermal



reaction gave a >9:1 ratio and the Lewis acid catalyzed version gave a >50:1 ratio. In this case, the adduct was subjected to acetoxylation and elimination to **51** to constitute a regiospecific diosphenol synthesis. In addition to the unusual regiochemistry shown by these dienes, they show a high reactivity as illustrated by the excellent cycloaddition to cyclohexenone. Chart I summarizes the structural variations available via this method. Note that the ease with which sulfur can be replaced by hydrogen allows a 1,3 orientation of the oxygen (or presumably other substituent) and the electron-withdrawing group (EWG), an orientation not available by the direct cycloaddition.





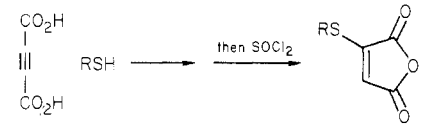
Incorporation of the sulfur substituent in the dienophile also generates interesting reagents. The thio-

(54) Y. Masuyama, Y. Ueno, and M. Okawara, *Tetrahedron Lett.*, 2967 (1976).

(55) (a) B. M. Trost and A. J. Bridges, *J. Am. Chem. Soc.*, **98**, 5017 (1976); (b) B. M. Trost, J. Ippen, and W. C. Vladuchick, *ibid.*, **99**, 8116 (1977).

(56) Also see T. Cohen, A. J. Mura, Jr., D. W. Shull, E. R. Fogel, R. J. Ruffner, and J. R. Falck, *J. Org. Chem.*, **41**, 3218 (1976).

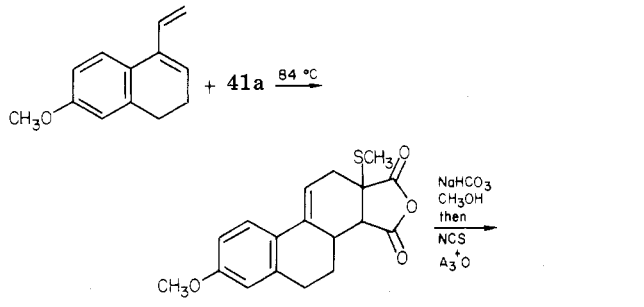
maleic anhydrides are readily available from acetylenedicarboxylic acid and the thiols as outlined in eq 21.[57] Cycloaddition proceeds smoothly with either **52a**



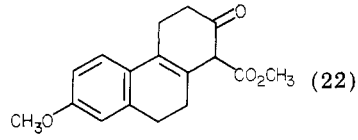
(21)

a, R = CH_3
b, R = Ac

or **52b**, the latter being considerably more reactive. Equations 22 and 23 illustrate the contrasting regio-

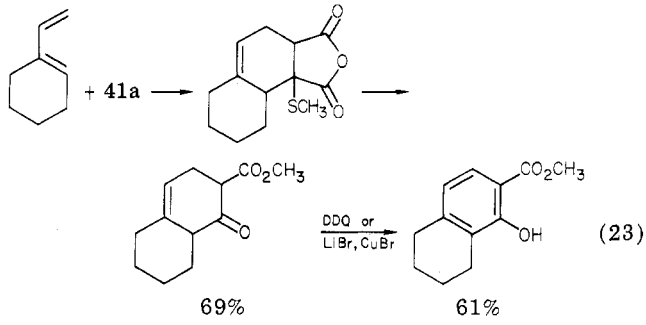


82%



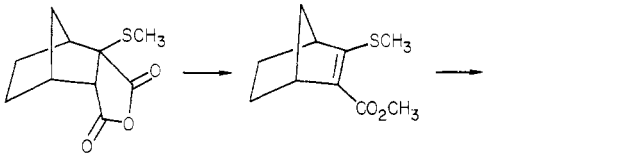
(22)

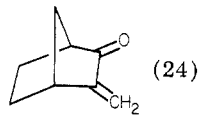
61%



69% 61%

(23)

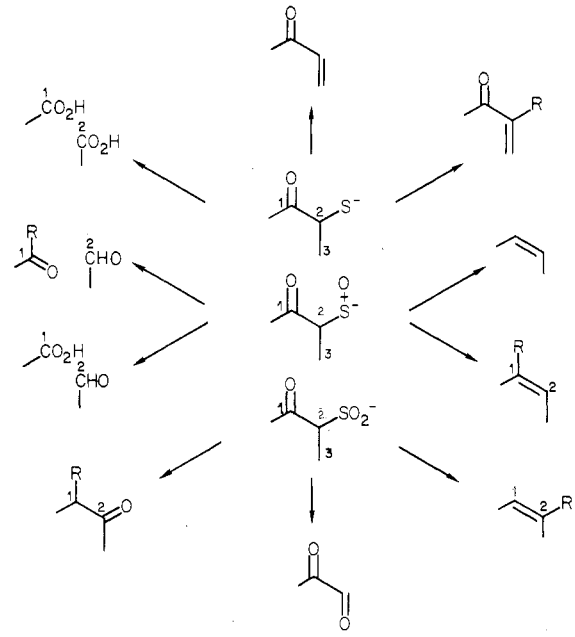


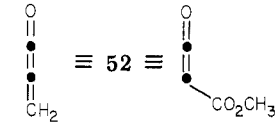


(24)

chemistry observed with 1,2-disubstituted dienes. The utility of the adducts stems from the presence of an α-thiocarboxylic acid which, when subjected to the conditions of oxidative decarboxylation, produces β-keto esters in an annulative approach. The ability to oxidize such substrates to salicylic esters (eq 22) makes this method a good synthesis of this important class of aromatics. In bicyclic systems, the enol thioethers are normally the direct products of oxidative decarboxylation, as shown in eq 24. By having the ketone group so masked, reduction of the ester and hydrolysis make this an annulative approach to α-methylenecyclohexanones. Thus, these maleic anhydrides are synthetically equivalent to a carbomethoxyketene or methyleneketene in cycloadditions.

Chart II
α-Thiocarbonyl Compounds in Synthesis





Conclusion

Chart II summarizes some of the adjustments in oxidation level achievable via these versatile intermediates. Many more can be added now and will be added as a result of future work. The ability to generate many new conjunctive reagents containing such structural features opens a vast area for exploration from which much greater efficiency in synthetic design will surely follow.

I wish to thank the many collaborators who contributed extensively to these programs in our laboratories. They are individually acknowledged in the references. Continuing financial support from the National Science Foundation and the National Institutes of Health has made all of our work possible, and we express our gratitude.

(57) B. M. Trost and G. Lunn, *J. Am. Chem. Soc.*, **99**, 7079 (1977); B. M. Trost and H. Diehl, unpublished observations.