Radical Translocation Reactions of Vinyl Radicals: Substituent Effects on 1,5-Hydrogen-Transfer Reactions

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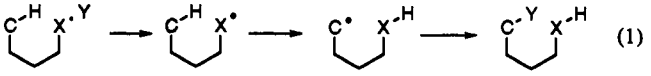
Abstract: A systematic study of the radical translocation (1,5-hydrogen-transfer) reactions of vinyl radicals is described. The effects of monoalkoxy, dialkoxy, monoalkylthio, dialkylthio, thiohemiketal, phenyl, allyl, carboxylate ester, nitrile, and tertiary, secondary, and primary alkyl substituents on the transferring C–H bond were studied. The protocol was first to generate vinyl radicals which were next translocated to new carbon centers by 1,5-hydrogen atom transfer processes. Rapid radical cyclization followed translocation. Stork's catalytic tin hydride method, a standard stoichiometric tin hydride method, and a syringe pump method were used to run the radical reactions, and all gave comparable results under standard conditions. Most substituents gave similar rates of 1,5-hydrogen atom transfer (generally 50–100% of the vinyl radicals were translocated to new carbon centers) except for some strong C–H bonds which gave no hydrogen atom transfer (for example, epoxide and methyl). Generally, sulfur substituents activated the C–H bonds best; however, in some cases, S_H2 reactions of vinyl radicals attacking the sulfur atoms or tin hydride desulfurizations interfered with the desired 1,5-hydrogen atom transfer processes. Rate constants for 1,5-hydrogen transfer are typically in the range of 10^6 s^{-1}. Substituent effects on intra- and intermolecular hydrogen-transfer reactions are compared, and implications of the results are discussed.

Introduction

Hydrogen abstractions from C–H bonds are among the most common reactions of heteroatom-centered radicals.[2] These reactions are driven by the bond strength of the forming X–H bond, and intramolecular hydrogen transfers are especially selective and valuable. Thanks to a number of thorough experimental[3] and theoretical studies,[4] substituent effects on the rates and selectivity of hydrogen abstractions of heteroatom-centered radicals are quite well understood. From a preparative standpoint, intramolecular 1,5-hydrogen-transfer reactions are usually used for "remote functionalization"—the replacement of a carbon–hydrogen bond with a carbon–heteroatom bond (eq 1).



(1)

X = O, $\overset{+}{N}R_2$, NCOR, etc.

1,5-Hydrogen-transfer reactions of oxygen- and nitrogen-centered radicals form the basis of name reactions like the Barton reaction, the Hofmann–Löffler–Freytag reaction, and related transformations.[5] Longer distance hydrogen-transfer reactions are also known, and remote functionalizations have culminated in Breslow's elegant studies on 1,*n*-hydrogen transfer of complexed halogen radicals in steroid systems.[6]

The recent renaissance in synthetic applications of radical reactions is founded largely on carbon–carbon bond-forming reactions.[7,8] Methods for conducting such reactions must meet three requirements. Carbon radicals must (1) be generated rapidly and selectively, (2) have a sufficient lifetime to react, and (3) be trapped prior to radical–radical or radical–solvent reactions. Procedures that generate carbon-centered radicals by 1,5-hydrogen-transfer reactions of heteroatom-centered radicals have played a small role in the radical renaissance. This is probably because carbon-centered radicals generated in these procedures often have very short lifetimes. Only the fastest carbon–carbon bond-forming radical reactions can compete with reactions of the intermediate carbon-centered radicals with the efficient radical traps that are present. In short, requirements 1 and 3 are met, but requirement 2 is not.

Several years ago, we introduced an extension of the remote functionalization concept that we termed "radical translocation".[9] In this concept, radicals are generated at favorable sites and then "translocated" to new sites prior to a carbon–carbon bond-forming reaction. 1,5-Hydrogen-transfer reactions are prime candidates for radical translocation because they permit the indirect use of a carbon–hydrogen bond as a radical precursor (Figure 1). Though C–H bonds are the simplest conceivable radical precursors, the direct use of C–H bonds as radical precursors in typical methods like the tin hydride method is never possible because tin radicals will not abstract hydrogen atoms from C–H bonds.

With the goal of developing radical translocation reactions that could be conducted under standard radical conditions (like the tin hydride method), we have focused on 1,5-hydrogen-transfer reactions from C–H bonds to reactive *carbon-centered* radicals.[10,11] Hydrogen transfers to carbon radicals had been observed

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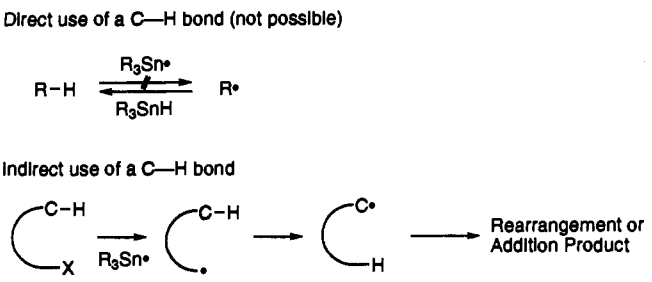


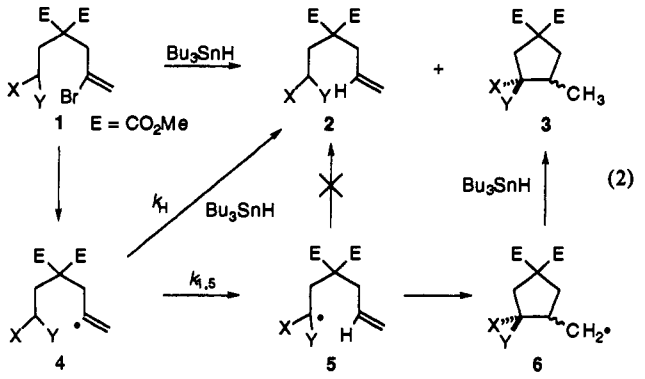
Figure 1. C–H Bonds as radical precursors in the tin hydride method.

on many occasions,[12] though most of these observations were accidental.[13] Indeed, such 1,5-hydrogen-transfer reactions have developed a reputation as a nuisance, often competing with other desired transformations (especially 6-exo cyclizations). We have recently harnessed the features that make 1,5-hydrogen-transfer reactions a nuisance and introduced a variety of new synthetic methods.[14] In many of these, a radical is initially generated in a "protecting group" and then translocated by 1,5-hydrogen-transfer prior to cyclization (single or tandem), addition (sometimes with asymmetric induction), isotopic labeling, or oxidative self-removal of the protecting group. Important contributions in translocation reactions of carbon-centered radicals have also come from the groups of Parsons,[15] De Mesmaeker,[16] Snieckus,[14] and others.[17] Several groups have recently introduced methods where radical translocation reactions of oxygen-[18-23] and nitrogen-centered[24] radicals can be conducted under modern conditions.

Recent rapid synthetic advances in radical addition and cyclization reactions have been fueled by prior mechanistic studies of substituent effects on rates of reactions.[7] A significant limitation in the use of preparative intramolecular hydrogen-transfer reactions of reactive (sp^2), carbon-centered radicals is the dearth of knowledge about substituent effects. Gilbert's detailed ESR studies provide the only body of data on substituent effects for one class of sp^2 radicals: the α,β-dicarboxy vinyl radical.[25] Hydrogen-abstraction reactions of sp^2 radicals have recently assumed a new biological relevance with the discovery that diradicals derived from Bergmann cyclizations of calicheamicin, esperamycin, neocarzinostatin, and dyenomycin abstract hydrogen atoms from DNA, an event which leads ultimately to DNA cleavage.[26,27] 1,5-Hydrogen-transfer reactions of these diradicals have already been observed and postulated to modulate biological activity.[27] We now report the details of a systematic study that we undertook to begin to fill the void in the knowledge of substituent effects on hydrogen-abstraction reactions of sp^2-hybridized carbon-centered radicals.

Results

Our primary goal was to determine the ability of substituents on the carbon-bearing hydrogen to promote or prevent 1,5-hydrogen transfer. Toward this end, we selected the structural motif shown in eq 2 because (1) radical **4** is representative of



(2)

typical substrates for 1,5-hydrogen-transfer reactions, (2) precursors **1** bearing different groups X and Y are readily prepared (see supplementary material), and (3) radicals **5** produced by 1,5-hydrogen-transfer are expected to cyclize very rapidly to **6** due to the presence of the geminal diester.[2]

Reduction of substrates **1** with tributyltin hydride should produce mixtures of directly reduced products **2** and reduced/cyclized products **3**. The standard chain mechanisms for the formation of **2** and **3** shown in eq 2 indicate that the ratio of **2**/**3** should depend on the efficiency of 1,5-hydrogen-transfer and on the concentration of the tin hydride. Product **3** must arise from 1,5-hydrogen-transfer of **4** to give **5**, followed by cyclization to **6** and hydrogen abstraction from tin hydride. In principle, product **2** could arise either from direct reduction of the vinyl radical **4** prior to 1,5-hydrogen-transfer or from 1,5-hydrogen-transfer followed by reduction of **5**. In practice, we felt that cyclization of **5** to **6** would be much faster than its reduction to **2**, and this assumption was verified by several control experiments (see below). Therefore, the ratio **2**/**3** represents a direct measure of the efficiency of 1,5-hydrogen-transfer.

We selected substrate **1b** for a detailed investigation to develop standard reaction conditions. Table I summarizes the results that we obtained when **1b** was reduced under a variety of typical

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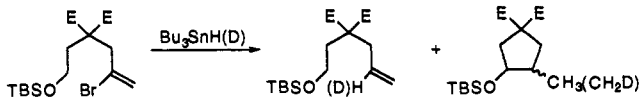
Table I. Reduction of **1b**



	1b E = CO_2Me		2b	3b-cis/trans		
entry	method	[1b]	[Bu_3SnH]	3b/2b	time (h)	$10^{-6}k_{1,5}$ (M^{-1} s^{-1})
1	catalytic	0.003	0.0003	>95/5		
2	catalytic	0.01	0.001	91/9	8	1
3	catalytic	0.03	0.0015	87/13	7	1
4	catalytic	0.05	0.005	88/12	6	3
5	catalytic	0.1	0.01	57/43	4	1
6	catalytic (EtOH)	0.02	0.004	27/73	5	
7	standard	0.01	0.015	80/20	5	3
8	syringe pump	0.01		94/6	6	
9	standard (Bu_3SnD)	0.067	0.1	19/81	10	

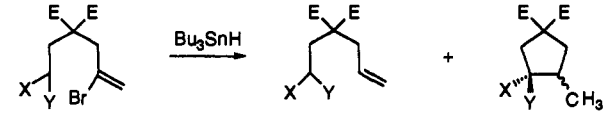
conditions. Reduction of a 0.01 M solution of **1b** with 1.5 equiv of Bu_3SnH provided an 80/20 mixture of cyclized product **3b** to directly reduced product **2b** (entry 7). Cyclic product **3b** was a 40/60 mixture of cis/trans isomers. Syringe pump addition of tin hydride provided a 94/6 ratio of **3b/2b** (entry 8). Catalytic procedures with 10% Bu_3SnCl and 2 equiv of sodium cyanoborohydride[28] gave product ratios that depended on the tin hydride concentration when *tert*-butyl alcohol was used as the solvent (entries 1–5). The use of ethanol as a solvent (entry 6) gave much lower **3a/2a** ratios, a result which we attribute to the reaction of vinyl radical **4** with ethanol.

We settled on the conditions shown in Table I, entry 4, as the best balance of our preparative and mechanistic needs. This is hereafter called standard catalytic conditions (method A). These conditions use known, fixed tin hydride concentrations, give convenient ratios of **3/2**, require reasonable reaction times, and employ only 10% tin reagent (thus facilitating purification). From the preparative standpoint, the best conditions for high **3/2** ratios are probably syringe pump addition of Bu_3SnH. However, concentrations of tin hydride are not known with certainty under such conditions, and this makes it dangerous to compare results from different experiments and impossible to estimate rate constants. A preparative experiment (2 mmol) under the conditions of Table I, entry 4, provided a mixture of **3b** and **2b** (88/12) in 86% yield. After careful chromatographic separation, pure **3b** was isolated in 66% yield.

To verify the sequence proposed in eq 2, we reduced **1b** with Bu_3SnD (Table I, entry 9). A relatively high concentration of Bu_3SnD was used to ensure that significant amounts of the reduced product **2b** were formed (because of the isotope effect,[29] little **2b** is formed under standard conditions). Both **2b** and **3b** were >98% monodeuterated according to a GCMS analysis. A ^1H NMR analysis demonstrated that cyclic product **3b** was deuterated exclusively in the methyl group while directly reduced product **2b** was deuterated exclusively in the 2°-vinyl position. No label adjacent to the OTBS group was detected. We made similar observations with substrate **1i**. These control experiments support the conclusion that radical **5** leads only to **3** and never to **2** under standard conditions.

Before selecting the catalytic conditions, we performed a key control experiment to verify that reduction of the tributyltin halide with $NaCNBH_3$ to give tin hydride was more rapid than chain propagation. Addition of $NaCNBH_3$ to a *tert*-butyl alcohol solution of tributyltin chloride followed by mixing for several seconds and rapid injection of a small sample into the GC showed only the presence of tin hydride; no tin chloride remained.[30] Since the preparative reactions take 4–7 h and the reduction of tin chloride (and presumably tin bromide) takes at most several seconds, it seems safe to assume that the tin hydride concentration at any given time is equal to the starting concentration of the tin chloride. By combining this assumption with an estimated rate constant for the reaction of a vinyl radical with tin hydride (k_H in eq 2 $\approx 1 \times 10^8$ M^{-1} s^{-1}),[31] we can then calculate rate constants for the 1,5-hydrogen-transfer reactions shown in the last column of Table I. Reactions conducted by the catalytic and standard procedures at significantly different concentrations give a rate constant ($k_{1,5}$) for **1b** in the range of $1–4 \times 10^6$ M^{-1} s^{-1}. Given the assumptions that are required and the large range of the calculated rate constant $k_{1,5}$, this and the other rate constants listed in Table II are only rough estimates.

Table II. Reductions of Substrates **1a–n**



	1 E = CO_2Me		2		3	
entry	X	Y	ratio 3/2[a]	totl yld (%)	yld 3 (cis/trans) (%)	$k_{1,5}$ (M^{-1} s^{-1})
a	$S(CH_2)_3S$		>96/<4	96	96	$>10^7$
b	TBSO	H	88/12	87	66 (40/60)	3×10^6
c	CH_3	CH_3	87/13	73	65	3×10^6
d	CH_3O	CH_3	86/14	89	82 (14/86)	3×10^6
e	Ph	H	78/22	76	54 (40/45/15)[b]	2×10^6
f	N≡C	H	78/22	61	52 (61/39)	2×10^6
g	MeO_2C	H	76/24	83	60 (82/18)	2×10^6
h	$O(CH_2)_3O$		67/33	83	56	1×10^6
i	$O(CH_2)_2O$		58/42	81	38	0.7×10^6
j	CH_2=CH	H	57/43[c]	87	11 (4/8/83/5)[d]	0.7×10^6
k	CH_3O	OCH_3	49/51	98	46	0.5×10^6
l	CH_3	H	48/52	73	28 (5.6/1)	0.5×10^6
m	OCH_2		<4/>96	69		$<10^5$
n	H	H	<4/>96	72		$<10^5$

[a] Ratios determined by ^1H NMR integration or GC analysis of the products before separation. [b] Ratio **3e-cis/3e-trans/7**. [c] Ratio may not be accurate due to the low yield of **2j** and **3j**. [d] Ratio **3j-cis/3j-trans/8/9**.

Table II lists the results of reductions of 14 substrates (**1a–n**) under standard catalytic conditions. In general, reactions were conducted on a 1–2-mmol scale and each reaction was repeated at least once. Product ratios and combined isolated yields were determined after removal of most of the catalytic tin residue; results were very reproducible. Isolated yields of cyclic products **3** were usually determined after chromatographic separation from directly reduced products **2**. In several cases, the R_f values of these two products were similar and the directly reduced product **2** was first converted to a more polar product by treatment of the crude mixture with MCPBA or ozone. Separation of cis/trans isomers was sometimes possible, and stereochemistry was usually assigned by γ-gauche effects in the ^{13}C NMR spectra[32] (see Experimental Section and supplementary material for full details).

In two cases, other products besides 5-exo cyclized product **3** and directly reduced product **2** were isolated. With phenyl-substituted precursor **1e**, a small amount of 6-endo product **7** formed alongside the 5-exo products (see Figure 2). It is not clear whether 6-endo product **7** has a kinetic or thermodynamic origin.[33] In the case of allylic substituent[15] **1j**, major products

(28) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.
(29) Isotope effects for deuterium transfer from Bu_3SnD to vinyl radicals are not known. Isotope effects for alkyl radicals are about 4. See: Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059. Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047.
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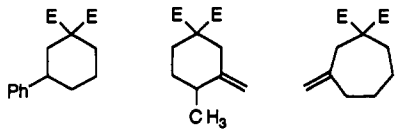
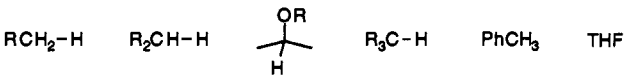


7 8 9

Figure 2. Side products in reductions of **1e** and **1j**.



0.03 0.3 1.4 1.6 1.7 5

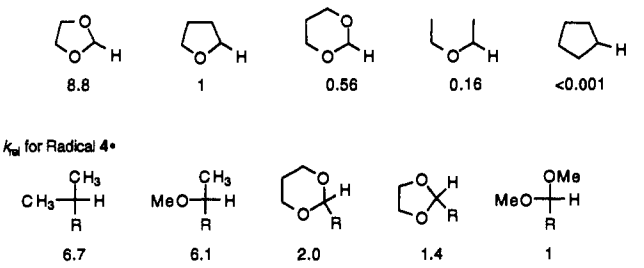
Figure 3. Representative rate constants ($\times 10^6$ M^{-1} s^{-1}) for H-abstraction reactions with Ph•.

8 and **9** resulted from direct vinyl radical cyclization[34] superseding 1,5-hydrogen-transfer. Major product **8** (76% isolated) arises from 6-exo cyclization while the apparent 7-endo product **9** (4%) probably arises from 6-exo cyclization followed by ring expansion of the resulting butenyl radical via a cyclopropylcarbinyl radical.[34]

The substrates are listed in Table II in order of decreasing rate of 1,5-hydrogen-transfer. The position of allylic substrate **1j** is suspect because such small amounts of products **2j** and **3j**[35] formed that their ratio may not be highly accurate; the other placements are secure. The extremes in efficiency of 1,5-hydrogen-transfer of precursors **1** correlate well with the C–H bond dissociation energy (BDE).[36] For example, the dithiane is exceptionally good at promoting 1,5-hydrogen transfer (entry a),[37] while the epoxide (entry m) and the bare methyl group (entry n) are exceptionally poor. In between, there is a large, compressed middle range where substituent effects are small and exceptions to the BDE correlation are common.

Reasonable trends for 1,5-hydrogen-transfer appear throughout the ether series and the alkyl series: $(CH_3)_2C$–H > $(CH_3)HC$–H ≫ H_2C–H (compare entries c, l, and n). The placement of ester and nitrile substituents also appears reasonable (entries f and g). However, allyl and phenyl groups are not especially good at promoting 1,5-hydrogen-transfer (entries e and j). Two methyl groups are as good as one methyl and one oxygen and are actually better than two oxygens (compare entry c with entries d, h, i, and k).

Comparisons of our results with related rates of bimolecular hydrogen transfers are interesting. Although we are not aware of any data for simple vinyl radicals, there are literally hundreds of measurements of bimolecular hydrogen abstraction reactions of phenyl radicals.[38] To ensure the best possible accuracy, we select, for comparison, rate data from the careful study of Scaiano and Stewart[39] and from Lorand and co-workers[40] (which Scaiano and Stewart recommend as in good agreement with theirs). Figure 3 shows these relative rates for bimolecular reactions, which are also in a rather narrow range. Inter- and intramolecular trends are similar. For example, in our system, abstraction of a 3°-hydrogen is 7.7 times more rapid than that of a 2°-hydrogen while in the bimolecular competition, a 3°-hydrogen is 5 times more reactive than a 2°-hydrogen. In both systems, the reactivity of benzylic hydrogens is lower than one might expect based on radical stabilization.



8.8 1 0.56 0.16 <0.001

k_{rel} for Radical 4•

6.7 6.1 2.0 1.4 1

Figure 4. Comparison of inter- (*t*-BuO•) and intramolecular hydrogen transfer.

The comparisons of absolute rate constants are also interesting. Direct comparisons require caution because Lorand's rate constants are at 25 °C, Scaiano's are at 45 °C, and ours are at 80 °C. Further, the bimolecular rate constants are probably considerably more accurate than our intramolecular ones. Nonetheless, it is clear that the rate constants for all these reactions are roughly comparable, in the range of 10^6 M^{-1} s^{-1}. Ingold and Beckwith have also noted that bimolecular and intramolecular 1,5-hydrogen-transfer reactions often have similar activation energies.[2] This seems surprising since entropy should favor the intramolecular 1,5-hydrogen-transfer reactions over their bimolecular analogs. For example, the hexenyl radical cyclization is at least 10^4 times faster than related bimolecular radical addition reactions.[2] Some of the reduced differences between inter- and intramolecular hydrogen transfers may be due to the already high bimolecular rate, which will naturally compress any rate-increasing effects. However, we doubt that this can completely account for the apparently low rate constants of intramolecular hydrogen transfer relative to those of one intermolecular counterpart. It is possible that stereoelectronics might be responsible for the lack of a significant rate increase in the intramolecular reactions. 1,5-Hydrogen transfers of these vinyl radicals may sacrifice energy because the radicals clearly cannot easily attain the most favorable 180° allignment of the C–H–C angle in the transition state for hydrogen transfer.[4,10] Calculations indicate that 1,5-hydrogen-transfers have an X–H–C angle of about 145°, but opinions differ over just how much energy it costs to bend from the favored 180° angle to the needed 145° one.[4,10]

We can also compare our results for several acetals with the results of Ingold, Beckwith, and co-workers.[41] They measured relative rates of bimolecular hydrogen abstraction from acetals by the *tert*-butoxy radical. Figure 4 shows this comparison. Ingold and co-workers observed a different ordering of groups and a much larger relative rate difference than we did. The hydrogen-abstraction reactions of the *tert*-butoxy radical are probably more exothermic than those of the vinyl radical, though we doubt that this is very important. The large difference in reactivity of the *tert*-butoxy radical with THF compared to that of cyclopentene must be due to polar effects with this electrophilic radical because our results do not mirror this difference. It is not clear whether the differences in the reactivity of the oxygenated substrates are best accounted for by polar effects (*tert*-butoxy radical is electrophilic and vinyl radical is nucleophilic) or by fundamental differences in inter- and intramolecular reactions.

It is interesting to ponder the generally poor performance of the acetals in reactions with vinyl radicals. Rüchardt has observed that acetal substituents enforce unexpectedly high bond dissociation energies on substituted ethanes, and he has explained this by invoking the anomeric effect.[42] Even though the two oxygens provide good stabilization of a forming radical, much of the ground-state anomeric effect must be sacrificed to gain this

(34) (a) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529. (b) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525.

(35) Products **3j-cis/trans** are known. See: Stork, G.; Reynolds, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 6911.

(36) Wayner, D. D. M.; Griller, D. *Advances Free Radical Chemistry*; Tanner, D. D., Ed.; JAI Press: Greenwich, 1990; Vol. 1, p 159.

(37) (a) Nishida, A.; Nishida, M.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 7035. (b) Viehe, H. G.; Janousek, Z.; Merényi, R. *Substitution Effects in Radical Chemistry*; Viehe, H. G., Ed.; D. Reidel Pulishing Co., 1986; p 314. (c) Pasto, D. J. *Tetrahedron Lett.* **1986**, *27*, 2941. (d) Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062.

(38) See: Radical Reaction Rates in Liquids; Fisher, H., Ed.; Springer-Verlag: Berlin, 1984; Vol. 13b.

(39) Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609.

(40) Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589.

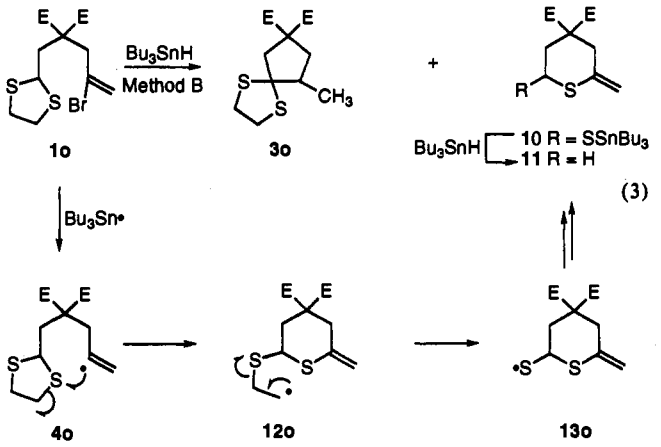
(41) (a) Beckwith, A. L. J.; Easton, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 615. (b) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609. (c) Malatesta, V.; Scaiano, J. C. *J. Org. Chem.* **1982**, *47*, 1455.

(42) Birkhofer, H.; Hädrich, J.; Pakush, J.; Beckhaus, H.-D.; Rüchardt, C.; Peters, K.; von Schnering, H. G. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer: Dordrecht, 1989; p 27.

stabilization. It appears that the ground-state stabilization of the anomeric effect is larger than the radical stabilizing energy of the two oxygens. The parallel of our observation and Rüchardt's suggests that his explanation is reasonable.

The superiority of the dithiane in promoting 1,5-hydrogen-transfer (Table II, entry a) encouraged us to test other classes of mono- and dithioacetals. Though we did not uncover a group that matched the dithiane, we did make some very interesting observations (eqs 3–5).

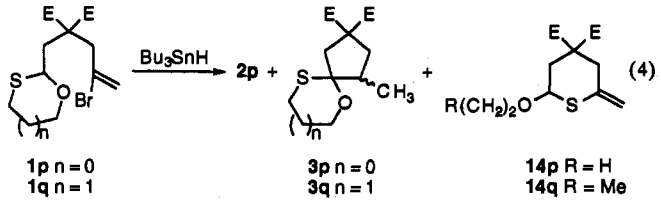
We first attempted the reduction of dithiolane **1o** under standard catalytic conditions (eq 3); however, the reaction stopped with more than half the starting material remaining. Reduction of **1o** with 1.5 equiv of tributyltin hydride (method B) was complete in 5 h. Separation of the crude mixture by flash chromatography afforded not only expected product **3o** (32%) but also two new cyclic products identified as **10** (15%) and **11** (12%). No directly reduced product **2o** was observed. These unusual cyclic vinyl sulfides **10** and **11** must arise by homolytic substitution on sulfur,[43] and we suggest the mechanism in eq 3. Bromine abstraction



1o 3o 4o 12o 13o (3)

from **1o** gives vinyl radical **4o**. This vinyl radical then partitions between 1,5-hydrogen-transfer to give **5o** (and ultimately **3o**) and homolytic substitution on sulfur to give **12o**. Rapid β-elimination[44] of **12o** gives **13o** which then evolves to **10**, perhaps by hydrogen abstraction from tin hydride followed by ionic reaction of the thiol with Bu_3SnBr.[45] Standard tin hydride reduction of **10** to **11** is a known reaction,[46] and purified **10** was indeed slowly reduced to **11** by tributyltin hydride (40% conversion after 6 h at 80 °C). Based on the mechanism in eq 3, we can explain why this reaction goes only to partial conversion under catalytic conditions: the tin sulfides produced are not rapidly reduced to tin hydrides by $NaCNBH_3$. Once the catalytic tin is all converted to tin sulfide, the reaction stops. Because no directly reduced product is formed, we can only estimate that the rate constants for both 1,5-hydrogen-transfer and homolytic substitution on sulfur are $>10^6$ M^{-1} s^{-1}.

We made qualitatively similar observations when we reduced oxathiolanes **1p** and oxathiane **1q** (eq 4). Neither reaction would

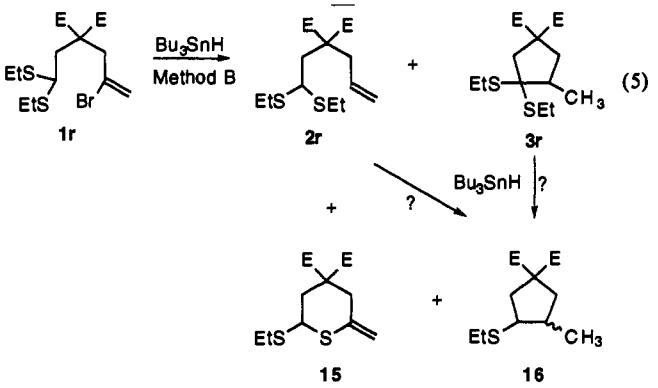


1p n = 0
1q n = 1
3p n = 0
3q n = 1
14p R = H
14q R = Me (4)

go to completion under standard catalytic conditions (method A), but both succeeded when 1.5 equiv of tin hydride was employed (method B). From the reduction of **1p**, we isolated an inseparable mixture of cis/trans **3p** and directly reduced **2p** (29% combined yield) and the pure cyclic vinyl sulfide **14p** (41%). The ratio of **3p**/**2p**/**14p** was 26/4/70. Vinyl sulfide **14p** presumably arises from a homolytic substitution like that depicted in eq 3. Radical **12p** (see eq 3, S = O) cannot fragment so it abstracts hydrogen from tributyltin hydride to give **14p**. Reduction of **1q** provided **3q** (69%) and **14q** (3%). We did not assign the configurations of **3p** or **3q**, which were formed as cis/trans mixtures.

The results indicate that all three thioacetals undergo rapid 1,5-hydrogen-transfer; however, the usefulness of dithiolane and oxathiolane is compromised by competing homolytic substitution on sulfur. Differences in ring strain can account for the increased reactivity of five-membered thioacetals **1o** and **1p** toward homolytic substitution. This homolytic substitution may be useful since it provides facile access to unusual cyclic vinyl sulfides.

Acyclic dithioacetal **1r** proved to be the most complicated substrate (eq 5). Reductions of **1r** by the standard catalytic procedure or with 1.2 or 1.5 equiv of tin hydride were all incomplete after 24 h. Reduction of **1r** with 2 equiv of tin hydride finally



1r 2r 3r 15 16 (5)

did go to completion. Chromatography of the mixture provided traces of cyclized reduced product **3r**, directly reduced product **2r** (inseparable, 2.7% combined yield), and cyclic vinyl sulfide **15** (1.5%). The major products were doubly reduced cyclized products **16**-cis/**16**-trans (85%, 32/68). These products **16** must arise either from reduction of **3r** or reductive cyclization of **2r**.[47,48] We feel that the former path is more likely, but we could not do the needed experiments to resolve this question because **2r** and **3r** were formed in very small amounts, and we could not separate them.

To further evaluate the potential of some of the activating groups, we prepared several other substrates as outlined in eqs 6 and 7. The first pair of substrates (**17a,b**, eq 6) was prepared to evaluate the relative ability of a free alcohol to promote 1,5-hydrogen transfer. This was impossible to do with original substrate **1** because the free alcohol rapidly formed a lactone with the esters. Equation 6 summarizes the results of the reductions of **17a,b** which indicate that a silyl ether is a marginally

(43) (a) Beckwith, A. L. J.; Boate, D. R. *J. Org. Chem.* **1988**, *53*, 4339. (b) Rao, A. V. R.; Reddy, K. A.; Gurjar, M. K.; Kunwar, A. C. *J. Chem. Soc., Chem. Commun.* **1988**, 1273. (c) Tada, M.; Matsumoto, M.; Nakamura, T. *Chem. Lett.* **1988**, 199. (d) Beckwith, A. L. J.; Boate, D. R. *Tetrahedron Lett.* **1985**, *26*, 1761. (e) Beckwith, A. L. J.; Boate, D. R. *J. Chem. Soc., Chem. Commun.* **1985**, 797.

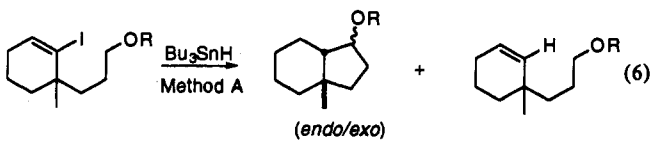
(44) Wagner, P. J.; Seton, J. H.; Lindstrom, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 2579.

(45) The thiol might also react in an acid/base reaction with tin hydride to give **10**. See: Ueno, Y.; Aoki, S.; Okawara, M. *J. Am. Chem. Soc.* **1979**, *101*, 5414. Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.* **1982**, *23*, 2575.

(46) (a) Gutierrez, C. G.; Summerhays, L. R. *J. Org. Chem.* **1984**, *49*, 5206. (b) Gutierrez, C. G.; Stringham, R. A.; Nitasaka, T.; Glasscock, K. G. *J. Org. Chem.* **1980**, *45*, 3393.

(47) Dithiolanes and related functional groups have been used as radical precursors for tin hydride and silicon hydride cyclizations. See: (a) Yadav, V.; Fallis, A. *Can. J. Chem.* **1991**, *69*, 779. (b) Arya, P.; Wayner, D. D. M. *Tetrahedron Lett.* **1991**, *32*, 6265.

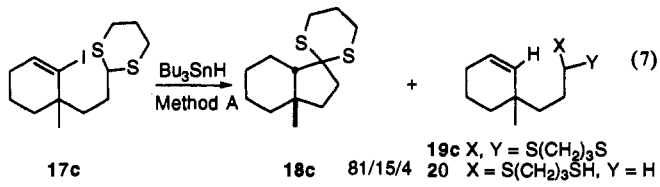
(48) To proceed through **2r**, we must postulate that the thioacetal group of **2r** is more reactive toward the tributyltin radical than both the vinyl bromide and thioacetal functions of **1r**. This seems unlikely; see: Curran, D. P.; Jasperse, C. P.; Totleben, M. J. *J. Org. Chem.* **1991**, *56*, 7169.



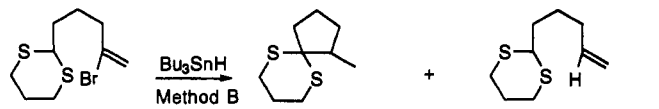
17a R = H **18a** (45% 63/37) 72/28 **19a**
17b R = TBS **18b** (37%, 45/55) 80/20 **19b**

better activating group than a free alcohol. We assume again that the ratio **18**/**19** is a direct measure of the rate of 1,5-hydrogen abstraction to reduction by tin hydride. Under comparable conditions (method A, 0.001 M tin), substrate **17b** gives a higher ratio of cyclized to reduced products (80/20) than **17a** (72/28).

We prepared the substrates shown in eq 7 to evaluate the ability of the dithiane to promote 1,5-hydrogen-transfer in other systems.



17c **18c** 81/15/4 **19c** X, Y = $S(CH_2)_3S$ **20** X = $S(CH_2)_3SH$, Y = H



21 **22** 76/24 **23**

Reductions of **17c** and **21** by a catalytic procedure (method A) did not succeed, but standard reduction at 0.01 M with 1.2 equiv of tributyltin hydride (method B) worked well. From **17c**, we isolated a mixture of three products in 61% yield. These products were identified as **18c**, **19c**, and **20**, and their ratio was 81/15/4. Once again, **17c** is less efficient at 1,5-hydrogen-transfer than its analog **1a**. It is somewhat surprising that direct reduction of dithiane **17c** to give **20** competes with iodine abstraction.[45] We speculate that the adjacent quaternary center in **17c** may reduce the rate of iodine transfer to the tributyltin radical. Reduction of **21** provided 65% of reduced cyclized product **22** and 20% of directly reduced product **23**.

Conclusions

We draw three important conclusions from this study: (1) intramolecular 1,5-hydrogen-transfer reactions of vinyl radicals exhibit characteristics typical of other radical reactions with early transition states, (2) there is a qualitative parallel between substituent effects on 1,5-hydrogen transfer and those on 5-exo hexenyl radical cyclizations, and (3) though limitations exist, 1,5-hydrogen-transfer reactions of vinyl radicals will be generally useful for radical-translocation procedures.

Regarding conclusion 1, the observations reported herein are similar to other atom- and group-transfer reactions with early transition states. There is some correlation of the rate of 1,5-hydrogen transfer and the C–H bond dissociation energy. However, with the exception of a few very good (sulfur-bearing) and very poor (epoxide, methyl) substituents on the C–H bond, the range of reactivity is surprisingly small. Neither resonance stabilization energy nor polar effects have powerful activating or deactivating effects. The overall geometry of the substrate is probably much more important than the substituents on the target C–H bond.

Regarding conclusion 2, inspection of the results in this paper and of others in the literature[14-19] suggests that there is a qualitative parallel between the rates of 5-exo cyclization of hexenyl radicals and the rates of 1,5-hydrogen-transfer reactions of structurally related radicals. In this study, the rates of 1,5-hydrogen-transfer decrease in the series shown in Figure 5. We think that it is

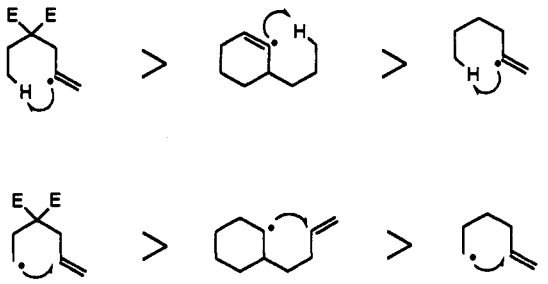


Figure 5. Comparison of 1,5-hydrogen transfer and cyclization.

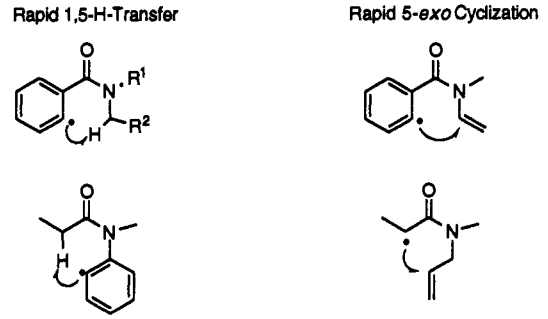


Figure 6. Amide radical H transfer and cyclization.

X = C 1,5-hydrogen transfer only X = C 5-*exo* cyclization only
X = R_2Si 1,5-, 1,6-, 1,7-hydrogen transfer X = R_2Si 5-*exo* + 6-*endo* cyclization

Figure 7. Silicon substitution in 1,5-hydrogen transfer and cyclization.

highly likely that the rates of the analogous 5-exo cyclizations would decrease in the same series.[2a]

Parallels from our other work[14] are shown in Figures 6 and 7.[49] Figure 6 shows two classes of exceptionally rapid 1,5-hydrogen-transfer reactions[14a,b] that are mirrored by two classes of rapid 5-exo cyclizations.[50] Model experiments have again established in these systems that it is the geometry and not the stabilization of the intermediate radical that is responsible for rapid 1,5-hydrogen transfer. Figure 7 compares the effect of a silicon substituent in a connecting chain. In the cyclization reaction, the 6-endo mode begins to compete with the 5-exo mode when silicon replaces carbon in the chain.[51] This is mirrored in the hydrogen-transfer reactions where 1,6- and 1,7-hydrogen transfers begin to compete with 1,5-transfers when silicon is inserted.

This parallel between hydrogen transfer and cyclization is not surprising. Both 5-exo cyclizations and 1,5-hydrogen-transfer reactions have early transition states. And while the transition-state geometry of the atoms directly involved in the cyclization is different from those directly involved in the hydrogen transfer, it is likely that the geometries of the connecting chains are similar.

The analogy between 5-exo cyclizations and 1,5-hydrogen-transfers should be considered qualitative for at least two reasons: (1) there are no rate studies comparing these two reactions and (2) the different transition states will almost surely upset a quantitative comparison. Further work is clearly needed to test the accuracy and usefulness of this analogy. However, our conclusions clearly suggest that the vast body of quantitative

(49) Also compare the results of cyclization and hydrogen transfer, with and without SO_2 substitution, in the following two papers: Pines, S. H.; Purick, R. M.; Reamer, R. A.; Gal, G. *J. Org. Chem.* **1978**, *43*, 1337. Beckwith, A. L. J.; Meijs, G. F. *J. Org. Chem.* **1987**, *52*, 1922.

(50) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

(51) (a) Wilt, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 5251. Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Saigo, K.; Tateishi, K.; Adachi, H.; Saotome, Y. *J. Org. Chem.* **1988**, *53*, 1572.

and qualitative data on rates of 5-exo radical cyclizations should be helpful in designing unusually rapid (or slow) 1,5-hydrogen-transfer reactions.

Regarding conclusion 3, diverse results from our group[14] and others[15-18] that have appeared since our preliminary communication[9] already testify to the general utility of vinyl and aryl radicals in radical-translocation reactions. We believe that considerable untapped potential remains.

Finally, though our studies are remote from reactions of aromatic diradicals with DNA, it may still be appropriate to tentatively extend our conclusions to these biological systems. We suggest that the geometry of an aromatic diradical bound to DNA is much more important in determining sites of hydrogen abstraction than the relative bond dissociation energies of the breaking C–H bonds.

Experimental Section

General Reaction Procedures. Method A. The substrate (1 or 2 mmol, 0.05 M), tributyltin chloride (0.1 equiv relative to the substrate, 0.005 M), AIBN (0.1–0.2 equiv), and sodium cyanoborohydride (2 equiv) were refluxed in *tert*-butyl alcohol (20 or 40 mL). The reaction was monitored by analytical GC for consumption of the starting material. After evaporation of most of the *tert*-butyl alcohol, the residue was diluted with anhydrous ether and filtered through layers of silica gel and anhydrous magnesium sulfate, eluting with ether and then ethyl acetate. The combined filtrate was then evaporated, and the residue was purified either by flash chromatography or MPLC.

Method B. The substrate (0.01 M), tributyltin hydride (0.012 M), and AIBN (0.1–0.2 equiv) were refluxed in benzene until GC showed no starting material. After evaporation of most of the solvent, wet ether (5–20 mL) was added followed by addition of DBU (1.5–2 equiv relative to the total tin compound).[52] A white precipitate formed, and the stirring was continued for 10 min. After addition of an equal volume of pentane (sometimes mixed with ethyl acetate depending on the solubility of the products), the mixture was filtered through a plug of silica gel and anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was then purified either by flash chromatography or MPLC.

Syringe Pump Addition of Tributyltin Hydride. To a solution of the substrate (0.01–0.5 M) and AIBN (0.01–0.1 equiv) in refluxing benzene was added tributyltin hydride (1.2 equiv, with additional AIBN dissolved in) by syringe pump over a period of 5–8 h. After all the tributyltin hydride was added, the reaction was continued for 0.5 h. The workup procedure was identical to that described above.

Specific Examples. Radical Reaction of 1a To Give Dimethyl 4-Methyl-6,10-dithiaspiro[4.5]decane-2,2-dicarboxylate (3a). Radical reaction of precursor **1a** was carried out by method A (2 mmol). Purification of the crude product was performed by MPLC with 10% ethyl acetate–hexane to afford a single product, **3a** (97%): ^{1}H NMR δ 3.73 (s, 3 H), 3.72 (s, 3 H), 3.66 (d, J = 14.0 Hz, 1 H), 3.16–2.95 (m, 2 H), 2.82–2.72 (m, 2 H), 2.64 (d, J = 14.0 Hz, 1 H), 2.63 (m, 1 H), 2.28 (m, 2 H), 2.11 (m, 1 H), 1.88 (m, 1 H), 1.16 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 172.7, 172.1, 59.5, 57.9, 53.1, 53.0, 48.8, 45.6, 39.7, 28.4, 26.5, 25.7, 14.1; IR 2955, 2903, 2875, 1738, 1733, 1435, 1256, 1199, 1146, 1055 cm^{-1}; MS m/e 59, 79, 106, 139, 170, 198, 230, 245, 273, 304 (rel intensity 100); HRMS calcd for $C_{13}H_{20}O_4S_2$ (M) 304.0803, obsd 304.0803.

Radical Reaction of Precursor 1b. Method A was used for the radical cyclization with **1b** (819 mg, 2 mmol, 0.02 M), tributyltin chloride (65 mg, 0.2 mmol, 0.002 M), and *tert*-butyl alcohol (100 mL). After the crude product was purified by MPLC with 5% ethyl acetate–hexane, a mixture (567 mg, 86% yield) of cyclic (**3b**) and reduced products (**2b**) was isolated.

Dimethyl *cis*-3-[(*tert*-butyldimethylsilyl)oxy]-4-methylcyclopentane-1,1-dicarboxylate (3b-cis): ^{1}H NMR δ 4.02 (q, J = 3.1 Hz, 1 H), 3.68 (s, 6 H), 2.37 (d, J = 1.8 Hz, 2 H), 2.20 (d, J = 4.8 Hz, 1 H), 2.17 (s, 1 H), 1.98 (m, 1 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.84 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR δ 173.8 (one carbonyl carbon observed), 78.7, 75.7, 58.6, 52.8, 52.6, 43.8, 40.1, 39.1, 38.6, 25.8, 18.1, 13.7, –4.72, –5.01; IR 2955, 2932, 2856, 1738, 1435, 1254, 1196, 1148, 1059, 1044, 833, 776 cm^{-1}; MS m/e 49, 73, 89, 107, 139, 180, 273 (rel intensity 100), 287, 299, 315; HRMS calcd for $C_{15}H_{27}SiO_4$ (M – MeO) 299.1679, obsd 299.1679.

Dimethyl *trans*-3-[(*tert*-butyldimethylsilyl)oxy]-4-methylcyclopentane-1,1-dicarboxylate (3b-trans): ^{1}H NMR δ 3.72 (s, 3 H), 3.71 (s, 3 H), 3.69 (dd, J = 6.8, 16.0 Hz, 1 H), 2.63 (m, 2 H), 2.02 (dd, J = 7.6, 13.5 Hz, 1 H), 1.90 (m, 1 H), 1.53 (dd, J = 10.3, 13.5 Hz, 1 H), 0.981 (d, J = 6.6 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR δ 173.3, 172.7, 78.9, 75.8, 56.6, 52.8, 42.2, 41.9, 38.7, 25.9, 17.2, 16.1, –4.5, –4.7; IR 2955, 2930, 2857, 1738, 1435, 1389, 1254, 1198, 1121, 1055, 1007, 912, 876, 837, 776 cm^{-1}; MS m/e 73, 89, 107, 139, 181, 241, 273 (rel intensity 100), 299; HRMS calcd for $C_{12}H_{21}SiO_5$ (M – C_4H_9) 273.1158, obsd 273.1159.

Radical Reactions of 1c. This reaction was conducted by method A. The crude product from DBU workup of the reaction was purified by MPLC with 6% ethyl acetate–hexane to afford (in order of elution) **2c** (8%) and **3c** (65%).

Dimethyl 3,3,4-trimethylcyclopentane-1,1-dicarboxylate (3c): ^{1}H NMR δ 3.65 (s, 3 H), 3.64 (s, 3 H), 2.34 (dd, J = 6.7, 13.5 Hz, 1 H), 2.19 (d, J = 13.8 Hz, 1 H), 2.02 (d, J = 13.9 Hz, 1 H), 1.91 (t, J = 12.3 Hz, 1 H), 1.65 (m, 1 H), 0.97 (s, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.69 (s, 3 H); ^{13}C NMR δ 173.7, 173.3, 57.4, 52.6, 52.5, 48.9, 43.6, 41.1, 27.6, 21.5, 12.9 (11 out of 12 expected peaks were observed); IR 2957, 2874, 1734, 1456, 1435, 1389, 1368, 1262, 1200, 1169, 1144, 1115, 1078, 953, 845 cm^{-1}; MS m/e 59, 93, 109, 122, 145 (rel intensity 100), 167, 186, 197, 227; HRMS calcd for $C_{12}H_{19}O_4$ (M – H) 227.1283, obsd 227.1283.

Radical Reaction of Precursor 1d. This reaction was run by method A. The separation was carried out by MPLC with 6% ethyl acetate–hexane to afford (in order of elution) **3d-cis** (14%), **2d** (7%), and **3d-trans** (68%).

Dimethyl *cis*-3-methoxy-3,4-dimethylcyclopentane-1,1-dicarboxylate (3d-cis): ^{1}H NMR δ 3.72 (s, 3 H), 3.70 (s, 3 H), 3.11 (s, 3 H), 2.92 (d, J = 14.3 Hz, 1 H), 2.36 (dd, J = 7.9, 14.3 Hz, 1 H), 2.18 (t, J = 12.5 Hz, 1 H), 1.85 (m, 2 H), 1.17 (s, 3 H), 0.92 (d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 173.9, 172.6, 83.3, 57.4, 52.8, 49.5, 45.2, 42.2, 40.4, 19.3, 18.5, 11.4; IR 2957, 2830, 1736, 1435, 1264, 1213, 1163, 1129, 1088, 1040 cm^{-1}; MS m/e 49, 59, 83, 93, 99, 138, 153, 170 (rel intensity 100), 185, 202, 213, 229, 244; HRMS calcd for $C_{11}H_{17}O_5$ (M – Me) 229.1076, obsd 229.1076.

Dimethyl *trans*-3-methoxy-3,4-dimethylcyclopentane-1,1-dicarboxylate (3d-trans): ^{1}H NMR δ 3.73 (s, 3 H), 3.71 (s, 3 H), 3.16 (s, 3 H), 2.71 (dd, J = 7.6, 13.7 Hz, 1 H), 2.54 (d, J = 14.1 Hz, 1 H), 2.33 (d, J = 14.1 Hz, 1 H), 2.15 (m, 1 H), 1.74 (dd, J = 8.2, 13.7 Hz, 1 H), 1.10 (s, 3 H), 0.99 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 173.1, 172.6, 84.9, 57.2, 52.8, 50.0, 43.2, 41.4, 40.1, 19.2, 17.9, 15.6; IR 2957, 2828, 1736, 1435, 1379, 1259, 1201, 1163, 1134, 1078 cm^{-1}; MS m/e 59, 72, 83, 93, 99, 138, 153, 170 (rel intensity 100), 181, 185, 202, 213, 229; HRMS calcd for $C_{11}H_{17}O_5$ (M - Me) 229.1076, obsd 229.1076.

Radical Reaction of 1e. The reaction was run by method A (1 mmol). The crude product was purified by MPLC with 5% ethyl acetate–hexane to afford an inseparable mixture of products **3e-cis**, **3e-trans**, **2e**, and **7** (211 mg, 76%). The products were identified by comparison with authentic samples.[53]

Ozonolysis of the Mixture from Radical Reaction of 1e. Ozone was bubbled through the mixture formed from precursor **1e** and sodium bicarbonate (1 g) in methylene chloride/methanol (5:1, 30 mL) at –78 °C until the solution turned blue. The flow of ozone gas was terminated, and methyl sulfide (1 mL) was added. After warming and standard workup, the crude product was purified by MPLC with 5% ethyl acetate–hexane to afford an inseparable mixture of **3e-cis**, **3e-trans**, and **7**.[53]

Radical Reaction of 1f. The reaction was carried out by method B (1 mmol). Purification of the crude product from DBU workup by MPLC with 12% ethyl acetate–hexane afforded (in order of elution) **2f** (40.4 mg, 19%), **3f-trans** (43.3 mg, 19%), and **3f-cis** (73.7 mg, 33%).

Dimethyl *cis*-3-cyano-4-methylcyclopentane-1,1-dicarboxylate (3f-cis): ^{1}H NMR δ 3.76 (s, 3 H), 3.74 (s, 3 H), 3.03 (q, J = 7.0 Hz, 1 H), 2.65 (dd, J = 3.7, 7.4 Hz, 2 H), 2.49 (dd, J = 6.6, 13.5 Hz, 1 H), 2.25 (m, 1 H), 2.07 (dd, J = 9.7, 13.5 Hz, 1 H), 1.21 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 172.0, 171.2, 119.8, 59.0, 53.15, 53.09, 40.9, 37.4, 36.1, 34.4, 16.5; IR 2240, 1738, 1732, 1460, 1436, 1274, 1267, 1204, 1170, 1145, 1128, 1082 cm^{-1}; MS m/e 59, 82 (rel intensity 100), 108, 134, 145, 172, 181, 194, 211, 224; HRMS calcd for $C_{10}H_{12}NO_3$ (M – MeO) 194.0817, obsd 194.0817.

Dimethyl *trans*-3-cyano-4-methylcyclopentane-1,1-dicarboxylate (3f-trans): ^{1}H NMR δ 3.76 (s, 3 H), 3.74 (s, 3 H), 2.81 (dd, J = 12.4, 18.6 Hz, 1 H), 2.66 (dd, J = 7.1, 13.7 Hz, 1 H), 2.42 (dq, J = 2.1, 11.4 Hz, 2 H), 2.33 (m, 1 H), 1.73 (dd, J = 10.9, 13.7 Hz, 1 H), 1.19 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 171.9, 171.5, 120.5, 58.6, 53.2 (two carbons), 41.5, 40.2, 37.9, 35.9, 17.6; IR 2959, 2936, 2877, 2242, 1738, 1732, 1436,

(52) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

(53) Chen, M.-H. Ph.D. Thesis, University of Pittsburgh, 1987.

1270, 1201, 1143, 1109, 1155 cm^{-1}; MS *m/e* 59, 82 (rel intensity 100), 108, 134, 145, 172, 194; HRMS calcd for $C_{10}H_{12}NO_3$ (M - MeO) 194.0817, obsd 194.0817.

Radical Reaction of Precursor 1g. The reaction was run by method A. The crude product was purified by MPLC with 8% ethyl acetate–hexane to afford a mixture of **3g-cis**, **3g-trans**, and **2g** (392.5 mg, 76%).

Epoxidation of the Product Mixture. The product mixture and MCPBA (873 mg, 5 mmol) were dissolved in methylene chloride and saturated sodium bicarbonate solution (1:1 volume, 40 mL). After 8 h, the reaction was complete. The crude product after ether workup was purified by MPLC with 8% ethyl acetate–hexane to afford a partially separated mixture of **3g-cis** and **3g-trans** (307 mg, 59.7% overall yield from **1g**).

Diastereomers of Trimethyl 4-Methylcyclopentane-1,1,3-tricarboxylate (3g-cis and 3g-trans). Cis diastereomer 3g-cis: ^{1}H NMR δ 3.74 (s, 3 H), 3.72 (s, 3 H), 3.67 (s, 3 H), 2.97 (q, J = 9.2 Hz, 1 H), 2.67–2.30 (m, 4 H), 2.13 (dd, J = 8.5, 13.2 Hz, 1 H), 0.93 (d, J = 7.7 Hz, 3 H); ^{13}C NMR (four quaternary carbons were not observed due to the dilution) δ 52.9, 52.8, 51.5, 47.7, 41.2, 36.5, 35.8, 16.0.

Trans diastereomer 3g-trans: ^{1}H NMR (partially separated, but still mixed with the cis diastereomer) signals assigned to **3g-trans** δ 1.73 (dd, J = 10.6, 14.3 Hz, 1 H), 1.07 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (assigned by subtraction of cis diastereomer from the spectrum of the mixture) δ 51.8, 51.2, 42.2, 38.7, 37.6, 35.8, 29.7, 18.5; IR (mixture) 2955, 1734, 1437, 1375, 1266, 1202, 1171, 1134, 1086, 1034 cm^{-1}; MS *m/e* (mixture) 59, 79, 107, 139, 145 (rel intensity 100), 166, 198, 227, 258; HRMS (mixture) calcd for $C_{12}H_{18}O_6$ (M) 258.1103, obsd 258.1103.

Radical Reaction of Precursor 1h. The reaction was carried out by method A (2 mmol). Purification of the crude products by MPLC with 12% ethyl acetate in hexane afforded **3h** (305.1 mg, 56%) and **2h** (147.5 mg, 27%).

Dimethyl 4-methyl-6,10-dioxaspiro[4.5]decane-2,2-dicarboxylate (3h): ^{1}H NMR δ 3.90 (m, 4 H), 3.72 (s, 6 H), 3.12 (d, J = 13.9 Hz, 1 H), 2.51 (dd, J = 7.8, 13.1 Hz, 1 H), 2.27 (d, J = 13.9 Hz, 1 H), 2.02 (m, 2 H), 1.86 (dd, J = 10.6, 13.2 Hz, 1 H), 1.39 (m, 1 H), 0.96 (d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 172.7, 172.3, 106.4, 62.4, 60.7, 56.3, 52.92, 52.86, 37.9, 37.4, 25.6, 12.2; IR 2957, 2873, 1738, 1732, 1454, 1268, 1157, 1096, 1060, 931 cm^{-1}; MS *m/e* 59, 67, 95, 113, 127, 140, 155, 172, 198 (rel intensity 100), 213, 230, 241, 172; HRMS calcd for $C_{13}H_{20}O_6$ (M) 272.1260, obsd 272.1260.

Radical Reaction of Precursor 1i. The reaction was run by method A (2 mmol). Purification of the crude product by flash chromatography with 10% ethyl acetate in hexane gave an inseparable mixture of **3i** and **2i** (total yield, 81%).

Epoxidation of the Mixture of 3i and 2i. The mixture (337.1 mg, 1 mmol) was added to a two-phase solution of *m*-chloroperoxybenzoic acid (540 mg, 3.1 mmol) in methylene chloride (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL). After 5 h, reduced product **2i** was totally consumed. After ether workup, the crude product was purified by flash chromatography with 10% ethyl acetate–hexane to give **3i** (99.2 mg, 38% from **1i**).

Dimethyl 9-methyl-1,4-dioxaspiro[4.4]nonane-7,7-dicarboxylate (3i): ^{1}H NMR δ 3.91 (m, 4 H), 3.72 (s, 6 H), 2.57 (d, J = 14.3 Hz, 1 H), 2.49 (dd, J = 7.6, 13.2 Hz, 1 H), 2.38 (d, J = 14.3 Hz, 1 H), 2.22 (m, 1 H), 0.94 (d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 172.7, 172.2, 116.1, 65.3, 64.8, 55.6, 42.8, 40.3, 38.8, 12.2; IR 2957, 2886, 1736, 1435, 1266, 1204, 1159, 1121, 1088, 1034 cm^{-1}; MS *m/e* 49, 73, 84, 99, 113, 126, 184 (rel intensity 100), 199, 216, 227, 258 (rel intensity <0.5); HRMS calcd for $C_{12}H_{18}O_6$ (M) 258.1103, obsd 258.1103.

Radical Reaction of Precursor 1j. The radical reaction was run by method A (2 mmol). Purification by MPLC with 3% ethyl acetate–hexane afforded (in order of elution) **2j** (11.7 mg, 3%), a mixture of **3j-cis**,[28] **3j-trans**,[28] and **9**, (64.4 mg, 14%), pure **3j-cis** (11.8 mg, 3%),[28] and **8** (286.7 mg, 64%).

Dimethyl 4-methyl-3-methylenecyclohexane-1,1-dicarboxylate (8): ^{1}H NMR δ 4.78 (s, 1 H), 4.70 (s, 1 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 2.92 (dd, J = 2.1, 13.4 Hz, 1 H), 2.51 (d, J = 13.6 Hz, 1 H), 2.37 (m, 1 H), 2.09 (m, 1 H), 1.82 (m, 2 H), 1.28 (m, 1 H), 1.03 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 172.2, 171.0, 148.2, 108.4, 57.0, 52.6, 52.3, 40.2, 36.4, 32.6, 30.8, 18.0; IR 2957, 2869, 1736, 1651, 1435, 1313, 1287, 1250, 1173, 1113, 1084, 1024, 899 cm^{-1}; MS *m/e* 53, 59, 79, 91, 107, 135, 151, 166 (rel intensity 100), 195, 226; HRMS calcd for $C_{12}H_{18}O_4$ (M) 226.1025, obsd 226.1024.

Dimethyl 3-Methylenecycloheptane-1,1-dicarboxylate (9). Compound **9** was identified in a mixture with **3g**: ^{1}H NMR (peaks assigned to **9**) δ 4.83 (s, 1 H), 4.78 (s, 1 H), 3.73 (s, 6 H), 2.80 (s, 2 H), 2.27 (m, 2 H), 2.05 (m, 2 H).

Radical Reaction of Precursor 1k. The reaction was run by method A (2 mmol). Purification of the crude product by flash chromatography with 10% ethyl acetate–hexane gave an inseparable mixture of **3k** and **2k** (98%). After ozonolytic workup (see **1e**), the crude product was purified by flash chromatography with 10% ethyl acetate–hexane to afford **3k** (242 mg, 0.92 mmol, 46% from **1k**).

Dimethyl 3,3-dimethoxy-4-methylcyclopentane-1,1-dicarboxylate (3k): ^{1}H NMR δ 3.73 (s, 3 H), 3.72 (s, 3 H), 3.22 (s, 3 H), 3.15 (s, 3 H), 2.64 (dd, J = 7.5, 13.5 Hz, 1 H), 2.58 (d, J = 14.1 Hz, 1 H), 2.48 (d, J = 14.1 Hz, 1 H), 2.26 (m, 1 H), 1.86 (dd, J = 5.6, 13.5 Hz, 1 H), 0.98 (d, J = 7.4 Hz, 3 H); ^{13}C NMR δ 172.6, 171.9, 110.0, 56.2, 52.9, 49.9, 48.7, 39.6, 38.8, 25.2, 23.5, 16.0; IR 2955, 2836, 1738, 1435, 1381, 1258, 1202, 1144, 1088, 1057, 934, 862 cm^{-1}; MS *m/e* 99, 109, 169, 186 (rel intensity 100), 201, 218, 229; HRMS calcd for $C_{11}H_{17}O_5$ (M - Me) 229.1076, obsd 229.1076.

Radical Reaction of 1l. The reaction was conducted by method A. The crude product from DBU workup of the reaction was purified by MPLC with 3% ethyl acetate–hexane to afford (in order of elution) pure **3l-cis** (15%), a mixture of all three products **3l** (cis and trans) and **2l** (64 mg, 30%), and pure **2l** (28%).

Dimethyl *cis*-3,4-dimethylcyclopentane-1,1-dicarboxylate (3l-cis): ^{1}H NMR δ 3.70 (s, 6 H), 2.39 (dd, J = 7.0, 13.6 Hz, 2 H), 2.10 (m, 2 H), 1.95 (dd, J = 7.0, 13.6 Hz, 2 H), 0.86 (d, J = 6.6 Hz, 6 H); ^{13}C NMR δ 173.7, 173.5, 59.2, 52.7, 41.2, 36.8, 14.9 (seven out of eight possible peaks observed); IR 2959, 2876, 1736, 1435, 1383, 1352, 1256, 1198, 1154, 1088, 1057, 1034, 943, 847; MS *m/e* 95, 113, 123, 145 (rel intensity 100), 155, 183, 199, 214; HRMS calcd for $C_{10}H_{15}O_3$ (M - MeO) 183.1021, obsd 183.1021.

Dimethyl *trans*-3,4-Dimethylcyclopentane-1,1-dicarboxylate (3l-trans). Trans isomer **3l** was a minor component in a mixture of products (**3l-cis/trans** and **2l**); only some of the peaks could be assigned: ^{1}H NMR δ 3.70 (s, 6 H), 2.51 (dd, J = 7.0, 14.5 Hz, 2 H), 1.72 (dd, J = 10.3, 14.2 Hz, 2 H), 0.96 (d, J = 6.6 Hz, 6 H).

Radical Reaction of Precursor 1o. This reaction was performed by a modified method B. Tributyltin hydride (283 mg, 0.975 mmol) was added to a solution containing substrate **1o** (300 mg, 0.975 mmol) and AIBN (10 mg) in benzene (81 mL). The reaction time was 5 h, and the workup was done by the DBU method. The crude product was purified by flash chromatography with 5% ethyl acetate–hexane to afford (in order of elution) **11** (22.4 mg, 12%), **3o** (76 mg, 32%), and **10** (65.7 mg, 15%).

Dimethyl 9-methyl-1,4-dithiaspiro[4.4]nonane-7,7-dicarboxylate (3o): ^{1}H NMR δ 3.73 (s, 3 H), 3.71 (s, 3 H), 3.22 (m, 4 H), 3.11 (d, J = 14.5 Hz, 1 H), 2.86 (d, J = 14.7 Hz, 1 H), 2.48 (dd, J = 6.7, 13.5 Hz, 1 H), 2.31 (m, 1 H), 2.04 (dd, J = 11.8, 13.2 Hz, 1 H), 1.11 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 172.8, 172.1, 76.8, 75.0, 56.9, 53.0, 52.9, 52.4, 45.5, 41.5, 39.8, 14.1; IR 2955, 2930, 2876, 1734, 1435, 1319, 1262, 1200, 1142, 1101, 1049, 1030, 853 cm^{-1}; MS *m/e* 59, 111, 145, 171, 188, 203, 216, 231, 262, 290 (rel intensity 100); HRMS calcd for $C_{12}H_{18}O_4S_2$ (M) 290.0647, obsd 290.0647.

Tributylstannyl 4,4-bis(methoxycarbonyl)-6-methylenethiane-2-thiolate (10): ^{1}H NMR δ 5.23 (s, 1 H), 5.19 (s, 1 H), 4.18 (dd, J = 3.6, 12.1 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.05 (d, J = 13.5 Hz, 1 H), 2.90 (m, 1 H), 2.71 (d, J = 13.5 Hz, 1 H), 2.08 (dd, J = 12.1, 13.6 Hz, 1 H), 1.58 (m, 6 H), 1.32 (m, 6 H), 1.24 (m, 6 H), 0.90 (t, J = 14.7 Hz, 9 H); ^{13}C NMR δ 170.8, 169.9, 139.4, 116.3, 60.4, 57.0, 53.1, 52.6, 43.1, 39.9, 39.1, 28.6, 27.1, 26.8, 14.7, 13.7; IR 2955, 2924, 2853, 1738, 1616, 1437, 1250, 1169, 1073, 772 cm^{-1}; MS *m/e* 111, 137, 167 (rel intensity 100), 211, 235, 265, 291, 361, 435, 461, 495, (M - Bu), 552.

Dimethyl 2-methylenethiane-4,4-dicarboxylate (11): ^{1}H NMR δ 5.25 (s, 1 H), 5.21 (s, 1 H), 3.74 (s, 6 H), 2.94 (s, 2 H), 2.79 (m, 2 H), 2.39 (m, 2 H); ^{13}C NMR δ 171.2, 133.8, 113.1, 53.0, 28.0, 24.1, 23.9, 13.7; IR 2955, 1788, 1632, 1455, 1296, 1190, 1132, 1200, 914, 795 cm^{-1}; MS *m/e* 60, 89, 102, 111, 139, 171 (rel intensity 100), 187, 199, 230; HRMS calcd for $C_{10}H_{14}O_4S$ (M) 230.0613, obsd 230.0613.

Radical Reaction of Precursor 1p. The reaction was run by method A (1 mmol). MPLC purification with 10% ethyl acetate–hexane gave (in order of elution) **14p** (41%), **3p-cis/trans** (stereochemistry not assigned), and **2p** (partially separated by MPLC, 29%).

Diastereomers of Dimethyl 9-Methyl-4-oxa-1-thiaspiro[4.4]nonane-7,7-dicarboxylate (3p). The diastereomer with shorter GC retention time: ^{1}H NMR δ 4.23 (m, 1 H), 3.87 (m, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 2.98 (m, 3 H), 2.50 (dd, J = 5.0, 10.3 Hz, 1 H), 2.42 (d, J = 14.6 Hz, 1 H), 2.19 (m, 2 H), 1.01 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 173.0, 172.1, 100.3, 70.1, 57.0, 53.0, 52.8, 48.5, 43.5, 40.1, 34.0, 11.5; IR 2955, 2876, 1736, 1437, 1267, 1202, 1115, 735 cm^{-1}; MS *m/e* 49 (rel intensity

100) 60, 67, 84, 113, 129, 140, 155, 172, 200, 214, 243, 274; HRMS calcd for $C_{12}H_{18}O_5S$ (M) 274.0875, obsd 274.0875.

The diastereomer with longer GC retention time: ^{1}H NMR δ 4.16 (m, 1 H), 3.94 (m, 1 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 2.99 (m, 3 H), 2.75 (d, J = 2.4 Hz, 1 H), 2.70 (dd, J = 7.4, 13.8 Hz, 1 H), 2.26 (q, J = 7.0 Hz, 1 H), 1.91 (dd, J = 6.9, 13.8 Hz, 1 H), 1.04 (d, J= 7.0 Hz, 3 H); ^{13}C NMR δ 172.6, 172.4, 82.5, 70.1, 57.0, 53.0, 52.7, 46.7, 43.3, 39.7, 33.4, 17.6; IR 2955, 2876, 1736, 1435, 1329, 1264, 1200, 1154, 1049, 943, 926, 862 cm^{-1}; MS *m/e* 60 (rel intensity 100), 67, 89, 95, 103, 113, 129, 140, 155, 172, 182, 200, 214, 243, 274; HRMS calcd for $C_{12}H_{18}O_5S$ (M) 274.0875, obsd 274.0875.

Dimethyl 2-ethoxy-6-methylenethiane-4,4-dicarboxylate (14p): ^{1}H NMR δ 5.33 (s, 1 H), 5.28 (s, 1 H), 4.62 (dd, J = 2.8, 4.0 Hz, 1 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.26 (m, 2 H), 2.77 (dd, J = 4.8, 14.4 Hz, 1 H), 2.64 (m, 2 H), 1.12 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 171.3, 170.6, 135.2, 118.0, 79.5, 53.02, 52.89, 52.24, 39.3, 37.1, 14.8; IR 2977, 2953, 1740, 1617, 1437, 1321, 1246, 1200, 1140, 1088, 1038, 970 cm^{-1}; MS *m/e* 59, 65, 72, 97, 113, 127, 141, 155, 169 (rel intensity 100), 196, 210, 228, 242, 274; HRMS calcd for $C_{12}H_{18}O_5S$ (M) 274.0875, obsd 274.0875.

Radical Reaction of Precursor 1q. The radical reaction was run by method A (0.27 mmole). DBU workup and purification by MPLC with 10% ethyl acetate–hexane afforded (in order of elution) **14q** (4.5 mg, 2.9%), the major (unassigned) diastereomer of **3q-cis/trans** (88.6 mg, 56.4%), and the minor diastereomer of **3q-cis/trans** (20.2 mg, 12.6%).

Diastereomers of Dimethyl 4-Methyl-10-oxa-6-thiaspiro[4.5]decane-2,2-dicarboxylate (3q-cis/trans). Major diastereomer (with longer GC retention time): ^{1}H NMR δ 3.88 (m, 2 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.17 (d, J = 13.8 Hz, 1 H), 2.98 (dt, J = 2.7, 11.2 Hz, 1 H), 2.70 (d, J = 13.8 Hz, 1 H), 2.71 (m, 1 H), 2.56 (dd, J = 7.7, 13.6 Hz, 1 H), 2.31 (m, 1 H), 2.02 (dd, J = 9.4, 13.6 Hz, 1 H), 1.89 (m, 1 H), 1.71 (m, 1 H), 1.07 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 172.6, 172.3, 91.7, 64.6, 56.9, 53.1 (two peaks overlapping), 44.5, 43.5, 38.4, 25.7, 24.4, 14.9; IR 2957, 1734, 1435, 1377, 1260, 1202, 1159, 1119, 1082, 1051, 1028, 994, 928 cm^{-1}; MS *m/e* 59, 67, 74 (rel intensity 100), 95, 113, 123, 140, 155, 182, 214, 229, 246, 257, 288; HRMS calcd for $C_{13}H_{20}O_5S$ (M) 288.1031, obsd 288.1031.

Minor diastereomer (with shorter GC retention time): ^{1}H NMR δ 3.87 (m, 2 H), 3.72 (s, 6 H), 3.64 (d, J = 14.4 Hz, 1 H), 3.08 (dt, J = 2.6, 11.2 Hz, 1 H), 2.65 (m, 1 H), 2.54 (m, 1 H), 2.38 (d, J = 14.4 Hz, 1 H), 2.09 (m, 2 H), 1.90 (m, 1 H), 1.71 (m, 1 H), 1.06 (d, J = 5.6 Hz, 3 H); ^{13}C NMR δ 172.8, 88.6, 62.7, 57.4, 53.0, 52.9, 45.0, 44.5, 39.2, 25.7, 25.6, 12.3; IR 2955, 1736, 1435, 1375, 1258, 1202, 1154, 1115, 1080, 1042, 1013, 970, 930, 857, 826 cm^{-1}; MS *m/e* 59, 67, 74, 95, 113, 127, 140, 155 (rel intensity 100), 182, 214, 229, 246, 257, 288; HRMS calcd for $C_{13}H_{20}O_5S$ (M) 288.1031, obsd 288.1031.

Dimethyl 2-propoxy-6-methylene-4,4-dicarboxylate (14q): ^{1}H NMR δ 5.33 (s, 1 H), 5.25 (s, 1 H), 4.72 (t, J = 3.0 Hz, 1 H), 3.73 (s, 3 H), 3.70 (m, 1 H), 3.69 (s, 3 H), 3.22 (m, 2 H), 2.79 (dd, J = 4.5, 14.2 Hz, 1 H), 2.66 (m, 2 H), 1.50 (m, 2 H), 0.88 (t, J = 7.4 Hz, 3 H).

Radical Reaction of Precursor 1r. The reaction was carried out by a modification of method B. A solution of **1r** (300 mg, 0.75 mmol), tributyltin hydride (328 mg, 1.13 mmol), and AIBN (19 mg) in benzene (75 mL) was refluxed for 4 h. All tributyltin hydride was consumed, but a significant amount of **1r** remained. Additional portions of tributyltin hydride (109 mg, 0.377 mmol) and AIBN (10 mg) were added. After 4 h of refluxing, DBU workup afforded a mixture of products which was purified by MPLC with 5% ethyl acetate–hexane to afford (in order of elution) **3r** and **2r** (mixture, 6.4 mg, 2.7%), **16-trans** (111.1 mg, 57%), **16-cis** (55.5 mg, 28%), and **15** (3.4 mg, 1.5%).

Dimethyl 3,3-bis(ethylthio)-4-methylcyclopentane-1,1-dicarboxylate (3r) and dimethyl 2-(2,2-bis(ethylthio)ethyl)-2-propenyl-1,1-dicarboxylate (2r): ^{1}H NMR (assigned to **3r**) δ 2.84 (dd, J = 7.7, 9.1 Hz, 1 H), 1.87 (m, 1 H), 1.08 (d, J = 7.1 Hz, 3 H); (assigned to **2r**) δ 5.63 (m, 1 H), 5.14 (d, J = 5.2 Hz, 1 H), 5.10 (s, 1 H), 3.86 (t, J = 6.8 Hz, 1 H); other peaks overlapped.

Dimethyl 2-(ethylthio)-6-methylenethiane-4,4-dicarboxylate (15): ^{1}H NMR δ 5.26 (m, 2 H), 4.20 (dd, J = 3.1, 11.7 Hz, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.07 (d, J = 14.4 Hz, 1 H), 2.84–2.67 (m, 4 H), 2.12 (dd, J = 12.6, 14.0 Hz, 1 H), 1.30 (t, J = 7.2 Hz, 3 H); IR 2957, 2930, 2872, 1738, 1618, 1437, 1256, 1206, 1171, 1127, 1076, 1061 cm^{-1}; HRMS calcd for $C_{12}H_{18}O_4S_2$ (M) 290.0626, obsd 290.0621.

Dimethyl *cis*-3-(ethylthio)-4-methylcyclopentane-1,1-dicarboxylate (16-cis): ^{1}H NMR δ 3.73 (s, 3 H), 3.72 (s, 3 H), 3.24 (q, J = 6.6 Hz, 1 H), 2.67–2.50 (m, 6 H), 2.19 (m, 1 H), 1.24 (t, J = 7.3 Hz, 3 H), 1.02 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 173.3, 172.5, 58.6, 52.91, 52.86, 48.8, 40.7, 40.4, 38.0, 25.8, 15.7, 14.9; IR 2957, 2930, 2872, 1736, 1437, 1377, 1263, 1198, 1173, 1142, 1103, 1055, 951, 853, 799 cm^{-1}; MS *m/e* 59, 79, 113, 145 (rel intensity 100), 171, 199, 229, 260; HRMS calcd for $C_{12}H_{20}O_4S$ (M) 260.1082, obsd 260.1082.

Dimethyl *trans*-3-(ethylthio)-4-methylcyclopentane-1,1-dicarboxylate (16-trans): ^{1}H NMR δ 3.72 (s, 6 H), 2.85 (dd, J = 7.5, 13.8 Hz, 1 H), 2.60 (m, 4 H), 2.15 (dd, J = 3.5, 13.7 Hz, 1 H), 1.87 (m, 1 H), 1.73 (dd, J = 10.7, 13.7 Hz, 1 H), 1.26 (t, J = 7.3 Hz, 3 H), 1.09 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 172.8, 172.4, 57.8, 52.7, 50.4, 46.3, 42.7, 41.7, 40.4, 25.1, 17.7; IR 2957, 2930, 2872, 1736, 1437, 1377, 1263, 1200, 1173, 1142, 1103, 1055, 951, 853, 799 cm^{-1}; MS *m/e* 59, 79, 113, 145 (rel intensity 100), 171, 186, 199, 229, 260; HRMS calcd for $C_{12}H_{20}O_4S$ (M) 260.1082, obsd 260.1081.

Radical Reaction of 17a. The radical reaction was carried out by the syringe pump method with tributyltin hydride (698 mg, 2.40 mmol), **17a** (560 mg, 2 mmol), and AIBN (50 mg) in refluxing benzene (20 mL) over 5 h. DBU workup followed by MPLC separation with 12% ethyl acetate–hexane afforded (in order of elution) **18a-endo** (83.9 mg, 30.0%), **18a-exo** (45.8 mg, 16.4%), and **19a** (57.3 mg, 20.5%).

***endo,cis*-1-Methylbicyclo[4.3.0]nonan-7-ol (18a-endo)**: ^{1}H NMR δ 4.52 (dd, J = 6.7, 15.3 Hz, 1 H), 2.16 (m, 1 H), 1.84 (m, 1 H), 1.75–1.01 (m, 12 H), 0.91 (s, 3 H); ^{13}C NMR δ 75.6, 49.1, 40.2, 36.1, 32.2, 31.3, 30.1, 24.8, 22.23, 22.16; IR 3347 (br, 3200–3500), 2926, 2870, 1460, 1067, 1048 cm^{-1}; MS *m/e* 55, 67, 81, 97 (rel intensity 100), 110, 121, 136, 154; HRMS calcd for $C_{10}H_{18}O$ (M) 154.1358, obsd 154.1357.

***exo,cis*-1-Methylbicyclo[4.3.0]nonan-7-ol (18a-exo)**: ^{1}H NMR δ 4.22 (m, 1 H), 2.13 (m, 1 H), 1.88 (br, 1 H), 1.68–1.11 (m, 10 H), 1.03 (s, 3 H); ^{13}C NMR δ 75.5, 53.6, 39.6, 38.6, 34.6, 31.9, 26.0, 22.6, 22.3, 21.5; IR 3341, 2928, 2863, 1456, 1365, 1048 cm^{-1}; MS *m/e* 55, 67, 81, 97 (rel intensity 100), 121, 136, 152, 154; HRMS calcd for $C_{10}H_{18}O$ (M) 154.1358, obsd 154.1357.

Radical Reaction of Precursor 17b. The radical reaction was run by method A (1 mmol) with tributyltin hydride. DBU workup and purification by MPLC with hexane afforded an inseparable mixture of products **18b-endo**, **18b-exo**, and **19b** (total 267 mg, 85%). Identification and spectral information were obtained by chemical correlation with the **a** series above. See the supplementary material for details.

Radical Reaction of 17c. The reaction was carried out by method B (0.14 mmol). DBU workup and purification by MPLC (1% ethyl acetate–hexane) afforded (in order of elution) **18c** (21.9 mg, 66%), **19c** (2.3 mg, 7%), and **20** (5.8 mg, 18%).

***cis*-7,7-(1,3-Propanediyldithio)-1-methylbicyclo[4.3.0]nonane (18c)**: ^{1}H NMR δ 3.16 (dt, J = 2.6, 13.5 Hz, 1 H), 3.00 (dt, J = 2.6, 13.5 Hz, 1 H), 2.71 (dt, J = 14.5, 3.9 Hz, 2 H), 2.55 (m, 1 H), 2.38 (m, 1 H), 2.07 (m, 1 H), 1.90 (m, 2 H), 1.65 (m, 5 H), 1.53 (m, 3 H), 1.35 (m, 2 H), 1.09 (s, 3 H); ^{13}C NMR δ 56.9, 40.9, 40.8, 40.0, 35.5, 29.7, 27.9, 27.8, 25.7, 23.3, 22.5, 20.7 (12 of 13 expected peaks observed); IR 2934, 2861, 1691, 1458, 1445, 1422, 1375, 1273, 1239, 1017, 1001, 911, 891, 862, 756 cm^{-1}; MS *m/e* 55, 67, 79, 93, 106, 113, 132, 135, 145 (rel intensity 100), 153, 167, 187, 209, 227, 242; HRMS calcd for $C_{13}H_{22}S_2$ (M) 242.1165, obsd 242.1177.

3-(((Mercaptopropyl)thio)propyl)-3-methylcyclohex-1-ene (20): ^{1}H NMR δ 5.65 (dt, J = 10.1, 4.3 Hz, 1 H), 5.36 (d, J = 10.1 Hz, 1 H), 2.97 (t, J = 7.1 Hz, 1 H), 2.55 (m, 4 H), 1.89 (m, 4 H), 1.63 (m, 4 H), 1.43 (m, 3 H), 1.28 (m, 2 H), 0.96 (s, 3 H); MS *m/e* 67, 84, 96, 108, 133, 151 (rel intensity 100), 173, 183, 207, 240.

Radical Reaction of 21. Method B was used to run the radical reaction to afford (in order of elution) directly reduced product **23** (20%) and cyclic product **22** (65%).

1-Methyl-6,10-dithiaspiro[4.5]decane (22): ^{1}H NMR δ 3.03 (m, 1 H), 2.92 (m, 1 H), 2.78 (m, 2 H), 2.54 (m, 1 H), 2.10 (m, 3 H), 1.99 (m, 1 H), 1.92 (m, 1 H), 1.76 (m, 2 H), 1.51 (m, 1 H), 1.13 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 41.3, 35.8, 31.8, 28.5, 27.0, 26.1, 21.6, 15.7 (eight out of nine expected resonances observed); IR 2957, 2903, 2868, 1453, 1433, 1424, 1375, 1275, 1238, 903 cm^{-1}; MS *m/e* 55, 71, 81 (rel intensity 100), 114, 132, 145, 155, 188; HRMS calcd for $C_9H_{16}S_2$ 188.0693, obsd 188.0693.

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Supplementary Material Available: Details of the preparation and characterization of all the radical precursors used in this study and information about configuration assignments of some of the products (33 pages). Ordering information is given on any current masthead page.