linked to an unsaturated system.

A wide range of structures can now be viewed as possessing a surface of delocalized charge density. Consider, for example, the molecular graph shown in Figure 3 for the $C_6H_6^{2+}$ cation, whose hexamethyl derivative was first synthesized by Hogeveen and Kwant.[21] The molecular graph is determined by a charge density obtained from an STO-3G wave function for an optimized geometry constrained to C_{5v} symmetry. The energy and geometrical parameters so obtained agree with those previously reported by Jemmis and Schleyer.[22]

This structure of $C_6H_6^{2+}$ consists of five fused three-membered rings.[23] Each CC bond in the plane of the five carbons has $n = 1.19$ and $\epsilon = 0.05$. Each of the long ($R_e = 1.711$ Å), curved bonds terminating at the apical carbon has a low bond order of 0.44, a large ellipticity equal to 1.84, and a low value of $|\nabla^2\rho| = 0.10$ Å^{-5}. These bonds are labile. The values of ρ at the critical points of the three-membered rings are only 0.004 Å^{-3} less than the values of ρ_b for the long CC bonds. There is therefore a ring of charge density of low and almost constant value, $\sim$0.07 Å^{-3}, linking the bond and ring critical points in the atomic surface of the apical carbon atom. Associated with each 3MR is a surface of delocalized charge density and each such surface is coupled with its neighboring surface by the major axes of the common ring bonds. Thus the apical carbon is bonded to the remaining five carbon atoms by one continuous surface or cap of delocalized charge. A summation of the CC bond orders shows that approximately six electrons contribute to this delocalized system. The topological theory of molecular structure enables one to identify the existence of three-membered rings and their associated surfaces of delocalized charge in such capped structures. The relationship between the energy of a system and the one- and two-dimensional mechanisms of charge delocalization is currently under investigation using expressions which relate the quantity $\nabla^2\rho(\mathbf{r})$ to the quantum mechanical stress tensor and kinetic energy density.[24]

Acknowledgment. We wish to thank Dr. R. F. Childs for many useful discussions and Dr. R. C. Haddon for kindly providing us with the optimized geometrical parameters for structures of $C_8H_9^+$ and $C_4H_5^+$ prior to publication. One of us (D.C.) wishes to acknowledge a research grant from the Deutsche Forschungsgemeinschaft and support provided by the Fonds der Chemischen Industrie and the "Rechenszentrum der Universität Köln".

Registry No. **1a**, 14973-56-9; **1b**, 25268-58-0; **1c**, 19067-43-7; **2a**, 39419-88-0; **2b**, 32731-02-5; **3b**, 12316-90-4; **4a**, 26812-57-7; **4b**, 32730-99-7; **4c**, 86013-58-3.

(21) Hogeveen, H.; Kwant, P. W. *J. Am. Chem. Soc.* **1974**, *96*, 2208–2214.
(22) Jemmis, E. D.; Schleyer, P. V. R. *Ibid.* **1982**, *104*, 4781–4788. These authors have recently reviewed and extended the use of the $4n + 2$ rule of aromaticity to account for the stabilities of capped structures.
(23) The surface of the apical carbon atom extends through the plane of the five carbon nuclei and there is no associated ring critical point. Hence the structure is not closed and does not form a cage.
(24) Bader, R. F. W. *J. Chem. Phys.* **1980**, *73*, 2871–2883. Bader, R. F. W.; Nguyen-Dang, T. T. *Adv. Quantum Chem.*, **1981**, *14*, 63–124.

Enol Thioethers as Enol Substitutes. An Alkylation Sequence

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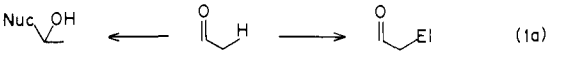
Abstract: Ionic bromination of enol phenyl thiolethers forms predominantly to exclusively 2-(phenylthio)-3-bromo-1-alkenes, an enolonium equivalent. The allylic bromide participates in displacements with stabilized and nonstabilized nucleophiles. The ability to hydrolyze the enol thioethers to their corresponding ketones equates this sequence to an equivalence of an enolonium ion. The versatility of the sulfur in selective introduction of allylic hydroxyl and amino groups as well as the ability to directly replace the sulfur substituent by hydrogen or alkyl imparts special significance to this approach. The sequence is highly regio- and chemoselective. Applications include the synthesis of lanceol and bisabolene and the introduction of steroid side chains.

The carbonyl group represents one of the most important functional groups in organic chemistry because of the ability to achieve selective nucleophilic additions to the carbonyl carbon atom and electrophilic substitution at the α-carbon atom (eq 1a).



(1a)

Limitations posed by these direct processes have initiated searches for substitutes. For example, the catalytic effect of secondary amines in nucleophilic additions to carbonyl groups underpins the classical Doebner modification of the Perkin condensation in which the higher susceptibility of iminium ions to nucleophilic addition enhances the rate of addition of the weakly nucleophilic malonate anion.[1] The use of enamines or metalloenamines to mediate α-substitution mainly derives from a concern for selectivity—chemoselectivity and diastereoselectivity.[2] From the above examples, nitrogen-based substitutes clearly have become imbedded into synthetic methodology.

The versatility offered by sulfur chemistry suggests that related sulfur systems may also have special roles to play. For carbonyl additions, the sulfur equivalent becomes a thionium ion **1**; for

1 2 3 4

α-substitutions, the critical intermediate becomes a vinyl sulfide, **2**. Further, the direct methods of synthesis of **1** and **2** without necessarily proceeding through carbonyl compounds provide even more incentive to explore this chemistry. For example, thioketals,

(1) Johnson, J. R. *Org. Reactions* **1942**, *1*, 210.
(2) Cook, "Enamines": Synthesis, Structure, Reactions"; Marcel Dekker: New York, 1969. Dyke, S. F. "The Chemistry of Enamines"; Cambridge University Press: London, 1973. Kuehne, M. E. *Synthesis* **1970**, 510. Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7.

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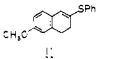
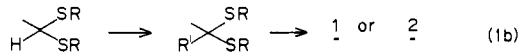
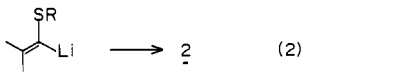
Table I. Preparation of Vinyl Sulfides with Mercuric Trifluoroacetate

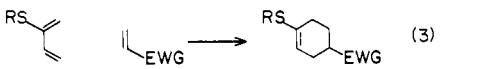
entry	ketone	thioketal	isolated yield, %	vinyl sulfide	isolated yield, %
					
1	$n = 1$	$n = 1$	90	(a) $n = 1$	68
2	$n = 2$	$n = 2$	77	(b) $n = 2$	67
3	$n = 4$	$n = 4$	27	(c) $n = 4$	84
4	$n = 8$	$n = 8$	83	(d) $n = 8$	50
5			51		85
					
6a		Ar = Ph	78	(a) Ar = Ph	82
6b		Ar = p-$CH_3OC_6H_4$-	78	(b) Ar = p-$CH_3OC_6H_4$-	65
7					88
8			72		53

which are directly available by alkylation of thioacetals, represent a precursor for both **1** and **2** (eq 1b).[3] α-Metalated vinyl sulfides

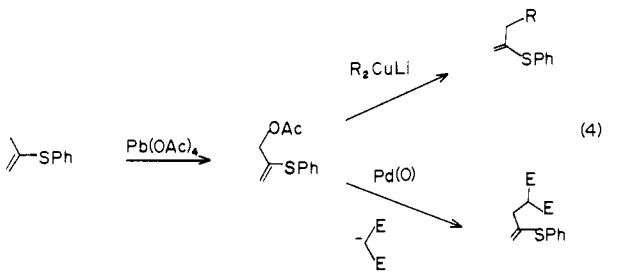

(1b)

(eq 2)[4] and 2-thiosubstituted-1,3-dienes (eq 3)[5,6] offer direct entries into vinyl sulfides of defined structure.

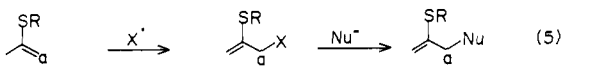

(2)


(3)

We initiated a systematic investigation into the chemistry of **1**[7,8] and **2**.[9] In the latter regard, our attention focused on an equivalent of an enolonium ion, **3**,[10-12] which becomes **4**. In its simplest version, a vinyl sulfide could be envisioned to be allylically oxidized as in eq 4 to permit smooth coupling with cuprates and


(4)

palladium-initiated displacements with stabilized anions.[9a] In order to expand the horizon of such a strategy to a broader range of nucleophiles, we turned our attention to an examination of allylic halogenation[13,14] and subsequent displacement as in eq 5.


(5)

Oxygen-derived enolonium equivalents have evolved.[10-12] However, generalization to a broader range of ketones remains

(3) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. Lever, O. W., Jr. *Tetrahedron* **1976**, *32*, 1943. Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357.

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(9) (a) Trost, B. M.; Tanigawa, Y. *J. Am. Chem. Soc.* **1979**, *101*, 4413. (b) *Ibid.* **1979**, *101*, 4743. (c) Trost, B. M.; Ornstein, P. L. *Tetrahedron Lett.* **1981**, *22*, 3463.

(10) For a recent leading reference see Hosomi, A.; Shirahata, A.; Araki, Y.; Sakurai, H. *J. Org. Chem.* **1981**, *46*, 4631. Also see Trost, B. M.; Gowland, F. *J. Org. Chem.* **1979**, *44*, 3448.

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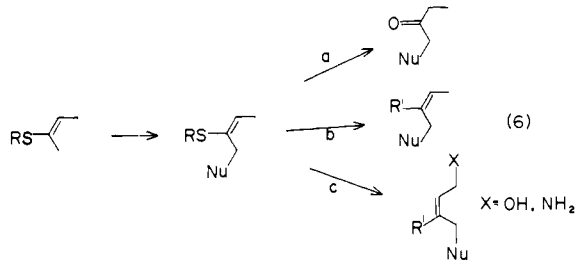
(12) For α-haloketones and their derivatives see (a) Sakai, T.; Amano, E.; Kawabata, A.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 43. (b) Cacchi, S.; Misiti, D.; Felici, M. *Synthesis* **1980**, 147. (c) Sacks, C. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *97*, 7372. Machinskaya, I. V. *J. Gen. Chem. USSR* (*Engl. Transl.*) **1959**, *29*, 2786.

(13) For chlorination of allyl sulfides see Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4433.

(14) For allylic halogenation of enol derivatives see Fleming, I.; Goldhill, J. *J. Chem. Soc., Perkin Trans. I* **1980**, 1493. Machinskaya, I. V.; Barkhash, V. A. *J. Gen. Chem. USSR* (*Engl. Transl.*) **1956**, *26*, 967. Rubin, M.; Armbrecht, B. *J. Am. Chem. Soc.* **1953**, *75*, 3513. Mousseron, M.; Winternitz, F.; Jacquier, R. *C. R. Hebd. Seances Acad. Sci.* **1974**, *224*, 1062.

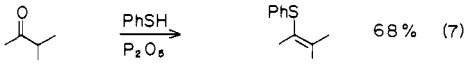
limited due to the inaccessibility of the requisite substitution pattern. Use of α-halo ketones directly suffers from a plethora of competing reactions (e.g., eliminations, Favorskii rearrangements, etc.) as well as the reactivity of the carbonyl group itself.[12] Conversion of the carbonyl group into an enol derivative attenuates such problems, but others arise. For example, allylic bromination of vinyl chlorides or ethers lacks regioselectivity.[14] The flexibility offered by sulfur attaches special significance to the use of vinyl sulfides in such a role. While hydrolysis to a ketone (eq 6, path



(6)

a) provides a formal enolonium equivalency, the fact that the carbonyl compound normally represents a stepping stone for further structural elaboration raises the question of direct utilization of the initial alkylated vinyl sulfide in such elaborations. For example, the efficient transition metal catalyzed coupling of vinyl sulfides with organometallics to give substituted olefins (eq 6, path b)[15] provides a more efficient approach to regiocontrolled trisubstituted olefin synthesis than the alternative route from the carbonyl group, which necessitates addition of an organometallic conjunctive reagent followed by dehydration. The alkylative allylic transposition from the vinyl sulfide (eq 6, path c) is considerably more efficient than any route starting from a saturated ketone.[16,17] We wish to report initial results that suggest enol thioethers offer promise as a general solution with enhanced flexibility.

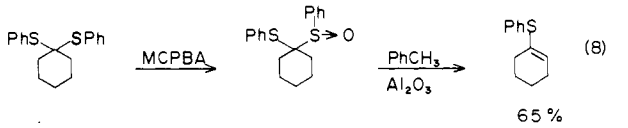
Synthesis of Vinyl Sulfides. The direct conversion of ketones to their corresponding sulfides proceeds under strong acid conditions,[17a,18] as illustrated by the preparation of 2-(phenylthio)-3-methyl-2-butene (**6**). A milder method invoked direct



68% (7)

6

elimination from a thioketal[19] in turn available by adding a catalytic amount of gaseous hydrogen chloride into a neat mixture of ketone and thiol at room temperature.[20] Mercuric trifluoroacetate[21,22] in acetonitrile in the presence of lithium carbonate smoothly effected the desired elimination (Table I). An alternative procedure involved the monooxidation of the thioketal followed by thermolysis as outlined in eq 8. In earlier work in



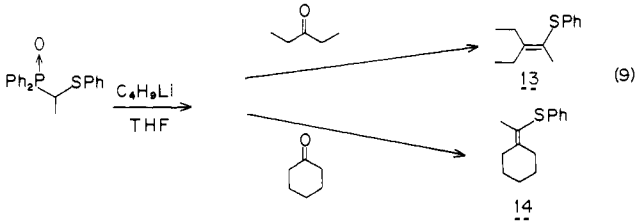
(8)

65%

these laboratories the enol thioethers derived from cyclopentanone, cyclohexanone, their 2-methyl derivatives, and 4-*tert*-butylcyclohexanone were prepared by this approach in yields generally ranging from 50% to 85%.[23] The mercury-based method proved more convenient on larger scales.

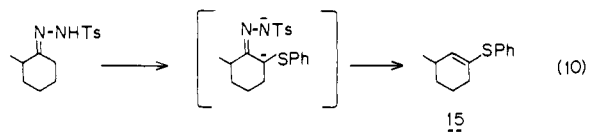
In the case of 6-methoxy-2-tetralone (Table I, entry 7), the intermediate thioketal did not form; the vinyl sulfide was the direct product of reaction.[18f] The regioselectivity generally reflected thermodynamic considerations (Table I, entries 5, 7, and 8). In the case of 2-methylcyclohexanone (Table I, entry 5), only the more highly substituted enol thioether **8** can be obtained by equilibration with *p*-toluenesulfonic acid in hot toluene.

An alternative use of carbonyl compounds as enol thioether precursors employs an olefination method (eq 9).[24] The phosphine



(9)

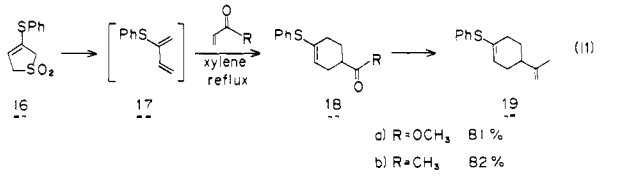
oxide modification[25] converted both an acyclic and cyclic ketone to their corresponding chain-extended enol thioethers. A third approach for formation of the enol thioethers from ketones takes advantage of the intermediacy of such compounds in a carbonyl transposition sequence (eq 10).[26] The chemoselectivity for de-



(10)

protonation of a *p*-toluenesulfonylhydrazone from the less substituted side translates into a regiocontrolled enol thioether synthesis.

For the direct production of more highly functionalized enol thioethers without proceeding through carbonyl compounds, we focused upon cycloaddition of 2-(phenylthio)-1,3-butadiene (**17**), which was conveniently generated in situ by the chelotropic extrusion of SO_2 from the sulfone **16** (eq 11).[6d] A Wittig me-



(11)

16 17 18 19

a) R=OCH3 81%
b) R=CH3 82%

(15) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. Wenkert, E.; Ferreira, T. W.; Michelotti, E. l. *J. Chem. Soc., Chem. Commun.* **1979**, 637. Takei, H.; Sugimura, H.; Miura, M.; Okamura, H. *Chem. Lett.* **1980**, 1209. Trost, B. M.; Ornstein, P. L. *J. Org. Chem.* **1982**, *47*, 748.

(16) Evans, D. A.; Andrews, G. L. *Acc. Chem. Res.* **1974**, *7*, 147. Yamagiwa, S.; Sato, H.; Hoshi, N.; Kosugi, H.; Uda, H. *J. Chem. Soc., Perkin Trans. I* **1979**, 570. Trost,, B. M.; Rigby, J. H. *J. Org. Chem.* **1978**, *43*, 2938. Ortiz de Montellano, P. R.; Hsu, C. K. *Tetrahedron Lett.* **1976**, 4215.

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(19) Cohen, T.; Herman, G.; Falck, J. R.; Mura, A. J., Jr. *J. Org. Chem.* **1975**, *40*, 812.

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(22) This reaction was first studied in our laboratories by M. Vaultier.

(23) Tanigawa, Y. unpublished work in these laboratories. Also see Trost, B. M.; Bridges, A. *J. Org. Chem.* **1975**, *40*, 2014.

(24) Shahak, C. *Synthesis* **1969**, 170. Corey, E. J.; Shulman, J. l. *J. Am. Chem. Soc.* **1970**, *92*, 5522. Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 4474. Corey, E. J.; Watt, K. *Tetrahedron Lett.* **1972**, 4651. Bestmann, H. J.; Angerer, J. *Ann. Chem.* **1974**, 2085. Mukaiyama, T.; Shiono, M.; Sato, T. *Chem. Lett.* **1974**, 37. Mikolyczyk, M.; Grzeijszczak, S.; Korbacz, K. *Tetrahedron Lett.* **1981**, *22*, 3097. Matteson, D. S.; Arne, K. H. *Organometallics* **1982**, *1*, 280. lkeda, Y.; Furata, K.; Meguriya, N.; lkeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7663.

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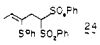
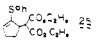
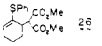
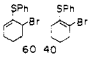
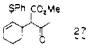
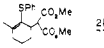
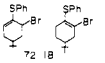
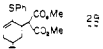
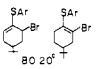
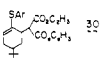
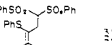
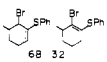
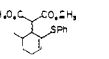
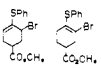
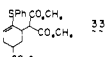
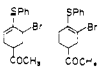
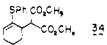
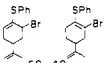
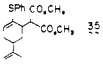
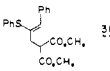
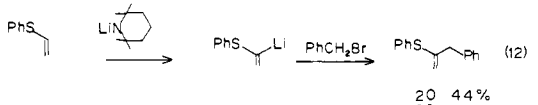
Table II. Bromination–Alkylation with Stabilized Anions

entry	enol thioether	bromide mixture	nucleophile	product	isolated yield, % uncor[a]	isolated yield, % cor[b]
1	6		$NaCH(SO_2Ph)_2$	 24	53	53
2	7a	 80 20	$NaCH(CO_2Et)_2$	 25	53	77
3	7b	 70 30	$NaCH(CO_2Me)_2$	 26	69	98
4	7b	 60 40	$NaCHCOCH_3$	 27	32	53
5	8		CO_2Me $NaCH_2(CO_2Me)_2$	 28	49	49
6	10a	 72 18	$NaCH(CO_2Me)_2$	 29	51	71
7	10b	 80 20[c]	$NaCH(CO_2Et)_2$	 30	76	95
8	14		$NaCH(SO_2Ph)_2$	 31	62	62
9	15	 68 32	$NaCH(CO_2CH_3)_2$	 32	44	63
10	18a	 67 33	$NaCH(CO_2CH_3)_2$	 33	34	51
11	18b	 65 35	$NaCH(CO_2CH_3)_2$	 34	51	78
12	19	 60 40	$NaCH(CO_2CH_3)_2$	 35	45	75
13	20		$NaCH(CO_2CH_3)_2$	 36	60	60

[a] Yield based upon starting enol thioether. [b] Yield based upon starting enol thioether but corrected for the ratio of allyl to vinyl bromide. [c] Ar = *p*-$CH_3OC_6H_4$.

thylenation smoothly converted the ketone **18** to the diolefin **19**. This facile approach provided a series of enol thioethers that contained a ketone, an ester, and an isolated olefin within the same molecule.

A final approach to a regiocontrolled synthesis of enol thioethers employs 1-(phenylthio)vinyllithium,[4] which permits ready access to terminal enol thioethers (eq 12). The product from alkylation



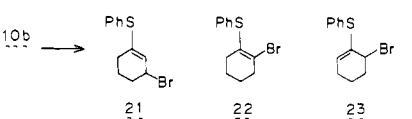
(12)

20 44%

with benzyl bromide is regioisomeric with what would be obtained from 1-phenyl-2-propanone.

Bromination Studies. Utilizing 1-(phenylthio)cyclohexene as a model substrate, we screened a variety of brominating agents[32-36] to maximize the yield of the allylic bromide **23** (Chart A-1 and Table A-1 in the supplementary material).

Allylic bromide **21** was not an observed product even under conditions attempting to reflect free radical conditions. However,



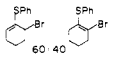
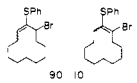
21 22 23

use of polar solvents[27] was clearly detrimental. Use of low temperatures or addition of tertiary amines as bases enhanced formation of the vinyl bromide **22** at the expense of the allyl bromide **23**. On the other hand, higher temperatures favored allyl bromide formation relative to vinyl bromide formation. For preparative purposes, we therefore adopted the use of *N*-bromosuccinimide (NBS) in chloroform at room temperature with no added base for di- and trisubstituted enol thioethers.

To investigate the regio- and chemoselectivity of this allylic bromination, we applied these conditions to the enol thioethers listed in Table I. Due to the sensitivity of the allyl bromides, they normally were only freed of the succinimide and analyzed by NMR before direct use in an alkylation reaction. We chose a stabilized anion as the nucleophile due to the dearth of alternative methods to introduce such structures α to a carbonyl group.[12a,b]

(27) Cf.: Offermann, W.; Vogtle, F. *Angew. Chem. Int. Ed. Eng.* **1980**, *19*, 464.
(28) Posner, G. H. *Org. Reactions* **1975**, *22*, 253.
(29) House, H. O.; Chiu, C.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.
(30) Vincent, J. E.; Chabala, J. C. *Tetrahedron Lett.* **1978**, 937.
(31) Pascual, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1966**, *49*, 164. Toby, S. *J. Org. Chem.* **1969**, *34*, 1281.
(32) Trost, B. M.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 1204.
(33) Calo, F.; Lopez, L.; Pesu, G.; Todesco, P. E. *Tetrahedron* **1973**, *29*, 1625.
(34) Lavoie, A.; Mao, M. T.; Burks, J. E., unpublished work in these laboratories.
(35) Cacchi, S.; Caslioti, L. *Synthesis* **1979**, 64.
(36) Kochi, J. K. *J. Am. Chem. Soc.* **1955**, *77*, 5274. Sollman, P. B.; Dodson, R. M. *J. Org. Chem.* **1961**, *26*, 4180. Nonhebel, D. C. *Proc. Chem. Soc., London* **1961**, 307. Glazier, E. B. *J. Org. Chem.* **1962**, *27*, 2937. Jemison, R. W. *Aust. J. Chem.* **1968**, *21*, 217.

Table III. Bromination–Cuprate Coupling of Enol Thioethers

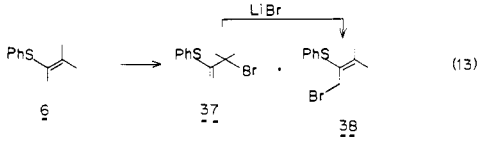
enol					isolated yields, %	
entry	thioethers	bromide[a]	cuprate	product	uncor	cor
1	6		$(CH_3)_2CuLi$	 43[c]	62	62
2	7b	 60:40	$(CH_3)_2CuLi$	 44	49	82
3	7b		Ph_2CuLi	 45	51	85
4	7b		$(PhC{\equiv}C)_2CuLi$	 46	34	57
5	7d	 90 10	$(CH_3)_2CuLi$	 47[d]	61	68
6	13		$(CH_3)_2CuLi$	 48	61	61
7	14	 [b]	$(CH_3)_2CuLi$	 49	61	61

[a] Bromination performed by using 1 equiv of NBS in $CHCl_3$ at room temperature. [b] In this case, bromination performed by using 1 equiv of NBS in CH_3CN followed by addition of LiBr. [c] The product contained less than 10% of the regioisomer 3,3-dimethyl-2-(phenylthio-1-butene. [d] The product is a 2:1 *Z*:*E* olefin mixture.

Table II summarizes the results for both the bromination and alkylation.

The cyclopentyl (Table II, entry 2) and cyclohexyl systems (Table II, entries 3, 4, 6, 7, 10, 11, and 12) that do not bear alkyl substituents on carbon α to the phenylthio group behave similarly in terms of the ratio of allyl to vinyl bromide. Since the vinyl bromide is unreactive toward displacements, this mixture was normally directly subjected to alkylation and purification effected at this point. Overall yields ranged from 32% to 76%. However, these yields do not reflect the fact that a fraction of the intermediate bromide mixture is incapable of leading to alkylation product. Thus, correcting these yields for the ratio of allyl to vinyl bromide reveals the actual yields range from 49% to 95%. In the case of **20**, bromination proceeded regioselectively to give only the allyl bromide as a 1:1 stereoisomeric mixture. The high regioselectivity in this case presumably reflects the thermodynamic preference for the double bond to be conjugated with the phenyl ring.

For tetrasubstituted enol thioethers, only the allylic bromide can and does form. However, both allylic isomers are initially observed, as illustrated in eq 13. Subjection of the mixture to

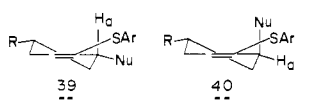


(13)

6 37 38

lithium bromide in dimethylformamide (DMF) smoothly isomerizes **37** to the more stable allylic bromide **38**. A one-pot operation emerges by treating **9** with **NBS** in acetonitrile for 5 min and then adding lithium bromide and continuing stirring for 3 h. This same procedure was applied to **14** (Table II, entry 8), which gave only the single primary allyl bromide depicted.

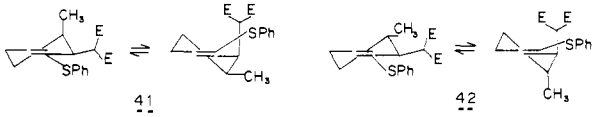
Entries 10, 11, and 12 illustrate the high chemoselectivity of this process in that a ketone, an ester, and an isolated olefin are all compatible with the sequence. The products of alkylation **33** and **35** as well as the 4-*tert*-butyl products **29** and **30** appear to be only one stereoisomer. In each case, H_a (see generalized formula **39** and **40**) appears between δ 2.8 and 3.0 as a very broad



39 40

absorption ($\delta\Delta W_{1/2} > 20$ Hz). This observation suggests this proton is axial and therefore the nucleophile is equatorial as depicted in **39**. This stereochemistry also corresponds to that predicted on the basis of preferential axial bromination followed by S_N2 displacement (vide infra).

The regioselectivity except for tetrasubstituted enol thioethers (vide supra) reflects the regioselectivity of the starting enol thioether. Thus, bromination of **20** gave only the primary bromide and subsequently the alkylation product **36** derived from attack at the primary carbon (Table II, entry 13). The NMR spectrum reveals two vinyl singlets, at δ 6.66 (minor) and 6.74 (major), and two methylene doublets (J = 7 Hz), at δ 2.79 (major) and 2.98 (minor)—an observation indicative of an approximately 55:45 mixture of *Z*:*E* isomers. The presence of a 3-alkyl substituent as in **15** did not change the regioselectivity (Table II, entry 9). The alkylation product is a 2:1 mixture of two stereoisomers. The major isomer exhibits a doublet (J = 7.5 Hz) for the methyl group at δ 0.97, a broadened doublet (J = 6 Hz) for the allylic methine proton at δ 2.65, and a broadened triplet (J = 4 Hz) for the vinyl proton at δ 6.24; the minor isomer exhibits these absorptions at δ 1.06 (d, J = 9 Hz), 2.94 (m), and 6.18 (distorted t, J = 3 Hz). The fact that the major isomer shows only small couplings to the allylic methine proton in addition to the normal vicinal coupling to the malonate methine proton indicates it is the cis isomer **41**;



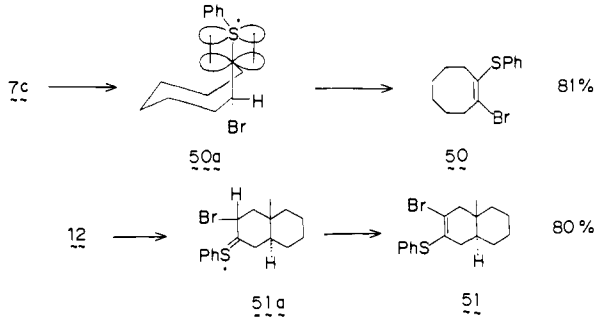
41 42

conversely, the larger couplings to the allylic methine proton in addition to the vicinal coupling to the malonate, as determined by its broad $W_{1/2}$, indicate the presence of an axial–axial coupling as found in at least one conformer of the trans isomer **42**. This assignment also derives from the anticipated shielding of the secondary methyl group due to its juxtaposition with respect to the shielding cone of the ester group in the cis isomer. The preferential formation of the cis alkylation isomer agrees with an anticipated predominantly trans bromination.

The allylic bromides react smoothly with less stabilized nucleophiles. Cuprate couplings, among the more versatile reactions for introduction of alkyl, aryl, etc. substituents,[28-30] proceed very well, as summarized in Table III. The higher selectivity for allylic bromination in the 1-(phenylthio)cyclododecene case (entry 5) compared to the simple six-membered ring case is noteworthy. As before, the tetrasubstituted enol thioether **13** produces only the primary bromide by use of the bromination–isomerization procedure. In the case of the unsymmetrical allyl bromides (Table III, entries 1, 6, and 7) alkyl transfer occurred with predominant (>90%) to exclusive coupling with *no* allyl inversion. Only in the case of Table III, entry 1, did the NMR spectrum reveal a small amount of the regioisomeric product 3,3-dimethyl-2-(phenylthio)-1-butene, as determined by a singlet for the *tert*-butyl group

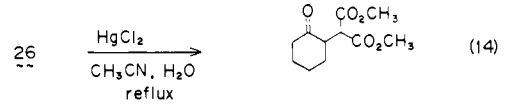
at δ 1.2 and two singlets for the terminal olefin at δ 4.48 and 5.07, mixed with the major product **43**. The 1-(phenylthio)cyclodecene, which is an ~60:40 mixture of *Z*:*E* isomers, produces a 2:1 mixture of *E*:*Z* alkylation products. The stereochemistry derives from assigning the isomer bearing the lower field vinyl proton as *Z* (δ 6.12 vs. 5.42).[31] It is interesting to note that no coupling products derived from the vinyl bromides were ever detected.

Three of the enol thioethers failed to give any allyl bromide. With **7c** and **12** only the vinyl bromides **50** and **51** form. In both

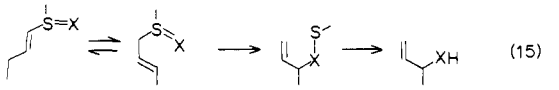


cases, conformational factors account for the observation. By analogy to the chair–boat conformation for 2-bromocyclooctanone,[37] **50a** represents a reasonable depiction for the intermediate bromothionium ion in the case of **7c**. The proton geminal to bromine is ideally aligned for overlap with the adjacent sp^2 carbon. This combined with the intrinsic enhanced acidity of this proton[38] accounts for its preferential removal. The bias for a *trans*-decalin to generate a 2,3-double bond[39] (even in the case of enolization of the *trans*-2-decalones) combined with the acidifying influence of the bromine accounts for the selective removal of the proton at C(3) in the intermediate thionium ion **51a**. 7-Methoxy-3-(phenylthio)-1,2-dihydronaphthalene (**11**) aromatized to give 2-(phenylthio)-7-methoxynaphthalene in 65% yield under the bromination conditions. The high propensity for the presumed allylic bromide intermediate to aromatize by loss of HBr accounts for the net dehydrogenation.

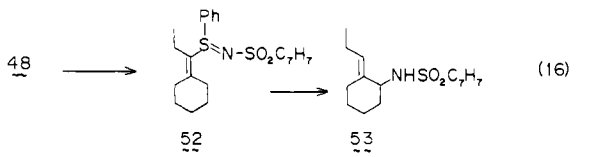
Some Transformations of the Products of Bromination–Alkylation. Hydrolysis[26,40] of the products of bromination–alkylation to liberate the ketone and thereby complete the formal equivalency of an enolonium ion was demonstrated explicitly only in the case of **26** (eq 14). Most attention focused on the unique properties



of the enol thioether for further structural elaboration as summarized in eq 15.[16,17] Indeed, the sulfilimine **52** derived directly



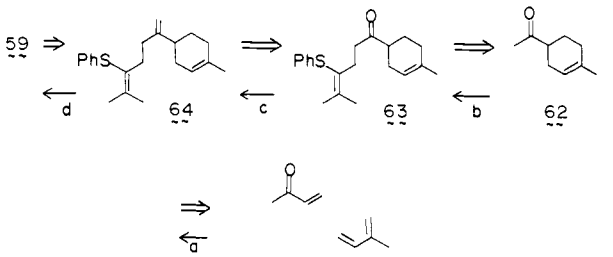
from **48** produces the *N*-allylsulfonamide **53** upon exposure to sodium ethoxide in ethanol at 55 °C for 1 h (eq 16).



The enol thioether can be converted to the sulfoxide or sulfilimine prior to the alkylation step. For example, **38** produces the

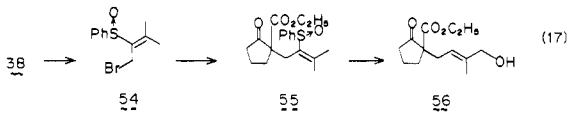
(37) Allinger, J.; Allinger, N. L. *J. Am. Chem. Soc.* **1957**, *81*, 5736. Allinger, J.; Allinger, N. L. *J. Org. Chem.* **1960**, *25*, 262.
(38) Jones, J. R. "The Ionization of Carbon Acids"; Academic Press: New York, 1973, Chapter 3.
(39) Bucourt, F. *Bull. Soc. Chim. Fr.* **1963**, 1262; *Top. Stereochem.* **1974**, *8*, 159.
(40) Corey, E. J.; Shulman, J. I. *J. Org. Chem.* **1970**, *35*, 777.

Scheme I. Retrosynthetic Analysis and Synthesis of Lanceol



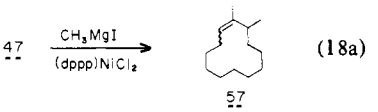
[a] BF_3·ether, CH_2Cl_2, −78 °C. [b] LDA, THF, 0 °C, 41, KI, DMF. [c] $Ph_3P^+CH_3Br^-$, KOC_4H_9-*t*, THF, Δ. [d] (i) MCPBA, CH_2Cl_2, −78 °C; (ii) $NaOC_2H_5$, C_2H_5OH.

crystalline sulfoxide **54** when reacted with 1 equiv of *m*-chloroperbenzoic acid (MCPBA). Alkylation of the sodium salt of 2-carbethoxycyclopentanone with **54** proceeds in 80% yield in DMF to give **55**. With sulfur already at the oxidation level of the sulfoxide, the alkylation product directly can undergo isomerization, rearrangement, and cleavage of the sulfenate upon refluxing with ethanolic sodium ethoxide to give **56** (eq 17). In



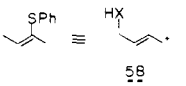
addition to this sequence being more convergent, it also circumvents any problems of oxidation if the nucleophilic partner should bear any easily oxidized groups.

Transition metal catalyzed couplings permit the direct replacement of the C—S bond by a C—C bond.[15] To illustrate, **47** produces the allylically alkylated trisubstituted olefin **57**.

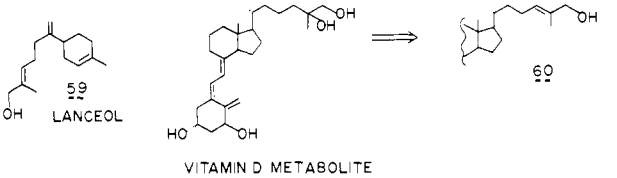


Considering that the ultimate precursor is a ketone, this sequence represents a highly regiocontrolled olefin synthesis.

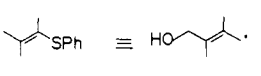
Applications of the Bromination–Alkylation Sequence. The fact that the enol thioethers are useful as enolonium ions as well as allyl alcohols or amines permits the structural equivalency represented in **58**. The fact that the 2,3-sigmatropic rearrangements



normally create one geometrical olefin isomer imparts further utility to this sequence. Natural products such as lanceol (**59**),

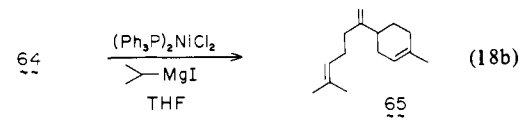


sirenin, and ceroplastol illustrate that the equivalency of **58** (X = O) can be quite useful in natural products synthesis. Furthermore, other oxidation patterns easily derive from such allyl alcohols. For example, the steroid side chain found in some vitamin D metabolites can be envisioned to evolve from Markovnikov hydration of a precursor such as **60**. From the perspective represented in **58**, enol thioether **6** becomes a natural building block as shown in **61**.



Lanceol (**59**) was chosen as a simple illustration of this methodology.[41,42] Scheme I illustrates a retrosynthetic analysis based upon this concept. The key step is the regiocontrolled alkylation of the ketone **62** with the brominated enol thioether **38**. A Diels–Alder reaction provides a direct approach to the requisite cyclohexenyl ketone **62**. Indeed, Lewis acid catalyzed Diels–Alder reaction of methyl vinyl ketone and isoprene provided only the desired regioisomer **62**—a fact that obviated the need for tedious separations as previously reported for the thermal reaction.[41a] Adding a solution of the lithium enolate of **62** in tetrahydrofuran (THF) to a DMF solution of **38** and potassium iodide (in situ halide exchange to generate the corresponding iodide) provided a 55% yield of **63**. Wittig olefination, chemoselective oxidation to the sulfoxide, and isomerization followed by sigmatropic rearrangement led smoothly to (±)-lanceol. The exclusive formation of the *E* olefin derives from the stereochemical demands of the 2,3-sigmatropic rearrangement as previously established.[16,42d,e]

To illustrate the flexibility that such a synthetic strategy offers as well as the ability to chemoselectively manipulate the enol thioethers, the intermediate **64** was subjected to desulfurization with bis(triphenylphosphine)nickel(II) chloride and isopropylmagnesium iodide (eq 18b).[9c] Even though the molecule contains

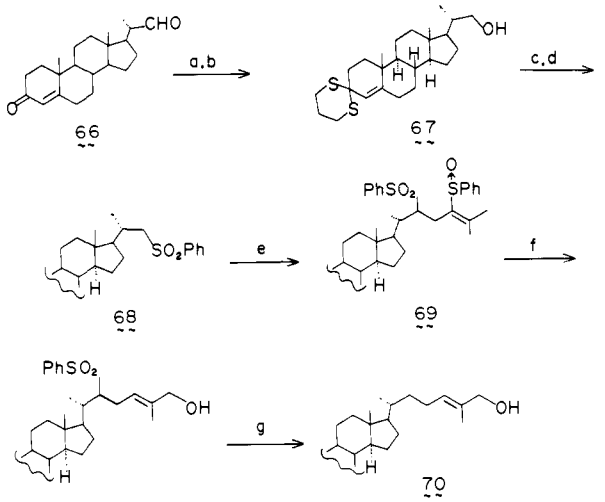


(18b)

three double bonds, no reduction nor isomerization accompanied the desulfurization. Thus **64** represents a common intermediate for both (±)-lanceol (**59**) and (±)-bisabolene (**65**).[43]

Introduction of the steroid side chain was briefly explored from the point of view of utilizing an intermediate such as **60** for the elaboration of some metabolites of vitamin D.[44] Dinorcholenaldehyde (3-oxo-4-pregnene-20-carboxaldehyde, **66**) was chemoselectively reduced with sodium borohydride to the primary alcohol and the enone protected as its dithiane derivative. The resultant hydroxydithiane **67** was converted to the sulfone **68** in straightforward fashion. Alkylation of the resultant lithium derivative was performed with **54** as the synthon for **61**. Choice of **54** was dictated by the desire to avoid an oxidation step due to the presence of the dithiane. This route resulted in a modest, unoptimized yield of the alkylated product **69** due to the lower reactivity of **54** compared to **38**. We suspect that higher yields can be obtained if this step is optimized. In addition, an alternative utilizing **38** may be preferred. Nevertheless, the sequence as performed validates the strategy. The utilization of the sulfoxide

Scheme II. Elaboration of Steroid Side Chain



[a] $NaBH_4$, CH_3OH, 0 °C. [b] $HSCH_2CH_2CH_2SH$, BF_3·ether, CH_2Cl_2, room temperature. [c] CH_3SO_2Cl, C_5H_5N, 0 °C to room temperature. [d] KI, DMF, 75 °C, then add $PhSO_2Na$, 75 °C. [e] *n*-C_4H_9Li, TMEDA, THF, -78 °C, 59, THF, HMPA, -78 °C to 10 °C. [f] $NaOC_2H_5$, C_2H_5OH, 70 °C. [g] 6% Na(Hg), CH_3OH, Na_2HPO_4.

for the stereocontrolled introduction of the allylic alcohol and the desulfonylation with buffered sodium amalgam[45] proceeded smoothly to complete the elaboration of the target allyl alcohol **70** as a single geometrical isomer.

Discussion

The utilization of enol thioethers as enol substitutes depends upon the nature of the further application. Whereas enol ethers[46] and enamines[2] substitute for enolates or enols due to the high nucleophilicity of the olefinic bonds, enol thioethers do not enjoy a high reactivity of this type. In fact, it is their stability that imparts some of their potential use. They can easily survive many types of synthetic reactions before being selectively manipulated. For example, additions to carbonyl groups or alkylations α to a carbonyl group proceed unimpaired by the presence of an enol thioether. Most importantly, the reverse now also seems to be possible, i.e., elaboration of an enol thioether without protecting a carbonyl group. Such possibilities evoke a strong driving force to explore the chemistry of enol thioethers.

In this study, we have focused on allylic substitution. While oxidation and halogenation of alkyl and aryl sulfides have been examined, such reactions of enol thioethers remained unexplored. Our first efforts focused on acetoxylation as outlined in eq 4.[9a] While the allylic acetates offer many advantages because of their subdued reactivity, the direct accessibility of the allylic halides offers enhanced versatility.

Among the brominating agents, NBS and the bromo analogue of Meldrum's acid[32] gave very similar results. Since the latter appears to be an ionic brominating agent, their comparative behavior suggests that both reactions are ionic in character. Introduction of a radical inhibitor fails to have an effect on the reaction—a further indication of an ionic rather than radical pathway. The response to solvents reinforces this conclusion. Carbon tetrachloride, an optimum solvent for free radical initiated allylic brominations with NBS, and other nonpolar solvents, such as cyclohexane, which do not solubilize NBS lead to very slow reactions. The fastest reactions are in polar solvents such as acetonitrile or DME. However, except for tetrasubstituted enol thioethers, the reaction appears less controllable under these conditions. Chloroform, methylene chloride, or similar chlorinated

(41) (a) Manjarrez, A.; Rios, T.; Guzman, A. *Tetrahedron* **1964**, *20*, 333. (b) Ruegg, R.; Pfiffner, A.; Montavon, M. *Recherches* **1966**, *15*, 3. (c) Vig, O. P.; Salota, J. P.; Vig, B.; Ram, B. *Indian J. Chem.* **1967**, *5*, 475. (d) Crawford, R. J.; Erman, W. F.; Broaddus, Ch. D. *J. Am. Chem. Soc.* **1972**, *94*, 4298. (e) Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1975**, *97*, 6870. (f) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925. (g) Cazes, B.; Julia, S. *Tetrahedron Lett.* **1978**, 4065.

(42) For related work on veruciferol see (a) Vig, O. P.; Vig, B.; Raj, l. *J. Indian Chem. Soc.* **1965**, *42*, 673. (b) Buchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1122. (c) Gast, A.; Naves, Y. R. *Helv. Chim. Acta* **1971**, *54*, 1369. (d) Evans, D. A.; Andrews, G. C.; Fujimoto, T. T.; Wells, D. *Tetrahedron Lett.* **1973**, 1389. (e) Grieco, P. A.; Finkelhor, R. S. *J. Org. Chem.* **1973**, *38*, 249. (f) Kondo, K.; Dunemoto, D. *Tetrahedron Lett.* **1975**, 1007. (g) Yamamoto, K.; Yoshitake, J.; Qui, N. T.; Tsuji, J. *Chem. Lett.* **1978**, 859. (h) Taber, D. F.; Saleh, S. A. *J. Org. Chem.* **1981**, *46*, 4817.

(43) Vig, O. P.; Matta, K. L.; Singh, G.; Raj, l. *J. Indian Chem. Soc.* **196**, *43*, 27. Manjarrez, A.; Guzman, A. *J. Org. Chem.* **1966**, *31*, 348. Knoll, W.; Tamm, Ch. *Helv. Chim. Acta* **1975**, *58*, 1162. Ho, T.; Liu, S. *Synth. Commun.* **1980**, 603. Ho, T. L. *Synth. Commun.* **1981**, *11*, 237.

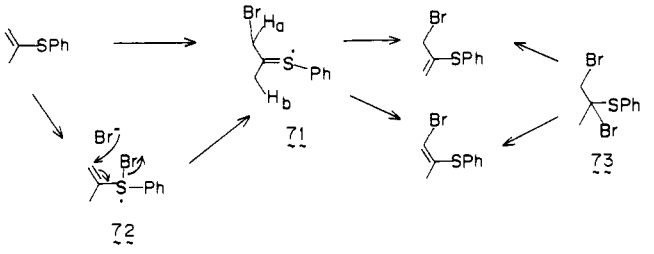
(44) For recent related work see: Ohmori, M.; Yamada, S.; Takayama, H.; Ochi, K. *Tetrahedron Lett.* **1982**, *23*, 4709. Byon, C. Y.; Gut, M.; Toone, V. *J. Org. Chem.* **1981**, *46*, 3901. Barner, R.; Hubscher, J.; Daly, J. J.; Schonholzer, P. *Helv. Chim. Acta* **1981**, *64*, 915. Yamada, S.; Nakayama, K.; Takayama, H. *Tetrahedron Lett.* **1981**, *22*, 2591. For reviews see Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 9. De Luca, H. F. *Annu. Rev. Physiol.* **1981**, *43*, 199. Uskokovic, M. R.; Partridge, J. J.; Narwid, T. A.; Baggiolini, E. G. In "Vitamin D: Basic and Clinical Nutrition"; Norman, A. W., Ed.; Marcell Dekker: New York, 1980; Vol. 2, p 1. For leading references see Schmuff, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404.

(45) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(46) Effenberger, F. *Angew. Chem. Int. Ed. Eng.* **1969**, *8*, 295. Fischer, P. In "The Chemistry of Functional Groups Supplement E, Part 2"; Patai, S.; Ed.; Wiley-Interscience: Chichester, 1980; p 781.

hydrocarbons represent a compromise of solvent polarity and solvating ability and have given the optimum results to date. In the case of tetrasubstituted enol thioethers, where bromination is directly followed by equilibration to the thermodynamically more stable allyl bromide, in a one-pot operation, acetonitrile is the solvent of choice.

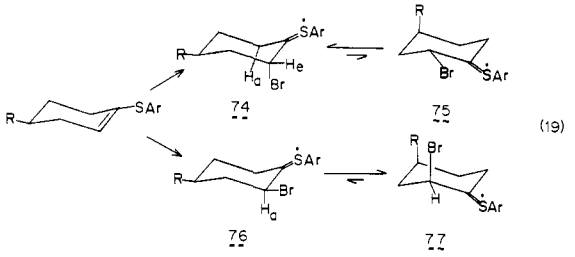
The regioselectivity of the bromination reinforces the conclusion of an ionic rather than free radical mechanism. In particular, bromine is introduced selectively at the vinyl carbon β to sulfur with the double bond then migrating. With an ionic mechanism likely, a bromothionium ion such as **71** represents a likely in-



termediate. It can be formed either directly by attack of Br^+ on the double bond or indirectly from a bromosulfonium species such as **72**. That partitioning of **71** accounts for the ratio of the allyl to vinyl bromides while dehydrobromination from the bromine adduct **73** does not. The latter was generated in situ by reaction of **7b** with dioxane–bromine complex and then dehydrobromination accomplished by addition of triethylamine. The almost exclusive formation of the vinyl bromide is in stark contrast to all the other runs.

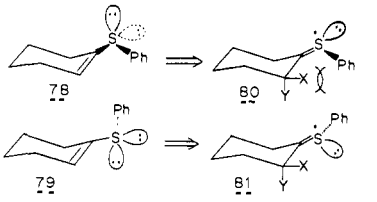
In order to determine whether the thermodynamically more stable vinyl bromide arose by partial isomerization of the allyl bromide due to the presence of HBr, various soluble and insoluble bases were added. In each case, the base had the opposite effect; i.e., it enhanced the amount of the vinyl bromide.

The partitioning of **71** between the two bromide isomers appears to be a function of (1) the acidity of H_a and H_b, (2) conformational factors, and (3) the thermodynamic stability of the resultant olefin. Bromine enhances the acidity of the proton geminal to itself.[38] Thus, a bias should exist for the deprotonation of H_a in **71** to give the vinyl bromide. The obtention of the allyl bromide may then be attributed to conformational effects. It is reasonable to propose that kinetic bromination of 1-(phenylthio)cyclohexene would be preferentially axial (eq 19). Such a reaction course has already



(19)

been established for the bromination of enols and their derivatives.[47] Furthermore, to minimize dipole–dipole effects,[48] the axial bromide **74** should dominate over the equatorial bromide **75**. For maximum overlap with the sp^2 carbon of the thionium ion, the axial proton H_a in **74** would be preferentially removed. These arguments derive directly from the case of the ketones for which similar observations have been recorded.[49] Thus, the combination of axial bromination and axial deprotonation dictates the formation of allyl bromide. Equatorial deprotonation from **74** (or axial deprotonation from the less stable conformer **75**) or equatorial bromination to give **76** followed by axial deprotonation would account for the vinyl bromide. The latter is disfavored for several reasons. As already stated, dipole–dipole effects in addition to stereoelectronic factors should raise the activation energy leading to **76** compared to that leading to **74**. Further, **71**, if formed, should flip to the thermodynamically more stable axial bromide **71** in which the proton geminal to bromine is once again equatorial. Secondly, no mention has yet been made of the geometry of the thionium ion. Maximum interaction between the lone pairs on sulfur and the double bond[50] leads to the prediction that the transoid arrangement of the lone pairs with respect to the double bond in **73** (i.e., syn conformer with respect to the sulfur substituent) would have the more nucleophilic double bond compared to the cisoid arrangement in **79** (i.e., anti conformer with respect to the sulfur substituent). Minimization of nonbonded interactions also leads to the prediction that **78** would be preferred over **79**.



To the extent that **78** leads to the initial product, the A strain[51] created by introducing an equatorial group in **80** would lead to a strong bias for axial attack.

Direct experimental evidence in support of axial bromination derives from the controlled bromination of 1-(phenylthio)-4-*tert*-butylcyclohexene. The kinetic allylic bromination product is a single isomer assigned as the axial bromide **82**, and as determined by the proton NMR spectrum (one *tert*-butyl absorption at δ 0.85, one methine proton at δ 4.74, and one vinyl proton at δ 6.24). Decoupling experiments establish J_{ab} = 14.2 Hz, J_{ad} = 12.3 Hz, and J_{ac} = 3.5 Hz. Since this coupling pattern establishes H_a as an axial proton, the 3.5-Hz coupling establishes H_e as an equatorial proton as depicted in **82**. Isolation of such kinetic bromination products is experimentally difficult due to their sensitivity to isomerization. Nevertheless, the stereochemical course of the bromination–alkylation for Table II, entries 6, 7, 10, and 12, suggests that rapid bromination followed by direct alkylation of the crude product retains the stereochemical integrity of the initial bromide.

The bias for axial vs. equatorial deprotonation in **71** depends upon where the transition state lies along the reaction coordinate. For example, it has been noted that there is a higher bias for axial protonation of enolates than for the reverse process of deprotonation of ketones.[52] In the former, an early transition state emphasizes the overlap in the enol which lies at the basis of the stereoelectronic preference for axial protonation; in the latter, a transition state that lies toward the ketone deemphasizes overlap between the departing hydrogen and the carbonyl group. At this time, it would be reasonable to conclude that the allyl to vinyl bromide ratio simply reflects deprotonation of an axial or equatorial proton in **74**.

One modification that does positively affect the allyl to vinyl bromide ratio is the substitution on sulfur. An enhancement of the allyl bromide resulted from addition of an electron-releasing methoxy group in the aromatic ring (Table II, entry 7). The ability of the *p*-anisylthio group to better stabilize the adjacent positive charge can shift the transition state further along the reaction coordinate. The more the transition state resembles the product,

(47) Shoppe, C. W.; Johnstone, G. A. R.; Lach, R. E. *J. Chem. Soc.* **1962**, 3604. For a discussion see House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: New York, 1972, pp 468–473.

(48) Corey, E. J. *J. Am. Chem. Soc.* **1953**, *75*, 2301. Kunler, W. D.; Huitrii, A. C. *Ibid.* **1959**, *78*, 3369. Allinger, J.; Allinger, N. L. *Tetrahedron* **1958**, *2*, 64.

(49) (a) Trimitis, G. B.; Van Dam, E. M. *J. Chem. Soc., Chem. Commun.* **1974**, 610. (b) Metzger, P.; Casadevall, E. *Tetrahedron Lett.* **1973**, 3341. Also see: (c) Fraser, R. R.; Champagne, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 657. (d) Corey, E. J.; Sneen, R. A. *Ibid.* **1956**, *78*, 6269.

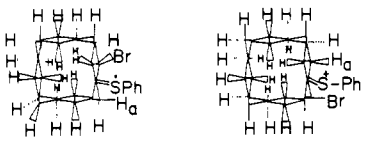
(50) Cf.: Deslongchamps, P.; Taillefer, R. J. *Can. J. Chem.* **1975**, *53*, 3029 and references therein. Lehn, J. M.; Wipff, A. *J. Am. Chem. Soc.* **1974**, *96*, 4048.

(51) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(52) Elks, J.; Phillips, G. H.; Walker, T.; Wyman, L. J. *J. Chem. Soc.* **1956**, 4330. Also see ref 49(d). For related work see Lyle, R. E.; Saavedra, J. E.; Lyle, G. G.; Fribush, H. M.; Marshall, J. L.; Lijinsky, W.; Singer, G. M. *Tetrahedron Lett.* **1976**, 4431.

the more important stereoelectronic factors favor removal of the axial proton in **71**.

Such conformational arguments accommodate the diametrically opposite results of the 8- and 12-membered rings. Whereas the former gives only vinyl bromide, the latter gives high selectivity for the allyl bromide. As already noted (vide supra), consideration of the most likely conformation for the bromothionium ion in the 8-member ring case favorably disposes the proton geminal to bromine towards removal. On the other hand, consideration of the most likely conformations in the 12-member ring case[53] **83a** and **83b** leads to the prediction that H_a is most suitably disposed

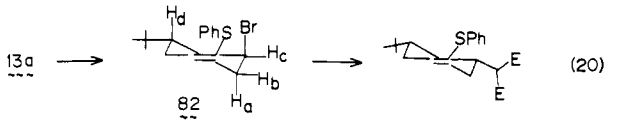


83a **83b**

for removal, leading to the (*E*)- and (*Z*)-3-bromo-3-(phenylthio)-1-cyclododecenes, respectively. Molecular mechanics calculations suggest a dihedral angle of 30–33° (for the syn and anti thionium ion isomers) for the proton geminal to bromine and the C=SPh bond, whereas the α'-methylene protons exhibit dihedral angles of 29–46° (for the proton trans to bromine) and 87–88° (for the proton cis to bromine). The latter proton is ideally situated for removal—a conclusion in excellent accord with the bias for formation of the allyl bromide.

In the tetrasubstituted enol thioethers, such problems do not arise. On the basis of the ionic mechanism of bromination, such an observation is easily understood, since the carbon bearing the bromine in the intermediate bromothionium ion does not bear a hydrogen (eq 13). The lability of the kinetic allyl bromide toward allyl inversion under the reaction conditions normally leads to partial isomerization, which is readily driven to completion upon the addition of excess bromide ion in a polar solvent.

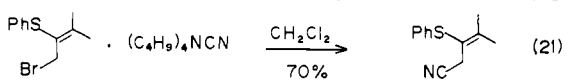
Except for the tertiary cases as represented in eq 13, high regioselectivity pertains in that the bromine occurs at the β-carbon of the initial enol thioether. The product of alkylation then derives by addition to that same carbon as summarized in eq 5. As expected for a S_N2 displacement in the alkylation step, the stereochemistry of the bromination dictates the stereochemistry of the final alkylation product. For example, in the case of 1-(phenylthio)-4-*tert*-butylcyclohexene, the alkylation product appears to be the *Z* isomer (Table II, entry 6 and eq 20). The



13a **82** (20)

fact that the bromide has been shown to have the *E* configuration supports that assignment. Similar reasoning accounts for the stereochemical consequences of this alkylation sequence for **18a** and **19**.

The nature of the nucleophile can be quite varied. Highly stabilized anions such as malonates and β-keto esters and highly reactive anions like cuprates react very well. Anions more stabilized than β-keto esters (such as cyanide) react well (eq 21).



(21)

Such a reaction is the equivalent of adding a carboxylic acid unit to a carbonyl group. At the present time, anions whose reactivities lie between these extremes, such as enolates or sulfone-stabilized anions, give varied results. In such cases, choice of counterion

(53) Anet, F. A. L.; Cheng, A. K.; Krane, J. *J. Am. Chem. Soc.* **1973**, *95*, 7877. Schneider, H. J.; Thomas, F. *Tetrahedron* **1976**, *32*, 2005. Anet, F. A. L.; Rawdah, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 7166. Maruet, P.; Fayet, J. P.; Marmillod-Bladet, D.; Mazerolles, P.; Faucher, A. *J. Chim. Phys. Phys.-Chim. Biol.* **1980**, *77*, 325.

Chart I. Structural Correlations via Enol Thioethers

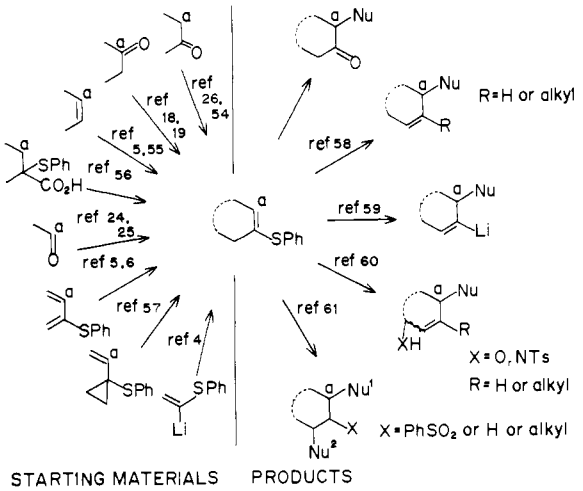
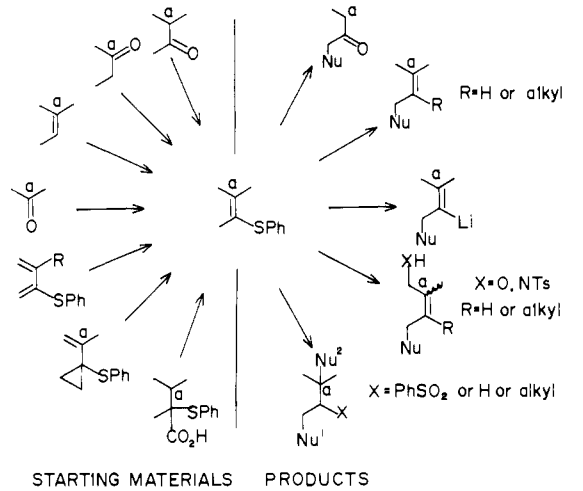


Chart II[a]. Structral Correlations for Tetrasubstituted Enol Thioethers

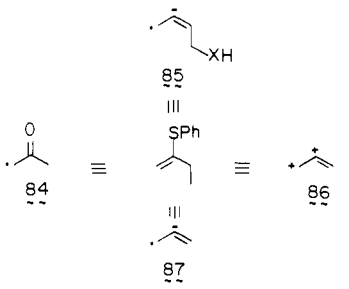


[a] See Chart I for appropriate references.

and solvent to maximize the rate of a S_N2 displacement appears critical. The fact that the crude bromination products are fairly pure allows their direct utilization in the alkylation step even with sensitive ketone enolates. As demonstrated in the experimental section, the tandem bromination–alkylation was performed with minimal intermediate purification.

This procedure offers a new strategy for structural elaboration. While the problem of allyl vs. vinyl bromide formation has not been resolved in all cases, in many it is not a serious problem (Table II, entries 1, 5, 8, and 13; Table III, entries 1, 5, 6, and 7). In the other cases, where significant amounts of vinyl bromide do arise, acceptable overall yields of alkylation product are still obtained. The exceptional versatility of sulfur makes such a direct sequence still very attractive.

The plethora of methods to synthesize enol thioethers combined with the many ways to manipulate them creates a tremendous array of structural transformations. Thus, an enol thioether now becomes a synthon for **84–87**. Charts I and II summarize some



85 **84** **86** **87**

of the types of structural transformations that combining the methodology outlined herein with known chemistry of enol thioethers permits. It would appear that enol thioethers, once considered the unwanted stepchild of carbonyl compounds, have a usefulness that can greatly enrich the chemistry of the carbonyl group, and an identity of their own that sets them apart.

Experimental Section

General. General experimental operations are outlined in the supplementary material.

Preparation of 2-(Phenylthio)-3-methyl-2-butene (6). To a stirred solution of 3-methyl-2-butanone (0.805 g, 9.36 mmol, 1 mL) and thiophenol (1.03 g, 9.36 mmol, 0.96 mL) in dichloromethane (10 mL) was added solid phosphorus pentoxide (2.65 g, 18.7 mmol). The reaction mixture was stirred for 18 h, at which time the dichloromethane was poured away from the residue. The residue was washed once with dichloromethane (15 mL), and the combined organic layers were washed with 10% aqueous sodium hydroxide solution (15 mL) followed by saturated aqueous sodium chloride solution (15 mL). The dried (potassium carbonate) organic layer was concentrated in vacuo and distilled (Kugelrohr) at 95 °C (0.15 torr) to yield 1.05 g (68%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.84 (br s, 3 H), 1.19 (br s, 3 H), 2.02 (br s, 3 H), 7.16 (m, 5 H); IR (thin film) 1582, 1478, 1440 cm^{-1}. Anal. Calcd for $C_{11}H_{14}S$: 178.0816. Found: 178.0821.

Preparation of Thioketals. Several representative procedures are detailed below and others appear in the supplementary material.

1,1-Bis(phenylthio)cyclohexane. Into a solution of cyclohexanone (2.00 g, 20.0 mmol) in thiophenol (4.7674 g, 43.0 mmol) was bubbled gaseous hydrogen chloride for 2 min. The reaction solidifies after approximately 2 h. The material was dissolved in dichloromethane (50 mL) and washed with 10% aqueous sodium hydroxide (2 × 30 mL) followed by saturated aqueous sodium chloride (30 mL). The dried (potassium carbonate) organic solution was concentrated in vacuo and the crude material recrystallized from ethanol to yield 4.64 g (77.4%) of the desired product: mp 79.5–80.5 °C (lit.[62] mp 82–85 °C); ^{1}H NMR (100 MHz, CCl_4) δ 1.25 (m, 2 H), 1.60 (m, 8 H), 7.12 (m, 6 H), 7.44 (m, 4 H); IR (CCl_4) 1475, 1441, 1308, 1178, 1070, 1030, 696 cm^{-1}. Anal. Calcd for $C_{18}H_{20}S_2$: 300.1007. Found: 300.0990.

4-*tert*-Butyl-1,1-bis(*p*-methoxyphenylthio)cyclohexane. As above, 4-*tert*-butylcyclohexanone (5.0 g, 0.033 mol) and *p*-methoxythiophenol (9.54 g, 0.068 mol, 8.37 mL) in the presence of a catalytic amount of gaseous hydrogen chloride for a reaction time of 18 h gave, after the usual workup, the crude adduct, which was recrystallized from 5% 2-propanol–95% absolute ethanol to yield 10.53 g (78%) of the desired product: mp 77.5–79 °C; ^{1}H NMR (100 MHz, CCl_4) δ 0.90 (s, 9 H), 1.60 (m, 9 H), 374 (s, 3 H), 3.78 (s, 3 H), 6.76 (m, 4 H), 7.48 (m, 4 H); IR ($CHCl_3$) 1591, 1572, 1446, 1468, 1445 cm^{-1}. Anal. Calcd for $C_{24}H_{32}O_2S_2$: C, 69.19; H, 7.74. Found: C, 69.24; H, 7.70.

Preparation of Enol Phenyl Thioethers from Thioketals. Several representative procedures are outlined and the remainder appear in the supplementary material.

1-(Phenylthio)cyclohexene (7b). 1,1-Bis(phenylthio)cyclohexane (1.00 g, 3.30 mmol) and lithium carbonate (1.48 g, 20.0 mmol) were suspended in 25 mL of acetonitrile and then treated with mercuric trifluoroacetate (1.42 g, 3.30 mmol). The reaction was stirred for 5 min, silica gel (Grace, 30 g) was added, and the solvent was removed under reduced pressure. The impregnated silica gel was placed in a conventional LC column and eluted with hexane, and the solvent was concentrated in vacuo to give the crude product. This material was purified via distillation (Kugelrohr) at 115 °C (0.1 mmHg) [lit.[63] 105–115 °C (0.1 mmHg)] to yield 0.424 g (67%) of the desired product as an oil: ^{1}H NMR (100 MHz, CCl_4) δ 1.64 (m, 4 H), 2.16 (m, 4 H), 6.13 (m, 1 H), 7.35 (m, 5 H); IR (thin film) 1580, 1463, 1438 cm^{-1}.

1-(Phenylthio)cyclopentene (7a). As usual, cyclopentanone (0.951 g, 0.011 mol) and thiophenol (2.60 g, 0.024 mmol) in the presence of a catalytic amount of hydrogen chloride for a reaction time of 12 h gave, after the normal workup and recrystallization from ethanol, 2.89 g (89%) of 1,1-bis(phenylthio)cyclopentane: mp 59.5–60.5 °C.

The above thioketal (2.5 g, 8.74 mmol) and lithium carbonate (3.23 g, 4.37 mmol) in acetonitrile (50 mL) were reacted with mercuric trifluoroacetate (3.73 g, 8.74 mmol) for 10 min to give after distillation (Kugelrohr) at 110 °C (0.1 mmHg) [lit.[63] 85 °C (0.2 mmHg)] 1.04 g (68%) of the desired product: ^{1}H NMR (CCl_4) δ 1.28 (m, 2 H), 1.89 (m, 4 H), 5.51 (m, 1 H), 7.06 (m, 5 H); IR (thin film) 1468, 1432 cm^{-1}. Anal. Calcd for $C_{11}H_{12}S$: 176.0659. Found: 176.0659.

1-(Phenylthio)cyclooctene (7c). As usual, cyclooctanone (2.00 g, 15.0 mmol) and thiophenol (3.67 g, 3.33 mmol) in the presence of a catalytic amount of gaseous hydrogen chloride for a reaction time of 4 h gave an oil which could only be induced to crystallize from 2-propanol in low yield: 1.40 g (27%); mp 64–64.5 °C.

The above thioketal (0.751 g, 2.3 mmol) and lithium carbonate (1.02 g, 13.7 mmol) in 20 mL of acetonitrile was reacted with mercuric trifluoroacetate (0.978 g, 2.3 mmol) for 10 min to give after distillation (Kugelrohr) at 110–120 °C (0.1 mmHg) [lit.[64] 110–115 °C (bath at 5 × 10^{-3} mmHg)] 0.419 g (84%) of a crystalline solid: mp 33.5–34 °C; ^{1}H NMR (CCl_4) δ 1.51 (m, 8 H), 2.22 (m, 4 H), 5.67 (t, J = 8 Hz, 1 H), 7.40 (m, 5 H); IR (CCl_4) 1472, 1462, 1438 cm^{-1}. Anal. Calcd for $C_{14}H_{18}S$: 218.1129. Found: 218.1134.

1-(Phenylthio)cyclododecene (7d). As usual, cyclododecanone (2.00 g, 0.11 mol) and thiophenol (2.54 g, 0.023 mol) in the presence of a catalytic amount of gaseous hydrogen chloride for a reaction time of 5 h gave, after the normal workup and recrystallization from ethanol, 3.50 g (83%) of 1,1-bis(phenylthio)cyclododecane, mp 64.5–66 °C.

The above thioketal (0.701 g, 1.83 mmol) and lithium carbonate (0.81 g, 11.0 mmol) in 20 mL of acetonitrile were reacted with mercuric trifluoroacetate (0.779 g, 1.83 mmol) for 5 min to give after the normal workup and distillation (Kugelrohr) at 160–170 °C (0.1 mmHg) 0.248 g (49.6%) of the desired product as a 1:1 mixture of *E*:*Z* isomers: ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.31 (m, 16 H), 2.24 (m, 4 H), 5.87 (t, J = 7 Hz, 0.5 H), 7.08 (t, J = 7 Hz, 0.5 H), 7.21 (m, 5 H); IR (thin film) 1711, 1586, 1480, 1462, 1443 cm^{-1}. Anal. Calcd for $C_{18}H_{26}S$: C, 78.77; H, 9.55; M_r 274.1755. Found: C, 78.97; H, 9.63; M_r 274.1748.

3-(Phenylthio)-7-methoxy-1,2-dihydronaphthalene (11). Into a solution of freshly distilled [102–108 °C (0.1 mmHg)] 6-methoxy-2-tetralone (4.33 g, 24.6 mmol) and thiophenol (5.68 g, 51.7 mmol) in methylene chloride (2 mL) was bubbled hydrogen chloride for 1 min. The reaction was stirred for 18 h, diluted with dichloromethane (35 mL), and washed with 10% aqueous sodium hydroxide (30 mL). The aqueous layer was washed with dichloromethane (15 mL), and the combined organic layers were subsequently washed with 10% aqueous sodium chloride (30 mL). The dried (potassium carbonate) organic solution was concentrated in vacuo, and the crude green oil recrystallized from ethanol to yield 5.8 g (88%) of the desired product: mp 52–53 °C; ^{1}H NMR (100 MHz, CCl_4) δ 2.36 (t, J = 8 Hz, 2 H), 2.80 (t, J = 8 Hz, 2 H), 3.72 (s, 3 H), 6.56–7.40 (m, 9 H); IR (thin film) 1600, 1493, 1432 cm^{-1}. Anal. Calcd for $C_{17}H_{16}OS$: C, 76.08; H, 6.01; M_r 268.0921. Found: C, 75.89; H, 5.93; M_r 268.0921.

3-Ethyl-2-(phenylthio)-2-pentene (13). To a solution of diphenyl(1-(phenylthio)ethyl)phosphine oxide (1.0 g, 3.07 mmol) in THF (50 mL) at −78 °C was added tetramethylenediamine (TMEDA) (0.390 g, 3.37 mmol) followed by *n*-butyllithium (2.1 mL, 1.6 M, 3.37 mmol). The orange solution was stirred for 20 min, at which time 3-pentanone (0.263 g, 3.07 mmol) was added and the reaction allowed to warm to room temperature over 1 h. The reaction mixture was poured into chloroform (50 mL) and saturated aqueous ammonium chloride (100 mL). The aqueous layer was extracted with chloroform (3 × 50 mL). The dried (magnesium sulfate) organic layers were concentrated, and crude material eluted through silica gel (20 g) with hexane and concentrated to yield 0.185 g (29%) of the desired product pure by TLC (1% ethyl acetate/10% toluene in hexane, R_f 0.48): ^{1}H NMR (100 MHz, CCl_4) δ 1.00 (t, J = 7 Hz, 3 H), 1.04 (t, J = 7 Hz, 3 H), 1.87 (s, 3 H), 2.21 (q, J = 7 Hz, 2 H), 2.42 (q, J = 7 Hz, 2 H), 7.20 (m, 5 H); IR (thin film) 1857, 1480, 1462, 1442 cm^{-1}. Anal. Calcd for $C_{13}H_{18}S$: 206.1129. Found: 206.1130.

(1′-(Phenylthio)ethylidene)cyclohexane (14). As above, a stirred solution of the lithiated diphenyl(1-(phenylthio)ethyl)phosphine oxide [generated from the phosphine oxide (1.57 g, 12.23 mmol) and tetra-

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methylenediamine (13.5 mmol, 2.17 mL) in THF at −78 °C with *n*-butyllithium (9.0 mL, 13.5 mmol, 1.5 M solution)] and cyclohexanone (1.32 g, 13.5 mmol, 1.4 mL) gave, after the normal workup and purification on a short column of silica gel (15 g, Grace, elution with hexane), 2.36 g (88%) of the desired product: ^{1}H NMR (CCl_4) δ 1.54 (m, 6 H), 1.92 (s, 3 H), 2.28 (m, 2 H), 2.58 (m, 2 H), 7.10 (m, 5 H); IR (thin film) 1586, 1479, 1441 cm^{-1}. Anal. Calcd for $C_{14}H_{18}S$: 218.1130. Found: 218.1106.

1-(Phenylthio)-3-methyl-1-cyclohexene (15). To a solution of 2-methylcyclohexanone tosylhydrazone (2.164 g, 7.73 mmol) in TMEDA (15 mL) at −43 °C (acetonitrile/CO_2) was added a previously cooled (−43 °C) solution of lithium diisopropylamide (LDA) (2.1 equiv) in TMEDA (10 mL). The burgundy red dianion was stirred for 10 min. To this solution was added solid diphenyl disulfide (1.69 g, 7.73 mmol). The reaction was stirred for a period of 15 min during which time it turned a cloudy yellow. An additional 1.1 equiv of LDA in THF was then added to regenerate a burgundy red dianion, which was slowly warmed to room temperature and stirred for 18 h. The reaction was quenched with saturated aqueous ammonium chloride (100 mL) and extracted with ether (200 mL). The organic layer was then washed with 10% aqueous sodium hydroxide (100 mL) and twice with saturated aqueous sodium chloride (100 mL). The dried (magnesium sulfate) ether solution was concentrated in vacuo and distilled (Kugelrohr) at 120 °C (0.1 mmHg) to yield 0.982 g (62.5%) of product. The oil was further purified by preparative TLC (2% ethyl acetate/hexane, R_f 0.56) to yield 0.480 g (31%) of the desired product: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06 (d, J = 7 Hz, 3 H), 1.2 (m, 1 H), 1.6 (m, 1 H), 1.7 (m, 2 H), 2.1 (m, 2 H), 2.2 (m, 1 H), 5.83 (m, 1 H), 7.16 (m, 5 H); IR (thin film) 1583, 1478, 1454, 1442 cm^{-1}. Anal. Calcd for $C_{13}H_{16}S$: 204.0972. Found: 204.0974.

1-(Phenylthio)-4-carbomethoxycyclohexene (18a). In a thick walled glass tube were combined 2-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (0.155 g, 0.069 mmol), and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (one crystal) in xylene (2 mL). The tube was frozen (N_2) and sealed under vacuum and then heated to 145 °C for 2.5 h. The solvent was removed under reduced pressure and the product obtained by distillation (129 °C (0.1 mmHg)) in a yield of 0.138 g (81%): ^{1}H NMR (100 MHz, CCl_4) δ 1.42–2.54 (m, 7 H), 3.55 (s, 3 H), 5.90 (m, 1 H), 7.15 (m, 5 H); IR (thin film) 1742, 1591, 1488, 1449 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49; M_r 248.0871. Found: C, 67.65; H, 6.33; M_r 248.0866.

1-(Phenylthio)-4-acetylcyclohexene (18b). A solution of 3-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (0.250 g, 1.11 mmol) and 3-*tert*-butyl-4-hydroxy-5-methyl phenyl sulfide (two crystals) in toluene (5 mL) was refluxed for 3 h, at which time TLC (10% ethyl acetate/chloroform) showed no remaining starting material. The system was cooled and then purged with N_2 for 5 min. To the above solution was added methyl vinyl ketone (0.232 g, 3.32 mmol), and the mixture was brought to reflux for 18 h. The toluene was removed under reduced pressure and the crude reaction mixture was purified by preparative TLC (4% ethanol/hexane, R_f 0.45) to yield 0.210 g (82%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.36–2.68 (m, 10 H), 5.98 (m, 1 H), 7.24 (m, 5 H); IR (thin film) 1715, 1587, 1480, 1443 cm^{-1}. Anal. Calcd for $C_{14}H_{16}OS$: C, 72.37; H, 6.94; M_r 232.0922. Found: C, 72.32; H, 6.89; M_r 232.0927.

Preparation of 1-(Phenylthio)-4-isopropenylcyclohexene (19). To a solution of ketone **18b** (0.166 g, 0.72 mmol) in THF (1.5 mL) at room temperature was added a solution of ylide prepared from methyltriphenylphosphonium iodide (0.347 g, 0.86 mmol) and potassium *tert*-butoxide (0.88 g, 0.79 mmol) in THF (1 mL) at 0 °C. This solution was refluxed for 16 h, then diluted with ether (10 mL) and filtered through a pad of Celite. The ether solution was washed with water (2 × 10 mL) and saturated aqueous sodium chloride (10 mL). The dried (magnesium sulfate) organic solution was concentrated in vacuo. Preparative TLC (4% ethanol in hexane (v/v), R_f 0.34) yielded 0.130 g (79%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.24–2.38 (m, 10 H), 4.66 (m, 2 H), 5.95 (m, 1 H), 7.16 (m, 5 H); IR (thin film) 1654, 1586, 1478, 1441 cm^{-1}. Anal. Calcd for $C_{15}H_{18}S$: 230.1129. Found: 230.1142.

Preparation of 3-Phenyl-2-(phenylthio)propene (20). To a THF (15 mL) solution of lithium tetramethylpiperidide, prepared from tetramethylpiperidine (0.492 g, 3.49 mmol) and TMEDA (0.426 g, 3.68 mmol) with *n*-butyllithium (2.33 mL, 3.49 mmol), was added at −78 °C phenyl vinyl sulfide (0.500 g, 3.68 mmol). The reaction was stirred for 1 h and then warmed to room temperature for 10 min, and benzyl bromide (0.943 g, 4.41 mmol) was added. The reaction was allowed to come to room temperature for 1 h. The reaction was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ether (40 mL). The organic layer was subsequently washed with 5% aqueous sodium hydrogen sulfate (15 mL), saturated aqueous sodium bicarbonate (15 mL), and saturated aqueous sodium chloride (15 mL). The dried (sodium sulfate) organic solution was concentrated in vacuo and the crude oil purified via preparative TLC (2% ethyl acetate/hexane, double elution, R_f 0.57) to yield 0.343 g (44%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 3.32 (s, 2 H), 4.76 (s, 1 H), 4.81 (s, 1 H), 6.90 (m, 10 H); IR (thin film) 1510, 1580, 1491, 1472, 1438 cm^{-1}. Anal. Calcd for $C_{15}H_{14}S$: 226.0817. Found: 226.0808.

Preparation of 1,1-Bis(phenylsulfonyl)-4-methyl-3-(phenylthio)-3-pentene (24). To a stirred solution of 2-(phenylthio)-3-methyl-2-butene (0.220 g, 1.24 mmol) in acetonitrile (2 mL) was added NBS (0.220 g, 1.24 mmol). The reaction was stirred for 5 min, a catalytic amount of lithium bromide (approximately 10 mg) was added, and the cloudy solution was stirred for 2.5 h. The reaction mixture was concentrated under reduced pressure. The crude product was suspended in carbon tetrachloride and filtered through a plug of silica gel (approximately 1 g); ^{1}H NMR (100 MHz) δ 1.96 (s, 3 H), 2.04 (s, 3 H), 4.03 (s, 2 H), 7.12 (m, 5 H).

The bromide was dissolved in DMF (1.5 mL) and added to a solution of the anion, prepared from bis(phenylsulfonyl)methane (0.607 g, 2.05 mmol) and washed (hexane) sodium hydride (0.041 g, 1.70 mmol), in DMF (1.5 mL). The alkylation reaction was stirred for 18 h at room temperature, poured into saturated aqueous ammonium chloride (20 mL), and extracted twice with ether (20 mL). The combined organic extracts were washed twice with saturated aqueous sodium chloride (20 mL) and dried over anhydrous magnesium sulfate. The organic solvent was removed in vacuo and the crude oil was purified by preparative thin layer chromatography (1% ethyl acetate/chloroform, double elution, R_f 0.65) to yield 0.311 g (53%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 2.01 (s, 3 H), 2.08 (s, 3 H), 3.12 (br d, J = 7.5 Hz, 2 H), 5.10 (t, J = 7.5 Hz, 1 H), 6.91–7.80 (m, 15 H); IR (thin film) 1588, 1482, 1451, 1443, 1330, 1162 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_4S_3$: 472.0837. Found: 472.0835.

Preparation of Diethyl (2-(Phenylthio)-1-cyclopenten-3-yl)malonate (25). To a stirred solution of **7a** (0.112 g, 0.636 mmol) in methylene chloride (1 mL) at 9 °C was added NBS (0.113 g, 0.626 mmol). After a period of 15 min the reaction was concentrated in vacuo. The crude material was suspended in carbon tetrachloride and filtered through a plug of Celite. The solvent was removed in vacuo to yield 0.156 g (96%) of the crude bromide: ^{1}H NMR (100 MHz, CCl_4) 7.40 (m, 5 H), 5.85 (m, 0.8 H), 4.80 (m, 0.8 H), 2.42 (m, 4.2 H).

As described for the preparation of **29**, the above bromide was alkylated with diethyl sodiomalonate generated from diethyl malonate (0.137 g, 0.856 mmol) and sodium hydride (0.019 g, 0.795 mmol) in DMF (1.5 mL). After the normal workup, the resulting oil was purified by preparative thin layer chromatography (10% ethyl acetate/chloroform, R_f 0.65) to yield 0.109 g (53%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.23 (t, J = 7 Hz, 6 H), 2.02–2.5 (m, 4 H), 3.32 (m, 1 H), 3.62 (d, J = 5 Hz, 1 H), 4.10 (q, J = 6 Hz, 4 H), 5.73 (m, 1 H), 7.80 (m, 5 H); IR (thin film) 1740, 1560, 1475, 1440, 1370 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_4S$: 334.1239. Found: 334.1229.

Preparation of Dimethyl (2-(Phenylthio)-1-cyclohexen-3-yl)malonate (26). To a solution of **7b** (2.093 g, 11.0 mmol) in chloroform (10 mL) was added solid NBS (1.96 g, 11.0 mmol) at room temperature. The reaction was stirred for 30 min and concentrated in vacuo. The crude material was suspended in carbon tetrachloride and filtered through a cotton plug. The organic solvent was removed in vacuo and the bromide dissolved in DMF (5 mL). The anion of dimethyl malonate, prepared by dropwise addition of dimethyl malonate (2.035 g, 15.4 mmol) to washed sodium hydride (0.357 g, 14.9 mmol) suspended in DMF (25 mL), was added to the bromide solution and stirred for 18 h. The reaction was diluted with ether (60 mL) and extracted with saturated aqueous ammonium chloride (50 mL). The aqueous layer was extracted with ether (40 mL), and the combined organic layers were washed with saturated aqueous sodium chloride (3 × 50 mL). The dried (magnesium sulfate) organic solution was concentrated in vacuo and the crude oil purified via preparative LC (10% ethyl acetate/hexane) to yield 2.43 g (69%) of desired product as a crystalline solid: mp 50–52 °C; ^{1}H NMR (100 MHz, $CDCl_4$) δ 1.5–2.3 (m, 6 H), 2.84 (m, 1 H), 3.6 (s, 6 H), 3.8 (d, J = 8 Hz, 1 H), 6.1 (m, 1 H), 7.14 (m, 5 H); IR (thin film) 1760, 1744, 1591, 1478, 1448 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_4S$: C, 63.73; H, 6.29; M_r 320.1082. Found: C, 63.68; H, 6.42; M_r 320.1082.

1-(Phenylthio)-2-bromocyclohexene (0.59 g (20%)) was also obtained: ^{1}H NMR (100 MHz, CCl_4) δ 1.72 (m, 4 H), 2.1 (m, 2 H), 2.65 (m, 2 H), 7.53 (m, 5 H); IR (thin film) 1618, 1588, 1478, 1442 cm^{-1}. Anal. Calcd for $C_{12}H_{13}BrS$: 267.9912. Found: 267.9917.

Preparation of Methyl 2-(2-(Phenylthio)-1-cyclohexen-3-yl)-3-oxobutyrate (27). The bromination of **7b** (0.134 g, 0.71 mmol) was carried out under the standard conditions (see preparation of **26**).

The bromide mixture was alkylated by the anion of methyl acetoacetate which was prepared from methyl acetoacetate (0.154 g, 1.33

mmol) and hexane-washed and dried sodium hydride (0.029 g, 1.21 mmol) in DMF (2 mL). After the usual workup, the crude material was purified via preparative TLC (2% ethyl acetate/chloroform, R_f 0.22) to yield 0.068 g (32%) of the desired product as an oil: ^{1}H NMR (100 MHz, CCl_4) δ 0.72 (m, 4 H), 2.11 (m, 5 H), 2.93 (m, 1 H), 3.68 (s, 3 H), 3.97 (m, 1 H), 6.26 (m, 1 H), 7.32 (m, 5 H); IR (thin film) 1740, 1722, 1640, 1583, 1479, 1441 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_3S$: 304.1133. Found: 304.1128.

Preparation of Dimethyl (2-(Phenylthio)-3-methyl-2-cyclohexenyl)malonate (28). A mixture of **8** and **9** (0.151 g, 0.74 mmol) was treated with *p*-methylbenzenesulfonic acid (10 mg, 0.058 mmol) in benzene (5 mL) at 75 °C for 1 h. The reaction was diluted with benzene (10 mL), washed with saturated aqueous sodium bicarbonate (10 mL), dried (magnesium sulfate), and concentrated in vacuo to yield 0.151 g (100%) of the tetrasubstituted olefin isomer: ^{1}H NMR (100 MHz, CCl_4) δ 1.46 (m, 4 H), 2.00 (s, 3 H), 2.22 (m, 4 H), 7.24 (m, 5 H).

To a solution of 1-(phenylthio)-2-methylcyclohexene (0.151 g, 0.74 mmol) in chloroform (0.6 mL) was added NBS (0.142 g, 0.74 mmol). The reaction was stirred for 30 min, concentrated in vacuo, suspended in carbon tetrachloride, and filtered through a plug of cotton. The organic solution was concentrated in vacuo and the crude bromide dissolved in DMF (0.5 mL). The resultant bromide was alkylated in the usual fashion with dimethyl sodiomalonate which was prepared from dimethyl malonate (0.161 g, 1.27 mmol) and hexane-washed sodium hydride (0.029 g, 1.2 mmol) in DMF (2 mL). After the usual workup, the crude oil was purified via preparative TLC (10% ethyl acetate/hexane, double elution, R_f 0.21) to yield 0.120 g (49%) of the desired product: ^{1}H NMR (CCl_4) δ 1.20–2.18 (m, 9 H), 2.82 (m, 1 H), 3.26 (m, 6 H), 3.82 (d, J = 5 Hz, 1 H), 6.91 (m, 5 H); IR (thin film) 1748, 1588, 1481, 1442 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_4S$: 334.1239. Found: 334.1239.

Preparation of Dimethyl (2-(Phenylthio)-5-*tert*-butyl-1-cyclohexen-3-yl)malonate (29). A solution of **10a** ((0.049 g, 0.199 mmol) in dichloromethane (0.2 mL) was brominated with NBS (0.035 g, 0.199 mmol) in the usual fashion; ^{1}H NMR (100 MHz, CCl_4) δ 0.85 (br s, 9 H), 1.20–2.30 (m, 6.4 H), 4.45 (m, 0.72 H), 5.95 (m, 0.72 H), 7.13 (m, 5 H).

The bromide mixture, dissolved in DMF (0.5 mL), was alkylated with dimethyl sodiomalonate prepared from dimethyl malonate (0.037 g, 0.279 mmol) and hexane-washed sodium hydride (0.006 g, 0.259 mmol) in DMF (1.5 mL). After the usual workup, the crude material was purified via preparative TLC (chloroform, double elution, R_f 0.4) to yield 0.038 g (51%) of the desired product: ^{1}H NMR (100 MHz) δ 0.92 (s, 9 H), 1.40–2.18 (m, 5 H), 2.88 (m, 1 H), 2.60 (br s, 6 H), 3.96 (d, J = 4 Hz, 1 H), 6.18 (m, 1 H), 7.12 (m, 5 H); IR (thin film) 1754, 1739, 1584, 1478, 1449 cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_4S$: C, 66.99; H, 7.55; M_r 376.1708. Found: C, 66.86; H, 7.53; M_r 376.1707.

Preparation of Diethyl (2-((*p*-Methoxyphenyl)thio)-5-*tert*-butyl-1-cyclohexen-3-yl)malonate (30). A stirred solution of **10b** (0.229 g, 0.83 mmol) in methylene chloride (1 mL) was brominated with NBS (0.148 g, 0.83 mmol) in the usual fashion to give a mixture of crude bromides: ^{1}H NMR (100 MHz, CCl_4) δ 7.40 (AA′ part of AA′BB′, J = 8 Hz, 2 H), 6.86 (BB′ part of AA′BB′, J = 8 Hz, 2 H), 5.96 (m, 0.8 H), 4.457 (m, 0.8 H), 3.80 (br s, 3 H), 2.14–2.45 (m, 7 H), 0.87 (br s, 9 H).

The above bromide mixture was alkylated with diethyl sodiomalonate prepared from hexane-washed sodium hydride (0.014 g, 0.563 mmol) and diethyl malonate (0.093 g, 0.584 mmol) in DMF (1.5 mL). After the usual workup the crude product was purified via preparative thin layer chromatography (4% ethyl acetate/hexane, double elution, R_f 0.30) to yield 0.36 g (76%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 0.92 (s, 9 H), 1.12–2.16 (m, 11 H), 2.83 (m, 1 H), 3.80 (s, 3 H), 4.0–4.29 (m, 5 H), 6.04 (m, 1 H), 6.85 (d, J = 8 Hz, 2 H), 7.32 (d, J = 8 Hz, 2 H); IR (thin film) 1752, 1739, 1594, 1498 cm^{-1}. Anal. Calcd for $C_{24}H_{34}O_5S$: 434.2127. Found: 434.2133.

Preparation of (3,3-Bis(phenylsulfonyl)-1-(phenylthio)propylidene)cyclohexane (31). To a stirred solution of **14** (0.324 g, 1.49 mmol) in acetonitrile (3 mL) was added NBS (0.264 g, 1.49 mmol). The reaction was stirred for 5 min and a catalytic amount of lithium bromide (approximately 10 mg) was added. The resulting cloudy solution was stirred for 2 h and then concentrated under reduced pressure. The crude material was suspended in carbon tetrachloride and filtered through a plug of silica gel. The carbon tetrachloride was removed in vacuo and the bromide dissolved in DMF (1 mL). The crude bromide was alkylated with a nucleophile prepared from bis(phenylsulfonyl)methane (0.662 g, 2.24 mmol) and hexane-washed sodium hydride (0.045 g, 1.88 mmol) in DMF (1.5 mL). After the usual workup the crude oil was purified by preparative thin layer chromatography (chloroform, double elution, R_f 0.51) to yield 0.47 g (62%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.63 (m, 6 H), 2.56 (m, 4 H), 3.08 (d, J = 5 Hz, 2 H), 5.08 (t, J = 5 Hz, 1 H), 7.948 (m, 15 H); IR (thin film) 1581, 1479, 1448 cm^{-1}. Anal. Calcd for $C_{27}H_{28}O_4S_3$: C, 63.3; H, 5.5; M_r 512.1150. Found: C, 63.4; H, 5.6; M_w 512.1170.

Preparation of Dimethyl (2-(Phenylthio)-4-methyl-1-cyclohexen-3-yl)malonate (32). A solution of 1-(phenylthio)-3-methylcyclohexene (0.123 g, 0.603 mmol) in dichloromethane (0.5 mL) was brominated with NBS (0.017 g, 0.603 mmol) in the usual way; ^{1}H NMR (100 MHz, CCl_4) δ 1.01 (d, J = 5 Hz, 1.5 H), 1.99 (d, J = 6.5 Hz, 1.5 H), 1.33–2.6 (m, 5.5 H), 4.10 (m, 0.15 H), 4.29 (m, 0.35 H), 5.95 (m, 0.5 H), 7.70 (m, 5 H).

The bromide mixture, dissolved in DMF (0.5 mL), was alkylated with dimethyl sodiomalonate which was prepared from dimethyl malonate (0.111 g, 0.844 mmol) and hexane-washed sodium hydride (0.019 g, 0.800 mmol) in DMF (2.0 mL). After the normal workup, the material was purified via preparative TLC (dichloromethane) to yield 0.088 g (44%) of the alkylated products **52** and **53** (R_f 0.41) and 0.055 g (32%) of 1-(phenylthio)-2-bromo-3-methylcyclohexene (**54**) (R_f 0.82). The alkylated products **52** and **53**: ^{1}H NMR (270 MHz, CCl_4) δ 0.96 (d, J = 6 Hz, 2.1 H), 1.03 (d, J = 6 Hz, 0.89 H), 1.21–2.42 (m, 5 H), 2.67 (m, $W_{1/2}$ = 12 Hz, 0.7 H), 2.93 (m, $W_{1/2}$ = 18 Hz, 0.3 H), 3.68 (s, 3 H), 3.73 (s, 3 H), 3.82 (d, J = 8.5 Hz, 0.7 H), 4.01 (d, J = 8.5 Hz, 0.3 H), 6.19 (m, $W_{1/2}$ = 6 Hz, 0.3 H), 6.24 (m, $W_{1/2}$ = 10 Hz, 0.7 H), 7.22 (m, 5 H); IR (thin film) 2947, 2910, 1737, 1532, 1331, 1264, 1661, 1028, 748, 698 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_4S$: 334.1238. Found: 334.1205.

1-(Phenylthio)-2-bromo-3-methylcyclohexene (54): ^{1}H NMR (100 MHz, CCl_4) δ 0.91–2.1 (m, 6 H), 1.25 (d, J = 7 Hz, 3 H), 2.65 (m, 1 H), 7.20 (m, 5 H); IR (thin film) 1582, 1478, 1440 cm^{-1}. Anal. Calcd for $C_{13}H_{15}BrS$: 282.0072. Found: 282.0074.

Preparation of Dimethyl (2-(Phenylthio)-5-carbomethoxy-1-cyclohexen-3-yl)malonate (33). A solution of **18a** (0.109 g, 0.44 mmol) in dichloromethane (0.5 mL) was brominated with NBS (0.078 g, 0.440 mmol) in the usual fashion; ^{1}H NMR (100 MHz, CCl_4) δ 1.36 (m, 1 H), 1.98–3.44 (m, 5.4 H), 3.82 (s, 3 H), 4.76 (m, 0.67 H), 6.32 (t, J = 5 Hz, 0.67 H), 7.64 (m, 5 H).

The bromide mixture, dissolved in DMF (0.5 mL), was alkylated with dimethyl sodiomalonate which was prepared by dropwise addition of dimethyl malonate (0.081 g, 0.615 mmol) to a suspension of hexane-washed and dried sodium hydride (0.014 g, 0.583 mmol) in DMF (1.5 mL) at ambient temperature as in the case of **26**. After a similar workup, the crude material was purified via preparative TLC (2% ethyl acetate/chloroform, R_f 0.36) to yield 0.056 g (34%) of the desired product as an oil: ^{1}H NMR (100 MHz, CCl_4) δ 2.0–3.16 (m, 6 H), 3.73 (br s, 10 H), 6.32 (m, 1 H), 7.35 (m, 5 H); IR (thin film) 1738, 1587, 1483, 1443 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_6S$: 378.1137. Found: 378.1120.

Preparation of Dimethyl (5-Acetyl-2-(phenylthio)-1-cyclohexen-3-yl)malonate (34). A solution of **18b** (0.114 g, 0.491 mmol) in chloroform (0.2 mL) was brominated with NBS (0.087 g, 0.491 mmol) in the usual fashion; ^{1}H NMR (100 MHz, CCl_4) δ 1.39 (m, 0.6 H), 2.0–3.3 (m, 5.4 H), 3.77 (m, 1 H), 3.84 (s, 3 H), 4.76 (m, 0.65 H), 6.32 (t, J = 5 Hz, 0.65 H), 7.66 (m, 5 H).

The bromide mixture, dissolved in DMF (0.5 mL), was alkylated with dimethyl sodiomalonate, which was prepared by dropwise addition of dimethyl malonate (0.091, 0.688 mmol) to a suspension of hexane-washed sodium hydride (0.015 g, 0.638 mmol) in DMF (1 mL), and worked up as in the preparation of **26**. The crude material was purified via preparative TLC (2% ethyl acetate/chloroform, R_f 0.19) to yield 0.091 g (51%) of the desired product as an oil: ^{1}H NMR (100 MHz, CCl_4) δ 1.90 (m, 2 H), 2.20 (s, 3 H), 2.24 (m, 2 H), 2.30 (m, 1 H), 2.82 (m, 1 H), 3.56 (br s, 6 H), 3.88 (m, 1 H), 6.08 (m, 1 H), 7.04 (m, 5 H); IR (thin film) 1736, 1580, 1479, 1440 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_5S$: 362.1188. Found: 362.1188.

Preparation of Dimethyl (5-Isopropenyl-2-(phenylthio)-1-cyclohexen-3-yl)malonate (35). A solution of **19** (0.128 g, 0.577 mmol) in chloroform (0.2 mL) was brominated with NBS (0.099 g, 0.557 mmol) in the usual fashion; ^{1}H NMR (100 MHz, CCl_4) δ 1.2–2.9 (m, 6.4 H), 1.76 (s, 1 H), 1.80 (s, 2 H), 4.71 (m, 0.6 H), 4.84 (m, 2 H), 6.25 (m, 0.6 H), 7.44 (m, 5 H).

The bromide mixture, dissolved in DMF (0.5 mL), was alkylated with dimethyl sodiomalonate, which was prepared via dropwise addition of dimethyl malonate (0.103 g, 0.779 mmol) to a suspension of hexane-washed sodium hydride (0.017 g, 0.723 mmol) in DMF (9.2 mL) as in the case of **26**. After a similar workup, the crude product was purified via preparative TLC (2% ethyl acetate/chloroform, R_f 0.53) to yield 0.090 g (45%) of the desired product along with 0.046 g (30%) of (1-(phenylthio)-2-bromo-4-isopropenyl)cyclohexane (R_f 0.75). The desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.79–2.4 (m, 8 H), 3.03 (m, 1 H), 3.73 (br s, 7 H), 4.84 (m, 2 H), 6.48 (m, 1 H), 7.44 (m, 5 H); IR (thin film) 1736, 1647, 1582, 1480, 1440 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_4S$: 360.1395. Found: 360.1395.

1-(Phenylthio)-2-bromo-4-isopropenylcyclohexene: ^{1}H NMR (100 MHz, CCl_4) δ 1.2–2.28 (m, 10 H), 4.8 (m, 2 H), 7.41 (m, 5 H); IR (thin film) 1650, 1622, 1588, 1481, 1443 cm^{-1}. Anal. Calcd for $C_{15}H_{17}BrS$: 308.2035. Found: 308.0236.

Preparation of Dimethyl (2-(Phenylthio)-3-phenyl-2-propenyl)-malonate (36). A stirred solution of **20** (0.104 g, 0.460 mmol) in chloroform (0.7 mL) was brominated with NBS (0.82 g, 0.460 mmol) in the usual fashion. The crude bromide, dissolved in DMF (0.5 mL), was alkylated with dimethyl sodiomalonate which was prepared by adding dimethyl malonate (0.085 g, 0.644 mmol) dropwise to a suspension of hexane-washed sodium hydride (0.015 g, 0.625 mmol) in DMF (2 mL) as in the preparation of **26**. After the normal workup, the crude oil was purified via preparative TLC (20 × 20 cm silica gel plate, 10% ethyl acetate/hexane, double elution, R_f 0.2) to yield 0.076 g (46%) of the desired product as a 1:1 mixture of *E*:*Z* isomers. ^{1}H NMR (100 MHz, CCl_4) δ 2.74 (d, J = 7 Hz, 0.5 H), 2.94 (d, J = 7 Hz, 0.5 H), 3.53 (m, 7 H), 6.63 (br s, 0.5 H), 6.70 (br s, 0.5 H), 7.12 (m, 10 H); IR (thin film) 1756, 1742, 1580, 1482, 1446 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_4S$: 356.1082. Found: 356.1088.

Preparation of 2-Methyl-3-(phenylthio)-2-pentene (43). A solution of **6** (0.246 g, 1.38 mmol) in acetonitrile (2.5 mL) was brominated with NBS (0.246 g, 1.38 mmol) and isomerized with lithium bromide (~10 mg) in the usual fashion. The bromide, dissolved in ether (1 mL), was added to a solution of lithium dimethylcuprate which was prepared from copper bromide, dimethyl sulfide (0.426 g, 2.07 mmol), and methyllithium (2.96 mL, 4.15 mmol) in ether (1 mL). After reaction and workup as below the crude product was purified via preparative TLC (1% ethyl acetate/10% toluene/hexane, R_f 0.45) to yield 0.164 g (62%) of the desired product contaminated with less than 8% of 3,3-dimethyl-2-(phenylthio)-1-butene as seen in the NMR spectrum: ^{1}H NMR (CCl_4) δ 1.00 (t, J = 6.5 Hz, 3 H), 1.86 (s, 3 H), 1.96 (s, 3 H), 2.22 (q, J = 6.5 Hz, 2 H), 7.04 (m, 5 H) [minor isomer, <10%, 1.21 (s), 4.48 (s), 5.08 (s)]; IR (thin film) 1589, 1482, 1333 cm^{-1}. Anal. Calcd for $C_{12}H_{16}S$: 192.0972. Found: 192.0968.

Preparation of 3-Methyl-2-(phenylthio)cyclohexene (44). A solution of 1-(phenylthio)cyclohexene (0.188 g, 0.989 mmol) in chloroform (0.8 mL) was brominated with NBS (0.176 g, 0.989 mmol) in the usual way; ^{1}H NMR (100 MHz, CCl_4) δ 1.70–2.80 (m, 7.5 H), 4.53 (m, 0.67 H), 6.41 (m, 0.67 H), 7.21 (m, 6 H).

The bromide mixture, dissolved in ether (1 mL), was added to a solution of lithium dimethylcuprate which was prepared by suspending copper(I) iodide (0.239 g, 1.29 mmol) in ether (1 mL) at −78 °C and adding methyllithium (1.84 mL, 1.4 M, 2.57 mmol). The reaction was allowed to come to ambient temperature over a 12-h period and quenched with saturated aqueous ammonium chloride. The reaction mixture was extracted with ether (15 mL). The combined organic layers were washed with saturated aqueous sodium chloride (10 mL). The dried (sodium sulfate) organic solution was concentrated in vacuo and the material purified via preparative TLC (2% ethyl acetate/hexane, R_f 0.68) to yield 0.099 g (49%) of the desired product as an oil: ^{1}H NMR (100 MHz, CCl_4) δ 1.13 (d, J = 6 Hz, 3 H), 1.4–2.3 (m, 7 H), 5.73 (m, 1 H), 7.03 (m, 5 H); IR (thin film) 1579, 1483, 1448 cm^{-1}. Anal. Calcd for $C_{13}H_{16}S$: 204.0973. Found: 204.0969.

Preparation of 2-(Phenylthio)-3-phenylcyclohexene (45). A solution of **7b** (0.209 g, 1.10 mmol) of chloroform (0.8 mL) was brominated with NBS (0.196 g, 1.10 mmol) in the usual way.

The bromide mixture, dissolved in ether (1 mL), was added to a solution of lithium diphenylcuprate which was prepared in ether (1 mL) and dimethyl sulfide (1.5 mL) at 0 °C by the addition of phenyllithium (1.65 mL, 1.6 M, 2.64 mmol) to a suspension of copper(I) bromide–dimethyl sulfide complex (0.771 g, 1.32 mmol). The reaction was allowed to come to ambient temperature over an 8-h period at which time it was quenched with saturated aqueous ammonium chloride (8 mL) and extracted with ether (3 × 10 mL). The combined organic washes were washed with saturated aqueous sodium chloride and dried with anhydrous sodium sulfate. The solvent was removed in vacuo and the crude material purified via preparative TLC (2% ethyl acetate/hexane, triple elution, R_f 0.52) to yield 0.150 g (51%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.2–2.23 (m, 6 H), 3.34 (m, 1 H), 6.02 (m, 1 H), 7.04 (m, 10 H); IR (thin film) 1589, 1498, 1482, 1458, 1435 cm^{-1}. Anal. Calcd for $C_{18}H_{18}S$: 266.1129. Found: 266.1119.

Preparation of 2-(Phenylthio)-3-(phenylethynyl)-1-cyclohexene (46). A solution of **7b** (0.270 g, 1.42 mmol) in chloroform (0.8 mL) was brominated with NBS (0.253 g, 1.42 mmol) in the usual fashion.

A solution of lithium bis(phenylethynyl)cuprate was prepared by treating phenylacetylene (0.393 g, 3.85 mmol) in THF (2 mL) at −78 °C with *n*-butyllithium (2.47 mL, 1.5 M, 371 mmol). The anion was stirred for 5 min at −78 °C, warmed to ambient temperature for 15 min, and then recooled to −78 °C, and copper(I) bromide–dimethyl sulfide complex (0.381 g, 1.85 mmol) suspended in THF (2 mL) was added. The cuprate solution was stirred for 45 min at −78 °C and warmed to 0 °C for 30 min, at which time a solution of the above prepared bromide in THF (1 mL) was added. The reaction was allowed to come to ambient temperature slowly over 10 h, quenched with saturated ammonium chloride (20 mL), and extracted with ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride (20 mL), dried (magnesium sulfate), and concentrated in vacuo. The crude material was purified via preparative TLC (10% toluene/hexane, double elution, R_f 0.51) to yield 0.207 g of a 2:1 mixture of **46** and 1-(phenylthio)-2-bromocyclohexene as determined by NMR integration and mass spectral analysis: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.93 (m, 10 H), 3.21 (m, 1 H), 5.91 (m, 1 H), 7.08 (m, 13 H); IR (thin film) 1582, 1491, 1479, 1441 cm^{-1}. Anal. Calcd for $C_{20}H_{18}S$: 290.1130. Found: 290.1127.

Preparation of 2-(Phenylthio)-3-methyl-1-cyclododecene (47). A solution of **7d** (0.328 g, 1.20 mmol) in chloroform (2 mL) was brominated with NBS (0.213 g, 1.20 mmol) in the usual way; ^{1}H NMR (100 MHz, CCl_4) δ 1.23 (m, 15 H), 2.05 (m, 3.1 H), 4.48 (m, 0.45 H), 5.10 (br t, J = 5 Hz, 0.45 H), 5.39 (m, 0.45 H), 6.36 (br t, J = 7 Hz, 0.45 H), 7.16 (m, 5 H).

The above bromide mixture, dissolved in ether (0.5 mL), was added at 0 °C to a solution of lithium dimethylcuprate prepared at −78 °C in ether (1.5 mL) from copper bromide–dimethyl sulfide complex (0.369 g, 1.795 mmol) and methyllithium (2.6 mL, 1.4 M, 359 mmol). After reaction and workup as above, the crude oil was purified by preparative TLC (1% ethyl acetate/10% toluene/hexane, R_f 0.82) to yield 0.211 g (61%) of the desired product as a 1:2 mixture of *E*:*Z* isomers: ^{1}H NMR (CCl_4) δ [0.99 (d, J = 7 Hz), 1.02 (d, J = 7 Hz), total 3 H], 1.28 (m, 16 H), 2.40 (m, 3 H), 5.42 (dd, J = 13, 4 Hz, 0.4 H), 6.12 (dd, J = 8, 6 Hz, 0.6 H), 7.13 (m, 5 H); IR (thin film) 1704, 1580, 1447, 1468, 1459, 1439 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 140.5, 140.0, 137.5, 136.4, 136.0, 128.8, 128.6, 127.1, 126.1, 124.7, 43.0, 33.3, 33.1, 32.6, 29.5, 26.8, 26.4, 26.1, 25.7, 25.5, 25.1, 24.9, 24.7, 24.2, 23.9, 23.8, 22.6, 22.5, 20.3, 19.7. Anal. Calcd for $C_{19}H_{28}S$: 288.1912. Found: 288.1905.

Preparation of (1′-(Phenylthio)propylidene)cyclohexane (48). A stirred solution of **14** (0.898 g, 4.12 mmol) in acetonitrile (10 mL) was brominated with NBS (0.733 g, 4.12 mmol) and isomerized with lithium bromide (~10 mg) as described in the preparation of **31**. The bromide, dissolved in ether (5 mL), was added at 0 °C to a solution of lithium dimethylcuprate, which was prepared by treating copper bromide–dimethyl sulfide complex (1.27 g, 6.18 mmol) with methyllithium (8.8 mL, 12.4 mmol, 1.4 M in ether) in ether (10 mL) at −78 °C for 5 min and warming to 0 °C for 15 min. After reaction and workup as described above, the crude oil was purified by preparative TLC (1% ethyl acetate/8% toluene/hexane, double elution, R_f 0.95) to yield 0.660 g (69%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.00 (t, J = 7.5 Hz, 3 H), 1.59 (m, 6 H), 2.12–2.62 (m, 6 H), 7.07 (m, 5 H); IR (thin film) 1590, 1483, 1446 cm^{-1}. Anal. Calcd for $C_{15}H_{20}S$: 232.1285. Found: 232.1285.

Preparation of 4-Ethyl-3-(phenylthio)-3-hexene (49). A solution of **13** (0.100 g, 0.49 mmol) in acetonitrile (1.0 mL) was brominated with NBS (0.086 g, 0.49 mmol) and subsequently isomerized with a catalytic amount of lithium bromide (~10 mg) as previously described in the preparations of **24** and **31**; ^{1}H NMR (100 MHz, CCl_4) δ 1.20 (t, J = 7 Hz, 6 H), 2.21 (m, 4 H), 4.01 (s, 2 H), 7.24 (m, 5 H).

The crude bromide, dissolved in ether (1.0 mL), was added to a solution of lithium dimethylcuprate, which was prepared by adding methyllithium (0.83 mL, 1.4 M, 1.17 mmol) to a suspension of copper(I) bromide–dimethyl sulfide complex (0.120 g, 0.58 mmol) in ether (2.0 mL) at −78 °C and allowing it to come to 0 °C over 30 min. After reaction and workup as above, the crude material was purified via preparative TLC (1% ethyl acetate/10% toluene/hexane, R_f 0.37) to yield 0.065 g (61%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 0.96 (t, J = 7.5 Hz, 9 H), 2.10 (q, J = 7.5 Hz, 2 H), 2.33 (m, 4 H), 7.08 (m, 5 H); IR (thin film) 1587, 1480, 1461, 1442, 1380 cm^{-1}. Anal. Calcd for $C_{14}H_{20}S$: 220.1286. Found: 220.1283.

Preparation of Dimethyl (2-Oxocyclohexyl)malonate. To a solution of dimethyl 2-(phenylthio)-2-cyclohexenylmalonate (0.218 g, 0.68 mmol) in acetonitrile (6 mL) and water (2 mL) was added mercuric chloride (0.370 g, 1.36 mmol). The reaction was refluxed for 4 days and the mixture diluted with ether (20 mL). The mixture was filtered through a sintered glass funnel, concentrated in vacuo, and purified via preparative TLC (1% ethyl acetate/chloroform, R_f 0.33) to yield 0.050 g (33%) of the desired product: ^{1}H NMR (CCl_4) δ 1.52–2.52 (m, 8 H), 3.06 (m, 1 H), 3.56 (d, J = 8.5 Hz, 1 H), 3.68 (s, 6 H); IR (thin film) 1752, 1736, 1709, 1439 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_5$: 228.0998. Found: 228.0996.

Preparation of *p*-Toluenesulfilimine (52). To a solution of **48** (0.334 g, 1.44 mmol) in methanol (6 mL) was added chloramine-T (0.655 g, 2.88 mmol). The reaction was stirred for 18 h and poured into water (25

mL) and ether (30 mL). The aqueous layer was washed a second time with ether (20 mL). The combined organic layers were washed with 10% aqueous sodium hydroxide (25 mL) and saturated aqueous sodium chloride (25 mL). The dried (magnesium sulfate) solution was concentrated in vacuo and the crude material recrystallized from absolute ethanol to yield 0.269 g (47%) of the desired product: mp 134–136 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.64 (t, J = 7 Hz, 3 H), 1.60 (m, 6 H), 2.60 (m, 4 H), 2.36 (s, 3 H), 7.44 (m, 10 H); IR (KBr) 1631, 1600, 1498, 1479, 1449, 1331, 1302, 1228, 1150 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_2S_2$: C, 65.47; H, 7.24. Found: C, 65.39; H, 7.28.

Preparation of *N*-(2-Propenylidenecyclohexyl)-*p*-toluenesulfonamide (53). Sodium (15 mg, 0.6 mmol) dissolved in absolute ethanol (1 mL) was added to sulfilimine **52** in absolute ethanol (1 mL) at room temperature. The solution was brought from room temperature to 55 °C and stirred for 2 h. TLC (40% ethyl acetate/hexane) at this time showed no remaining starting material. The reaction mixture was cooled and poured into saturated aqueous sodium bicarbonate (5 mL) and extracted with chloroform (3 × 5 mL). The combined chloroform extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated in vacuo. The crude oil was purified by preparative TLC (40% ethyl acetate/hexane, R_f 0.33) to yield 0.030 g (48%) of the desired product: mp 96.5–97.5 °C; ^{1}H NMR (100 MHz, CCl_4) δ 0.80 (t, J = 6 Hz, 3 H), 1.2–2.1 (m, 10 H), 2.40 (s, 3 H), 3.61 (m, 1 H), 5.01 (t, J = 5 Hz, 1 H), 5.65 (d, J = 7 Hz, 1 H), 7.18 (AA′BB′, J = 8 Hz, 2 H), 7.65 (AA′BB′, J = 8 Hz, 2 H); IR (thin film) 3422, 3229, 1600, 1495, 1452, 1328, 1170 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 66.4; H, 8.0; M_r 293.1450. Found: C, 66.17; H, 8.06; M_r 293.1450.

Preparation of 1-Bromo-2-(phenylsulfinyl)-3-methyl-2-butene (54). To a solution of 1-bromo-2-(phenylthio)-3-methyl-2-butene (2.76 g, 10.7 mmol) in dichloromethane (20 mL) at −78 °C was added MCPBA (2.26 g, 10.7 mmol, 82% MCPBA). The reaction was stirred for 1 h, warmed to ambient temperature for 1.5 h, and then poured into saturated aqueous sodium carbonate (15 mL). The organic layer was separated and the aqueous layer washed with dichloromethane (20 mL). The combined organic layers were washed with saturated aqueous sodium carbonate (15 mL). The dried (magnesium sulfate) organic solution was concentrated in vacuo and the crude solid recrystallized from hexane/benzene (10/1) to yield 1.3 g (44.5%) of prisms: mp 77–78 °C. Concentration of the mother liquors gave 0.63 g (22%) of a yellow oil (one spot by TLC) for a total yield of 66.5%: ^{1}H NMR (CCl_4) δ 2.04 (s, 3 H), 2.53 (s, 3 H), 3.88 (AB, J = 11 Hz, 1 H), 4.23 (AB, J = 1 Hz, 1 H), 7.34 (m, 5 H); IR (CCl_4) 1635, 1583, 1479, 1448, 1382, 1372, 1254, 1211, 1168 cm^{-1}. Anal. Calcd for $C_{11}H_{13}BrOS$: 271.9870. Found: 271.9872.

Preparation of 2-carbethoxy-2-(2-(phenylsulfinyl)-3-methyl-2-butenyl)cyclopentanone (55). To a suspension of washed (hexane) and dried sodium hydride (0.029 g, 1.21 mmol) in DMF (0.5 mL) was added dropwise ethyl 2-oxocyclopentanecarboxylate (0.206 g, 1.32 mmol). The solution was stirred for 10 min at ambient temperature. The anion solution was added via cannula to a solution of the sulfoxide **54** (0.240 g, 0.88 mmol) in DMF (0.5 mL) and stirred at ambient temperature for 18 h. The reaction was diluted with ether (20 mL) and washed with saturated aqueous ammonium chloride (15 mL), followed by two washings with saturated aqueous sodium chloride (15 mL). The dried (magnesium sulfate) solution was concentrated in vacuo and the crude oil purified via preparative TLC (2% ethyl acetate/chloroform, R_f 0.21) to yield 0.224 g (80%) of the desired product: ^{1}H NMR ($CDCl_3$) δ 1.21 (br t, J = 8 Hz, 3 H), 1.86–2.45 (m, 12 H), 2.79 (AB, J = 12.5 Hz, 1 H), 3.04 (AB, J = 12.5 Hz, 1 H), 7.48 (m, 5 H); IR (thin film) 1751, 1727, 1445 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_4S$: 348.1395. Found: 348.1393.

Preparation of 2-Carbethoxy-2-(4-hydroxy-3-methyl-2(*E*)-butenyl)-cyclopentanone (56). A solution of sodium ethoxide, prepared from sodium (0.050 g, 2.13 mmol) and ethanol (1.5 mL) with stirring at ambient temperature over 30 min, was added to sulfoxide **55** (0.081 g, 0.233 mmol) in ethanol (1 mL). The reaction mixture was heated to 65 °C for 3 h, at which time TLC (10% ethyl acetate/chloroform, starting material, product R_f 0.35, R_f 0.18) showed no remaining starting material. The reaction mixture was diluted with saturated aqueous ammonium chloride (2 mL) and concentrated in vacuo to approximately half volume. This material was diluted with saturated ammonium chloride (10 mL) and extracted with chloroform (3 × 15 mL). The dried (sodium chloride) organic solution was concentrated in vacuo and the crude oil purified via preparative TLC (15% ethyl acetate/chloroform, R_f 0.18) to yield 0.025 g (44.7%) of the desired product as an oil: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 8 Hz, 3 H), 1.61 (m, 8 H), 2.22 (m, 4 H), 3.88 (m, 2 H), 4.04 (q, J = 8 Hz, 2 H), 5.24 (m, 1 H); IR (thin film) 1728, 1452, 1447 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: 240.1361. Found: 240.1361.

Preparation of 2,3-Dimethyl-1-cyclododecene (57). To a solution of **47** (0.087 g, 0.302 mmol) and 1,2-bis(diphenylphosphinopropane)nickel(II) chloride (0.013 g, 0.003 mmol) in THF (1 mL) was added methylmagnesium iodide (0.55 mL, 2.281 M, 1.21 mmol). The reaction was heated at 65 °C for 18 h. The reaction was diluted with ether (10 mL) and poured into saturated aqueous sodium bisulfate (10 mL). The aqueous layer was extracted once more with ether (10 mL) and the combined organic layers were washed with 10% aqueous sodium hydroxide (15 mL) and saturated aqueous sodium chloride (15 mL). The dried (magnesium sulfate) ether solution was concentrated in vacuo and the crude oil purified by preparative TLC (1% ethyl acetate/10% toluene/hexane, R_f 0.68) to yield 0.035 g (60%) of the desired product as a 2.5:1 ratio of *E*:*Z* isomers: ^{1}H NMR (270 MHz) δ 1.91 (d, J = 8 Hz, 0.87 H), 1.94 (d, J = 8 Hz, 2.13 H), 1.24 (m, 16 H), 1.49 (s, 3 H), 1.91 (m, 1 H), 2.22 (m, 1.7 H), 2.84 (m, 0.3 H), 5.02 (m, 0.3 H), 5.91 (m, 0.7 H); IR (thin film) 1416, 1381 cm^{-1}. Anal. Calcd for $C_{14}H_{26}$: 194.2035. Found: 194.2035.

Preparation of 4-Acetyl-1-methylcyclohexene (62). To a solution of isoprene (0.681 g, 10.0 mmol, 1 mL) and methyl vinyl ketone (0.771 g, 11.0 mmol, 0.892 mL) in dichloromethane (3 mL) at −40 °C was added dropwise boron trifluoride etherate (0.142 g, 1.0 mmol) over a 10-min period. The reaction was stirred for 1 h, poured into water (10 mL), and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride (10 mL) and dried over magnesium sulfate. This organic solution was concentrated in vacuo and then purified by Kugelrohr distillation (45–48 °C (0.5 mmHg)) to yield 1.16 g (84%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.36–2.70 (m, 13 H), 5.53 (m, 1 H); ^{13}C NMR (270 MHz, $CDCl_3$) 22.7, 24.4, 26.5, 27.2, 28.9, 46.5, 118.8, 133.0, 210.3; IR (thin film) 1712, 1440, 1379, 1335 cm^{-1}.

Preparation of 4-(4-(Phenylthio)-5-methyl-1-oxo-4-hexenyl)-1-methylcyclohexene (63). A stirred solution of **6** (0.491 g, 2.76 mmol) in acetonitrile (3 mL) was brominated with NBS (0.491 g, 2.76 mmol) and isomerized with lithium bromide (~15 mg) in the usual fashion. The bromide was dissolved in DMF (2 mL) to which potassium iodide (0.458 g, 2.76 mmol) was subsequently added and stirred for 20 min.

In a separate flask, a solution of LDA was prepared by dropwise addition of *n*-butyllithium (2.38 mL, 3.81 mmol) to a cooled (0 °C) solution of diisopropylamine (0.435 g, 4.30 mmol, 0.602 mL) in THF (3 mL). The LDA solution was stirred for 10 min and then ketone **62** (0.457 g, 3.31 mmol) was added dropwise and stirred for 15 min. This enolate solution was introduced by cannula into the DMF solution of the bromide and stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, poured into a saturated aqueous solution of sodium bisulfate (20 mL), and extracted with chloroform (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (20 mL) and saturated aqueous sodium chloride (20 mL). The dried (magnesium sulfate) organic solution was concentrated in vacuo and the crude oil purified via preparative TLC with double elution utilizing 5% ethyl acetate/10% toluene/hexane (R_f 0.47) to yield 0.475 g (55%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.81 (br s, 3 H), 1.76–2.53 (m, 17 H with two singlets at 1.94 and 1.99), 5.35 (m, 1 H), 7.16 (m, 5 H); IR (thin film) 1716, 1530, 1407, 1448 cm^{-1}. Anal. Calcd for $C_{20}H_{26}OS$: 314.1740. Found: 314.1740.

Preparation of 1-Methyl-4-(6-methyl-5-(phenylthio)-1,5-heptadien-2-yl)cyclohexene (64). A suspension of triphenylmethylphosphonium iodide (0.777 g, 1.92 mmol) in THF (2 mL) at 0 °C was stirred with potassium *tert*-butoxide (0.129 g, 1.15 mmol) for 10 min. To this yellow ylide solution was added ketone **63** (0.302 g, 0.924 mmol) dissolved in THF (2 mL). The reaction mixture was heated to reflux for 36 h, diluted with ether (10 mL), filtered, and concentrated under reduced pressure. The crude oil was purified by preparative TLC (5% ethyl acetate/10% toluene/hexane, R_f 0.83) to yield 0.200 g (67%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.30–2.40 (m, 20 H with three singlets at δ 1.59, 1.88, 1.98), 4.61 (m, 2 H), 5.28 (m, 1 H), 7.06 (m, 5 H); IR (thin film) 1648, 1591, 1485, 1448 cm^{-1}. Anal. Calcd for $C_{21}H_{28}S$: 312.1911. Found: 312.1915.

Preparation of 1-Methyl-4-(6-methyl-5-(phenylsulfinyl)-1,5-heptadien-2-yl)cyclohexene. To a stirred solution of sulfide **63** (0.157 g, 0.503 mmol) in dichloromethane (2 mL), at −78 °C was added MCPBA (0.102 g, 0.503 mmol, 85%). The reaction was stirred for 20 min, at which time TLC (5% ethyl acetate/10% toluene/hexane) showed remaining starting material. Small portions of MCPBA (~25 mg, total) were added until the reaction was complete. The reaction mixture was diluted with ether (15 mL) and washed with saturated aqueous sodium bisulfite (10 mL), 10% aqueous sodium hydroxide (10 mL), and saturated aqueous sodium chloride (10 mL). The dried (magnesium sulfate) organic solution was concentrated in vacuo and the crude oil purified via preparative TLC (5% ethyl acetate/10% toluene/hexane, R_f 0.50) to yield 0.160 g (97%) of the desired product: ^{1}H NMR (100 MHz, CCl_4) δ 1.22–2.41 (m, 11 H), 1.61 (br s, 3 H), 1.88 (br s, 3 H), 2.23 (br s, 3 H), 4.56 (m, 2 H), 5.28 (m, 1 H), 7.36 (m, 5 H); IR (thin film) 1646, 1449, 1383 cm^{-1}. Anal.

Calcd for $C_{21}H_{28}OS$: 328.1861. Found: 328.1860.

Preparation of (±)-Lanceol. A stirred solution of the above sulfoxide (0.154 g, 0.47 mmol) dissolved in ethanol (4.0 mL) which had previously been treated with sodium (50 mg, 2.2 mmol) was refluxed for 15 h. The reaction mixture was then poured into saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (3 × 10 mL). The dried organic solution (magnesium sulfate) was concentrated in vacuo and the crude oil subjected to preparative TLC (5% ethyl acetate/5% toluene/chloroform, R_f 0.28) to yield 0.058 g (60%) of the desired product: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.47 (m, 2 H), 1.65 (s, 3 H), 1.68 (s, 3 H), 1.80–2.30 (m, 9 H), 4.00 (s, 2 H), 4.75 (s, 1 H), 4.77 (s, 1 H), 5.42 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (d), 23.4 (q), 26.4 (t), 28.4 (t), 30.8 (t), 31.5 (t), 24.5 (t), 39.8 (q), 68.9 (t), 107.4 (t), 120.7 (d), 126.0 (d), 133.7 (s), 134.9 (s), 153.9 (s); IR (CCl_4) 3300, 3230, 1640, 1451, 1439, 1379 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O$: 220.1828. Found: 220.1833.

Preparation of (±)-Bisabolene. To a solution of sulfide **64** (0.100 g, 0.321 mmol) in THF (0.7 mL) was added bis(triphenylphosphino)nickel(II) chloride (0.011 g, 0.0016 mmol) and isopropylmagnesium bromide (0.69 mL, 1.28 mmol), 1.86 M in ether). The very dark solution was refluxed for 36 h. The reaction mixture was cooled then poured into saturated aqueous sodium hydrogen sulfate (10 mL) and saturated aqueous sodium chloride (10 mL). The dried (magnesium sulfate) organic solution was concentrated in vacuo and the crude oil subjected to preparative thin layer chromatography (20% ether/pentane, R_f 0.54) to yield 0.011 g of starting material (11%) and 0.023 g (35%) of the desired product: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (m, 1 H), 1.48 (m, 1 H), 1.61 (s, 3 H), 1.65 (s, 3 H), 1.68 (s, 3 H), 1.86 (m, 1 H), 2.08 (m, 7 H), 4.76 (m, 1 H), 5.13 (m, 1 H), 5.40 (m, 1 H); ^{13}C NMR (27 MHz, $CDCl_3$) δ 17.7, 23.4, 25.6, 29.96, 28.5, 30.8, 31.5, 34.97, 39.9, 107.2, 120.9, 124.4, 131.4, 133.7, 154.3; IR (thin film) 1648, 1449, 1388 cm^{-1}. Anal. Calcd for $C_{15}H_{24}$: 204.1878. Found: 204.1878.

Preparation of 23,24-Dinor-22-(phenylsulfonyl)spiro[4-cholene-3,2′-(1′,3′-dithiacyclohexane)] (68). Bisnorcholenaldehyde **66** (1.345 g, 4.10 mmol) was suspended in ethanol (15 mL), cooled to 0 °C, and treated with sodium borohydride (0.148 g, 4.10 mmol) for 15 min. The reaction was diluted with water (20 mL) and extracted with chloroform (3 × 20 mL). The dried (magnesium sulfate) solution was concentrated under reduced pressure to give 1.35 g (100%) of the C(22) alcohol as a foam which was pure by TLC (50% ethyl acetate/hexane, R_f 0.28); ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.76 (s, 3 H), 1.04 (d, J = 7 Hz, 3 H), 1.21 (s, 3 H), 1.10–2.45 (m, 21 H), 3.51 (m, 2 H), 5.70 (br s, 1 H); IR ($CHCl_3$) 3445, 1708, 1611 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_2$: 330.2559. Found: 330.2559.

The C(22) alcohol (1.35 g, 4.09 mmol) and 1,3-propanedithiol (0.903 g, 8.36 mmol) were combined in dichloromethane (10 mL) and treated with boron trifluoride etherate complex (0.059 g, 0.418 mmol). The reaction was stirred for 12 h, diluted with dichloromethane (25 mL), and extracted with 10% aqueous sodium hydroxide (10 mL). The aqueous layer was backwashed with dichloromethane (20 mL), and the combined organic layers were washed with 10% aqueous sodium hydroxide (25 mL). The dried (potassium carbonate) organic solution was concentrated under reduced pressure to yield 1.05 g (61%) of the C(3)-dithiane C-(22)-alcohol **67**, which was pure by TLC (50% ethyl acetate/hexane, R_f 0.49): ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.66 (s, 3 H), 1.00 (s, 3 H), 1.01 (d, J = 7 Hz, 3 H), 0.90–3.00 (m, 27 H), 3.48 (m, 2 H), 5.35 (br s, 1 H); IR (CCl_4) 3620, 1442, 1382, 1273 cm^{-1}. Anal. Calcd for $C_{25}H_{40}OS_2$: 420.2520. Found: 420.2421.

The alcohol **67** (1.05 g, 2.5 mmol) was dissolved in pyridine (10 mL) and treated with methanesulfonyl chloride (0.959 g, 8.4 mmol) at 0 °C with slow warming to ambient temperature over 3 h. The reaction was diluted with chloroform (30 mL) and washed with saturated aqueous sodium bisulfate (25 mL). The aqueous layer was backwashed once with chloroform (15 mL). The combined organic layers were washed a second time with saturated aqueous sodium bisulfate (20 mL) followed by saturated aqueous sodium bicarbonate (30 mL) and saturated aqueous sodium chloride (30 mL). The dried (magnesium sulfate) organic solution was concentrated under reduced pressure and the crude material purified via preparative TLC (dichloromethane, R_f 0.52) to yield 1.013 g (87%) of the corresponding mesylate: ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.68 (s, 3 H), 1.00 (s, 3 H), 1.05 (d, J = 6 Hz, 3 H), 1.10–3.00 (m, 28 H), 3.94 (m, 2 H), 5.29 (br s, 1 H). Anal. Calcd for $C_{26}H_{42}O_3S_3$: 498.2296. Found: 498.2296.

The above mesylate (0.979 g, 2.10 mmol) was dissolved in DMF (5 mL), heated to 75 °C, and treated with potassium iodide (0.523 g, 3.15 mmol) for 6 h, at which time TLC (CH_2Cl_2) showed no remaining starting material (R_f 0.37) but did show a new spot presumably corresponding to the iodide (R_f 0.64). The reaction mixture was then treated with sodium benzenesulfinate (0.517 g, 3.15 mmol) at 74 °C for 12 h. The reaction was diluted with water (10 mL) and extracted with ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride (2 × 15 mL), dried (magnesium sulfate), and concentrated under reduced pressure. The crude material was purified via preparative TLC (dichloromethane, R_f 0.4) to yield 0.910 g (62%) of the desired product as a foam: ^{1}H NMR (100 MHz, CCl_4) δ 0.72 (s, 3 H), 1.06 (s, 3 H), 1.18 (d, J = 6 Hz, 3 H), 1.20–3.04 (m, 29 H), 5.20 (br s, 1 H), 7.45 (m, 3 H), 7.75 (m, 2 H); IR ($CHCl_3$) 1448, 1321, 1310 cm^{-1}. Anal. Calcd for $C_{31}H_{44}O_2S_3$: 544.2503. Found: 544.2502.

Preparation of 24-(Phenylsulfinyl)-22-(phenylsulfonyl)spiro[4,24-cholestadiene-3,2′-(1′,3′-dithiacyclohexane)] (69). The sulfone **68** (0.161 g, 0.296 mmol) was dissolved in THF (9.5 mL) at −78 °C along with TMEDA (0.069 g, 0.592 mmol) and treated with *n*-butyllithium (0.394 mL, 1.5 M, 0.592 mmol) for 1 h. To this yellow-orange solution was added sulfoxide **54** (0.170 g, 0.622 mmol) dissolved in THF (0.3 mL) along with hexamethylphosphoramide (0.053 g, 0.296 mmol). The reaction mixture was stirred at −78 °C for 15 min and then warmed to −45 °C (acetonitrile/dry ice) for 1 h, over which time the bright orange color faded. The reaction was allowed to warm to 10 °C over a period of 30 additional min, quenched with saturated aqueous ammonium chloride (10 mL), and extracted with chloroform (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium bisulfate (20 mL) and saturated aqueous sodium bicarbonate (20 mL) and dried (magnesium sulfate). The organic solution was concentrated under reduced pressure and the crude material purified via preparative TLC (2% acetone/dichloromethane, R_f 0.45) to yield 0.039 g of the desired product as a foam along with 0.041 g of the starting material (R_f 0.60). The yield based on recovered starting material was 24%; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.62 (s, 3 H), 1.01 (s, 3 H), 1.36 (d, J = 7 Hz, 3 H), 1.89 (s, 3 H), 2.29 (s, 3 H), 0.8–2.44 (m, 20 H), 2.82 (m, 6 H), 4.24 (m, 1 H), 5.28 (s, 1 H), 6.19 (d, J = 5.5 Hz, 2 H), 7.24 (m, 3 H), 7.64 (m, 3 H), 7.78 (d, J = 5.5 Hz, 2 H), 7.324 (m, 3 H), 7.64 (m, 3 H), 7.78 (d, J = 5.5 Hz, 2 H); IR ($CHCl_3$) 1442, 1300, 1142, 1082 cm^{-1}.

Preparation of 26-Hydroxy-22-(phenylsulfonyl)spiro[4,24-cholestadiene-3,2′-(1-,3′-dithiacyclohexane)]. The sulfoxide **69** (0.030 g, 0.041 mmol) was dissolved in a 1 M solution of sodium ethoxide in ethanol (0.40 mL) and heated to 70 °C for 2 h, at which time TLC showed no remaining starting material. The reaction was diluted with saturated aqueous ammonium chloride (5 mL) and extracted with chloroform (3 × 8 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried (magnesium sulfate), and concentrated under reduced pressure. The crude material was purified via preparative TLC (2% acetone/dichloromethane, R_f 0.18) to yield 0.018 g (70%) of the desired product as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.59 (s, 3 H), 1.01 (s, 3 H), 0.8–2.6 (m, 24 H), 1.32 (d, J = 8.5 Hz, 3 H), 1.48 (s, 3 H), 2.84 (m, 5 H), 3.88 (s, 2 H), 5.04 (m, 1 H), 5.32 (s, 1 H), 7.50 (m, 3 H), 7.79 (d, J = 9.5 Hz, 2 H); IR ($CHCl_3$) 3600, 3480, 1448, 1379, 1303, 1235, 1147, 1079 cm^{-1}. Anal. Calcd for $C_{36}H_{52}S_3O_3$: 628.3079. Found: 628.3076.

Preparation of 26-Hydroxyspiro[4,24-cholestadiene-3,2′-(1′,3′-dithiacyclohexane)] (70). The above hydroxy sulfone (0.006 g, 0.0096 mmol) was suspended in methanol (0.20 mL) along with disodium hydrogen phosphate (0.005 g, 0.038 mmol) and treated with 6% sodium amalgam (0.05 g). The reaction was stirred at ambient temperature for 1 h, diluted with water (5 mL), and extracted with chloroform (3 × 8 mL). The dried (magnesium sulfate) organic solution was concentrated under reduced pressure and the crude material purified via preparative TLC (2% acetone/dichloromethane, R_f 0.44) to yield 0.0042 g (90%) of the desired product as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.63 (s, 3 H), 0.89 (d, J = 7.5 Hz, 3 H), 1.20 (s, 3 H), 1.51 (s, 3 H), 0.74–2.48 (m, 27 H), 2.93 (m, 4 H), 3.96 (m, 2 H), 5.34 (m, 2 H); IR ($CHC6_3$) 3590, 1514, 1465, 1438, 1329, 1225 cm^{-1}. Anal. Calcd for $C_{30}H_{48}OS_2$: 488.3146. Found: 488.3146.

Preparation of 1-Cyano-3-methyl-2-(phenylthio)-2-butene. A solution of **6** (0.420 g, 2.36 mmol) in acetonitrile (3 mL) was brominated with NBS (0.420 g, 2.36 mmol) and isomerized with lithium bromide (approximately 10 mg) in the usual fashion. After the crude bromide was dissolved in dichloromethane (5 mL), tetraethylammonium cyanide (0.696 g, 2.59 mmol) was added and the reaction stirred for 2 h. It was diluted with additional dichloromethane (20 mL) and poured into water (20 mL). The organic solution was extracted 2 times with water (15 mL), dried (magnesium sulfate), and concentrated in vacuo. The crude dark oil was purified by preparative TLC (25% ethyl acetate/hexane, R_f 0.28) to yield 0.333 g (70%) of the desired product: ^{1}H NMR (CCl_4) δ 1.97 (s, 3 H), 2.08 (s, 3 H), 3.16 (s, 2 H), 7.24 (m, 5 H); IR (thin film) 2252, 1589, 1482, 1446 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NS$: 203.0768. Found: 203.0769.

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**46**, 85895-11-0; (*E*)-**47**, 85895-12-1; (*Z*)-**47**, 85895-13-2; **48**, 85895-14-3; **49**, 85895-15-4; **50**, 85895-16-5; **51**, 85895-17-6; **52**, 85895-18-7; **53**, 85895-19-8; **54**, 85895-20-1; **55**, 85895-21-2; **56**, 85895-22-3; (*E*)-**57**, 84098-64-6; (±)-**59**, 18681-09-9; **62**, 6090-09-1; **63**, 85895-23-4; **64**, 85895-24-5; (±)-**65**, 4891-79-6; **66**, 3986-89-8; **67**, 85895-25-6; **68**, 85895-28-9; **69**, 85895-29-0; **70**, 85895-30-3; **73**, 85895-32-5; 3-methyl-2-butanone, 563-80-4; thiophenol, 108-98-5; 1,1-bis(phenylthio)cyclohexane, 37457-08-2; cyclohexanone, 108-94-1; 4-*tert*-butyl-1,1-bis(*p*-methoxyphenylthio)cyclohexane, 85895-33-6; 4-*tert*-butylcyclohexanone, 98-53-3; *p*-methoxythiophenol, 696-63-9; **66** C-(22)-alcohol derivative, 40736-33-2; **67** mesylate, 85895-26-7; **67** iodide derivative, 85895-27-8; **70** C(22)-phenylsulfonyl derivative, 85895-31-4; cyclopentanone, 120-92-3; 1,1-bis(phenylthio)cyclopentane, 85895-34-7; cyclooctanone, 502-49-8; 1,1-bis(phenylthio)cyclooctane, 85895-35-8; cyclododecanone, 830-13-7; 1,1-bis(phenylthio)cyclododecane, 85895-36-9; 6-methoxy-2-tetralone, 2472-22-2; diphenyl(1-(phenylthio)ethyl)-phosphine oxide, 66164-48-5; 3-pentanone, 96-22-0; 2-methylcyclohexanone tosylhydrazone, 52826-41-2; diphenyl disulfide, 882-33-7; methyl acrylate, 96-33-3; methyl vinyl ketone, 78-94-4; phenyl vinyl sulfide, 1822-73-7; benzyl bromide, 100-39-0; bis(phenylsulfonyl)methane anion, 25809-66-9; diethyl sodiomalonate, 996-82-7; dimethyl malonate anion, 33673-07-3; methyl acetoacetate anion, 53519-67-8; dimethyl sodiomalonate, 18424-76-5; 1-(phenylthio)-2-bromo-4-isopropenylcyclohexane, 85895-37-0; lithium dimethylcuprate, 15681-48-8; 3,3-dimethyl-2-(phenylthio)-1-butene, 1886-64-2; lithium diphenylcuprate, 23402-69-9; lithium bis(phenylethynyl)cuprate, 62374-50-9; dimethyl (2-oxocyclohexyl)malonate, 63965-89-9; chloramine-T, 127-65-1; ethyl 2-oxocyclopentylcarboxylate sodio derivative, 13697-91-1; methylmagnesium iodide, 917-64-6; 1-methyl-4-(6-methyl-5-(phenylsulfinyl)-1,5-heptadien-2-yl)cyclohexene, 85895-38-1; isopropylmagnesium bromide, 920-39-8; 1,3-propanedithiol, 109-80-8; sodium benzenesulfinate, 873-55-2; 1-cyano-3-methyl-2-(phenylthio)-2-butene, 85895-39-2; tetramethylammonium cyanide, 13435-20-6; (1*S**)(6*S**)-1-methyl[4.4.0]bicyclodecan-4-one, 938-07-8; (1*S**)(6*S**)-4,4-bis(phenylthio)-1-methyl-[4.4.0]bicyclodecane, 85908-84-5; 1-(phenylthio)cyclooctene, 52113-72-1; 2-methoxy-6-(phenylthio)naphthalene, 85895-40-5; 3-(phenylthio)-7-methoxy-1,2-dihydronaphthalene, 64740-99-4; 2-methylcyclohexanone, 583-60-8; 1,1-bis(phenylthio)-2-methylcyclohexane, 85895-41-6; 5-bromo-1-(phenylthio)cyclopent-1-ene, 85895-42-7; 1-bromo-2-(phenylthio)cyclopent-1-ene, 85895-43-8; 3-bromo-1-methyl-2-(phenylthio)-cyclohex-1-ene, 85895-44-9; 6-bromo-4-*tert*-butyl-1-(phenylthio)cyclohex-1-ene, 85895-45-0; 2-bromo-1-(phenylthio)-4-*tert*-butylcyclohex-1-ene, 85895-46-1; 6-bromo-4-*tert*-butyl-1-(4-methoxyphenylthio)cyclohex-1-ene, 85895-47-2; 2-bromo-4-*tert*-butyl-1-(4-methoxyphenylthio)-cyclohex-1-ene, 85895-48-3; [1-(phenylthio)-2-bromoethylidene]cyclohexane, 85895-49-4; 1-(phenylthio)-6-bromo-5-methylcyclohexene, 85895-50-7; 1-(phenylthio)-2-bromo-3-methylcyclohexene, 85895-51-8; methyl 5-bromo-4-(phenylthio)cyclohex-3-enecarboxylate, 85895-52-9; methyl 3-bromo-4-(phenylthio)cyclohex-3-enecarboxylate, 85895-53-0; 1-(phenylthio)-4-acetyl-6-bromocyclohex-1-ene, 85895-54-1; 1-(phenylthio)-4-acetyl-2-bromocyclohex-1-ene, 85895-55-2; 1-(phenylthio)-6-bromo-4-isopropenylcyclohexene, 85895-56-3; 1-(phenylthio)-2-bromo-4-isopropenylcyclohexene, 85895-57-4; (*E*)-1-phenyl-2-(phenylthio)-3-bromoprop-1-ene, 85895-58-5; (*Z*)-1-phenyl-2-(phenylthio)-3-bromoprop-1-ene, 85895-59-6; 1-(phenylthio)-12-bromocyclododec-1-ene, 85895-60-9; 1-(phenylthio)-2-bromocyclododec-1-ene, 85895-61-0; 1-bromo-2-(phenylthio)-3-etyhylpent-2-ene, 85895-62-1; 4-*tert*-butyl-1,1-bis(phenylthio)cyclohexane, 85895-63-2; isoprene, 78-79-5; (*Z*)-**57**, 84098-63-5.

Supplementary Material Available: Chart of brominating agents, table of bromination conditions, general experimental introduction, and preparations of 1,1-bis(phenylthio)-2-methylcyclohexane, (1*S**,6*S**)-4,4-bis(phenylthio)-1-methyl[4.4.0]bicyclodecane, 4-*tert*-butyl-1,1-bis(phenylthio)cyclohexane, **8**, **9**, **10a**, **10b**, **12**, **50**, **51**, and 2-methoxy-6-benzenethionaphthalene (9 pages). Ordering information is given on any current masthead page.

Stereoelectronic Control of Intramolecular Michael Addition Reactions

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Abstract: Concepts of stereoelectronic control lead to the conclusion that the 5-endo-trig ring closure of (*E*)-2-methyl-3-oxo-5-phenylpent-4-en-2-ol should be disfavored. However, the acid-catalyzed ring closure in trifluoroacetic acid occurs readily, suggesting an alternative mechanism of 5-exo-trig form, proceeding through the protonated species. This explanation involves reversed electronic effects between inter- and intramolecular Michael additions, whereby the ring-closure and ring-opening processes for the above compound can be accelerated by electron-donating substituents in the 5-phenyl ring and decelerated by electron-withdrawing substituents. Detailed kinetic examination of these circumstances, in which the key point established is that the accelerative effect of electron-donating substituents is far greater than could be explained by their influence in increasing the amount of reactive carbonyl-protonated enone, gives insight into the nature of stereoelectronic control in such reactions. Concomitant reaction, trifluoroacetylation of the hydroxyl group of the open-chain compounds, is investigated.

The significance of orbital overlap in controlling the course of organic reactions has long been recognized. Particular landmarks appropriate to cite here are the recognition of antiperiplanar E2 eliminations by Hughes and Ingold,[1] Deslongchamps' theory of stereoelectronic control,[2] and Baldwin's rules for ring closure.[3] Baldwin has shown[4,5] that ring closure of (*E*)-2-methyl-3-oxo-5-phenylpent-4-en-2-ol (**1a**) cannot be effected under basic conditions. However, acidic conditions (refluxing in 1,2-dichloroethane with *p*-toluenesulfonic acid) readily gave 2,2-dimethyl-5-

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