$$[9] = [9]_0e^{-\lambda_1 t}$$

$$[10] = [10]_0e^{-\lambda_2 t}$$

$$[11] = [11]_0 - [9]_0k_H^c(e^{-\lambda_1 t} - 1)/\lambda_1 - [10]_0k_H^l(e^{-\lambda_2 t} - 1)/\lambda_2$$

$$[12] = [12]_0 - [9]_0k_D^l(e^{-\lambda_1 t} - 1)/\lambda_1 - [10]_0k_D^c(e^{-\lambda_2 t} - 1)/\lambda_2$$

where

$$\lambda_1 = k_H^c + k_D^l$$

$$\lambda_2 = k_D^c + k_H^l$$

This system of equations is underdetermined as the Simplex procedure converges to different sets of optimized variables, depending on the input set. The convergence is univocal when the number of variables is reduced by the substitutions $k_H^c = ik_D^c$ and $k_H^l = ik_D^l$, where the KIE i is assumed to be the same for the cis and trans rearrangements.

The differential equations describing kinetic Scheme V are as follows:

$$d[16]/dt = k_H^r[18] - (k_A^c + k_T^l)[16]$$

$$d[18]/dt = k_A^c[16] - (k_H^r + k_H^i)[18]$$

$$d[15]/dt = k_H^i[18] - k_T^c[15]$$

$$d[17]/dt = k_T^c[15] + k_T^l[16]$$

The integrated equations are as follows:

$$[16] = Ae^{-\lambda_1 t} + Be^{-\lambda_2 t}$$

$$[18] = C(e^{-\lambda_1 t} - e^{-\lambda_2 t})$$

$$[15] = De^{-\lambda_1 t} + Ee^{-\lambda_2 t} + (F + [15]_0)e^{-\lambda_3 t}$$

$$[17] = [16]_0b/\lambda_1\lambda_2 + [15]_0 + Ge^{-\lambda_1 t} + He^{-\lambda_2 t} + (I - [15]_0)e^{-\lambda_3 t}$$

where

$$\lambda_1, \lambda_2 = (a \pm \sqrt{(a^2 - 4b)})/2$$

$$\lambda_3 = k_T^c$$

$$a = k_A^c + k_H^r + k_H^i + k_T^l$$

$$b = k_A^ck_H^i + k_T^l k_H^i + k_T^l k_H^r$$

$$A, B = [16]_0(k_H^r + k_H^i - \lambda_{1,2})/(\lambda_{2,1} - \lambda_{1,2})$$

$$C = [16]_0k_A^c/(\lambda_2 - \lambda_1)$$

$$D, E, F = [16]_0k_A^ck_H^i/(\lambda_{2,1,1} - \lambda_{1,2,3})(\lambda_{3,3,2} - \lambda_{1,2,3})$$

$$G, H = [16]_0k_T^l(k_H^r + k_H^i - \lambda_{1,2})/\lambda_{1,2}(\lambda_{2,1} - \lambda_{1,2}) + [16]_0k_A^ck_H^ik_T^c/\lambda_{1,2}(\lambda_{2,1} - \lambda_{1,2})(\lambda_3 - \lambda_{1,2})$$

$$I = [16]_0k_A^ck_H^i/(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)$$

Supplementary Material Available: Figures 4 and 5 graphically illustrating the presence of systematic errors when the rearrangements of ions **15**, **16**, **17**, and **18** are fitted into the equations in the Appendix, constraining k_T^l to 0 or k_H^i and k_H^r to the same value (3 pages). Ordering information is given on any current masthead page.

Cyclizations of Unsaturated ·CR(COX)$_2$ Radicals. Manganese(III) Acetate Oxidative Cyclizations of Unsaturated Acetoacetates and Atom-Transfer Cyclizations of Unsaturated Haloacetoacetates Give the Same Radicals

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Abstract: Comparable regio- and stereochemical results were obtained when cyclizations of a series of 2-substituted 3-oxohept-6-enoate (or oct-7-enoate) esters (acetoacetates) were conducted by manganese(III) acetate oxidation or by iodine or bromine atom transfer cyclization. The observed trends support the conclusion that free radicals **6b** (rather than Mn(III)-complexed radicals **5b**) are involved in the Mn(III)-mediated oxidative cyclization of tertiary malonates and acetoacetates. Most cyclizations proceeded under kinetic control, and several showed large temperature dependences on stereoselectivity. An apparent discrepancy was resolved by demonstrating that ring opening of radical **43** (a reverse 6-exo cyclization) was faster than bromine transfer, but slower than iodine transfer or Cu(II) oxidation. In the process of ring closure/ring opening, a *Z*-alkene is converted to an *E*-alkene. Since the *E*- and *Z*-alkenes provide distinct stereochemical results on cyclization, the observed stereochemical ratio becomes a very sensitive probe for this radical ring opening. This observation presages the design and use of related probes for radical ring opening.

Introduction

Radical cyclizations of alkenes have rapidly emerged as powerful reactions for ring construction.[2] The precursors and the products for such cyclizations can vary as a function of the method chosen to conduct the cyclization, and methods based on reduction, isomerization, and oxidation are popular. Oxidative methods have

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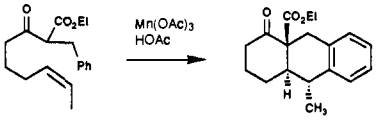
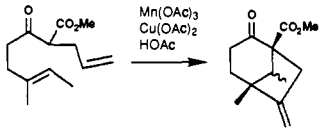
an important feature for synthetic applications: the level of functionality in the product is retained or increased relative to that in the starting material. Among the various oxidative methods available, the manganese(III)-based oxidation of enolizable dicarbonyl compounds is an especially powerful option.[3] Such Mn(III)-promoted cyclizations have broad generality, often proceed with very high degrees of both regio- and stereoselectivity, and produce attractive products for subsequent synthetic transformations.[4] Further, cyclization precursors (even for sophisticated double and triple cyclizations[5]) are readily available by exploiting standard β-dicarbonyl enolate (and dienolate) chemistry. The required manganese salts are inexpensive, and the experimental procedures are straightforward. The exact nature of the products (alkenes, lactones, acetates, phenols) is readily anticipated on the basis of the structure of the starting material and the reaction conditions.

Although important mechanistic features have emerged,[6,7] a detailed understanding of the role of manganese in these oxidative cyclizations has lagged behind the synthetic advances. Specifically, it is not clear whether free radicals or manganese-complexed radicals are intermediates in these cyclizations. This situation is in direct contrast to typical radical chain reactions (tin hydride reductions, for example), where a solid mechanistic understanding preceded (and promoted) synthetic growth. We now report the results of a study that was undertaken to address this central mechanistic question: What is the nature of the reactive intermediate that cyclizes in a manganese(III) oxidative cyclization? This study was prompted by the observation of two general trends in Mn(III)-based cyclizations that, several years ago, did not seem to fit well with the *expected* behavior for free-radical intermediates. These trends were observed in the Mn(III) oxidation of a large number of unsaturated acetoacetates. First, the level of stereocontrol in 6-endo and 6-exo cyclizations was much higher than that of existing cyclizations of related radicals (eq 1).[5b] Second, a variety of substrates give good to excellent yields of products derived from 6-endo cyclizations (eq 2),[5a] while the vast majority of existing radical classes give major products derived from 5-exo cyclizations. Despite these apparent differences, we now find



(1)

First (6-exo) and second (6-endo) cyclizations are completely stereoselective

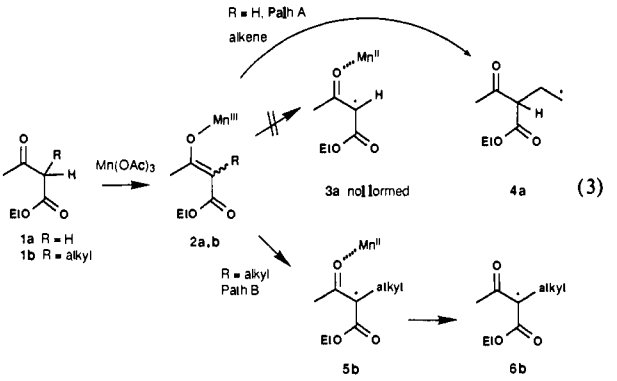


(2)

First cyclization is 6-endo, not 5-exo
11:1 mixture of endo/exo methyl groups

that identical mixtures of products are obtained from the cyclization of radicals substituted with two carbonyl groups and one alkyl group [$^{\bullet}CR(COX)_2$], whether they are generated by Mn(III)-based oxidative methods or by atom-transfer methods. This indicates that Mn-complexed radicals are not involved in the cyclization process, and that the regio- and stereoselectivities observed are inherent to the free-radical intermediates.[8]

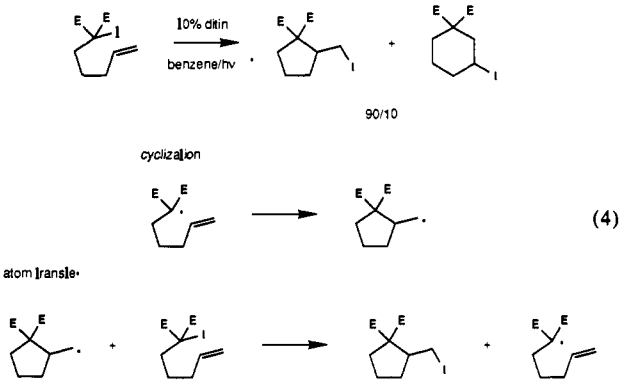
Equation 3 summarizes the current mechanistic picture of manganese(III) acetate promoted oxidations of acetoacetates. Several groups have observed that the rate of oxidation of acetoacetates with two α hydrogens (**1a**) is significantly accelerated by the presence of an alkene.[7] Such observations are inconsistent with the simple oxidation of acetoacetates to free radicals (path B), and indicate that adduct **4a** is formed without the intermediacy of radical **3a**. In contrast, Snider and co-workers observed that



(3)

acetoacetates with only one α hydrogen (**1b**) are oxidized by Mn(III) acetate at the same rate whether an alkene is present or not.[7] They presented evidence that the rate-determining step in these oxidations was the loss of a proton to form the manganese(III) enol **2b**. Rapid oxidation of the enol ligand of **2b** by Mn(III) should produce **5b**. Since **5b** is an odd-electron species, it might be the intermediate that is responsible for the radical-like additions and cyclizations observed in these oxidations. However, it is also conceivable that the enol ligand dissociates from **5b** to give free radical **6b**, or that dissociation is coupled with electron transfer so that **6b** is formed directly from **2b** (without the intermediacy of **5b**). To address the question of the nature of the reactive intermediate, we decided to generate free radicals by an unambiguous method, and to compare the chemistry of these free radicals to that observed in the Mn(III) oxidations.

To generate authentic free-radical intermediates, we selected the halogen atom transfer method[9] (eq 4) for several reasons. First, the mechanisms of these reactions are well-understood. Free-radical intermediates are formed, and kinetic cyclization products are generally obtained because atom transfer to cyclized radicals is more rapid than ring opening.[10] Second, the requisite



(4)

(2) Recent reviews: (a) Hart, D. J. *Science* **1984**, *223*, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Curran, D. P. *Synthesis* **1988**, Part 1, p 417; Part 2, p 489. (e) Curran, D. P. *Radical Addition Reactions* and *Radical Cyclization Reactions and Sequential Radical Reactions*, In *Compr. Org. Syn.* Trost, B. M., Fleming, I., Eds.; Pergamon, in press. (f) C-Radikale. In *Methoden der Organischen Chimie*; Regitz, M., Giese, B., Eds.; Houben-Weyl, 1989; Vol. E19A.

(3) (a) de Klein, W. J. In *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H., Eds.; Plenum Press: New York, 1986; p 261–314.

(4) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427.

(5) (a) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (b) Mohan, R.; Kates, S. A.; Dombroski, M. A.; Snider, B. B. *Tetrahedron Lett.* **1987**, *28*, 845.

(6) (a) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10. (b) Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, *42*, 3429.

(7) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137 and references therein.

(8) In a related study, it was recently shown by competitive rate measurements that free malonyl radical intermediates are generated when diethyl malonate is oxidized with cerium(IV) ammonium nitrate: Baciocchi, E.; Giese, B.; Farshchi, H.; Ruzziconi, R. *J. Org. Chem.* **1990**, *55*, 5688.

(9) (a) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265. (b) Curran, D. P. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer: Dordrecht, The Netherlands, 1989; p 37.

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

precursors would be readily available from the substrates previously used for Mn(III) cyclizations, and the interconversion of the halides produced in atom-transfer cyclizations with the alkenes produced in Mn(III) cyclizations was expected to be easy. Third, although there were as yet no examples of bromine- or iodine-transfer cyclizations of acetoacetates, an in-depth study of halomalonates[10] augured well for the success of the proposed atom-transfer cyclizations. And finally, the validity of the basic mechanistic approach has recently been demonstrated—a series of atom-transfer cyclization reactions provided evidence that palladium-promoted "enehalogenocyclization reactions" occur by a radical chain mechanism.[11]

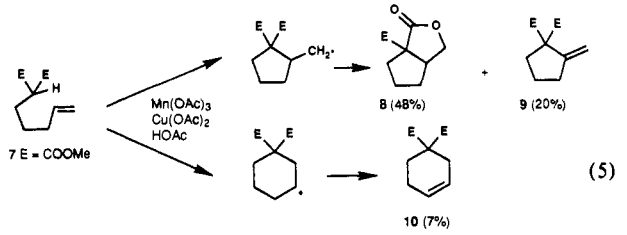
Results and Discussion

The type of mechanistic test that we propose cannot rely on comparison of a single substrate, but instead requires a series of substrates that incorporates as much diversity as possible. The substrates that we have selected fall into two broad classes: substituted hexenyl radicals (5-exo/6-endo cyclizations possible) and substituted heptenyl radicals (6-exo/7-endo cyclizations possible).

At the outset of this project, there were no examples of Mn(III) oxidations and atom-transfer cyclizations on substrates that would generate the same radical. To begin, we conducted a manganese(III) oxidation with a simple substrate whose atom-transfer chemistry was already established, and we continued by conducting atom-transfer cyclizations on a series of substrates whose Mn(III)-oxidation chemistry was established.

We have assumed in this study that, if radical intermediates are involved, isomer ratios will be sensitive neither to small variations in temperature (atom-transfer cyclizations are conducted at 70–80 °C, Mn(III) oxidations at 25–55 °C)[4,5] nor to large variations in solvent polarity (atom-transfer cyclizations are conducted in benzene, Mn(III) oxidations in acetic acid). Insensitivity to solvent effects is a standard characteristic of many radical reactions, so this should be a valid assumption. When temperature effects appeared to be important, we conducted the atom-transfer cyclizations and the Mn(III) oxidations at comparable temperatures. We have also assumed that the isolated product ratios are representative of the possible competing cyclization rates. In other words, we assume that all cyclic radicals are converted to final products with equal efficiency and that these final products are stable to the reaction conditions. This is probably a good assumption for the atom-transfer reactions, where high mass balances are the norm. We were less certain about this assumption for the Mn(III) oxidations. Mass balances are sometimes moderate, and cyclic radicals can be converted to stable products with differing efficiencies depending on their oxidation potentials. Therefore, we selected for comparison Mn(III) oxidations conducted in the presence of Cu(II), which is a more efficient oxidizer of alkyl radicals than Mn(III). That comparable mixtures of products were obtained in all cases ultimately validates this assumption.

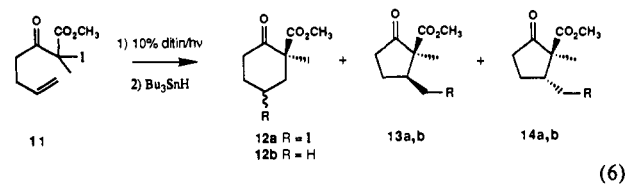
Equation 5 contains the results of Mn(III) oxidative cyclization of **7**; the parallel atom-transfer chemistry is presented in eq 4. Standard oxidation of **7** with 2 equiv of $Mn(OAc)_3$ (1 equiv of $Cu(OAc)_2$, HOAc, 55 °C, 43 h)[4,5] resulted in the formation of 5-exo products **8** and **9**, and 6-endo product **10** in a combined yield of 75%. Unreacted **7** was also recovered in 12% yield. Cyclization



(5)

occurs to give the cyclopentylmethyl radical, which is oxidized by Cu(II) to the lactone **8** and the methylenecyclopentane **9**, or the cyclohexyl radical, which is oxidized to give the cyclohexene **10**. The ratio of 5-exo/6-endo products was 90/10, which is identical with the ratio of regioisomers obtained in the atom-transfer cyclization of eq 4. That the ratios were identical despite differences in solvent polarity provided the first clue that free-radical intermediates might be involved in Mn(III)-promoted cyclizations.

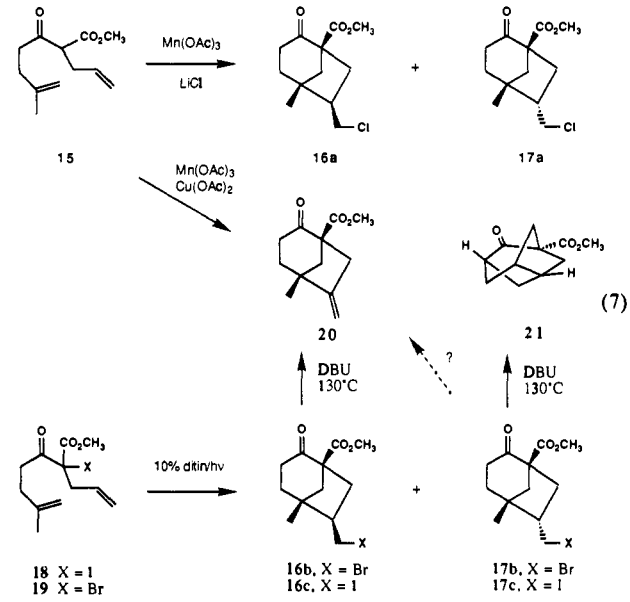
We next investigated regio- and stereoselectivity in an atom-transfer cyclization of an acetoacetate. On the basis of the Mn(III)-mediated oxidations of more complex substrates,[4] we anticipated that atom-transfer cyclization of iodoacetoacetate **11** (eq 6) should show a slight bias for the formation of 6-endo products over 5-exo (typical ratios in Mn cyclizations are 70/30).



(6)

Isomerization of **11** by the standard ditin procedure (10% $Me_3SnSnMe_3$, sunlamp irradiation in benzene) produced a mixture of four products, **12a–14a**, which was not easy to analyze. Direct reduction of the mixture with tributyltin hydride gave the 6-endo product **12b**[12] along with the 5-exo products **13b** and **14b**[13] (91% combined yield). The ratio of **12b**/(**13b** + **14b**) was 55/45. Although this ratio is slightly lower than the manganese precedents would indicate, we do not believe it is inconsistent with free-radical intermediates given the differences in the substrates. The modest stereoselectivity in favor of **13b** over **14b** (2.5/1) is in line with related Mn(III) oxidations.[4]

To provide a better comparison, we advanced to substrates whose Mn(III) oxidation products had already been established (eq 7). Oxidation of **15** with $Mn(OAc)_3$ and $Cu(OAc)_2$ gave **20** in 86% yield.[5a] Oxidation of **15** with $Mn(OAc)_3$ and LiCl gave stereoisomeric chlorides **16a** and **17a** in a 67/33 ratio (50%, eq 7). Iodination of **15** by the standard procedure (NaH, NIS) gave



(7)

iodoacetoacetate **18** in good yield; however, initial attempts to cyclize **18** were frustrated by its ionic reactivity. This led to some interesting discoveries that are presented at the end of this paper. To circumvent this problem we prepared bromide **19**, and it isomerized smoothly to a mixture of stereoisomers **16b** and **17b**

(11) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933.

(12) Compared with an authentic sample prepared by methylation of the anion derived from 2-carbomethoxycyclohexanone.

(13) Compared with an authentic sample: Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guēdin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

(65/35, 74% yield). We were later able to isomerize iodide **18**, and it gave **16c** and **17c** in the same ratio (64% yield). The spectra of all the halides **16a–c** and **17a–c** were very similar, and stereochemistry was assigned accordingly. Bromides **16b** and **17b** were converted to iodides **16c** and **17c**, respectively, by a standard Finkelstein reaction. Treatment of this mixture of **16c** and **17c** (72/28) with DBU (benzene, 130 °C) provided the products of elimination **20c** (from **16c**) and intramolecular alkylation **21** (from **17c**) in a ratio of 75/25. The structure assignment of **21** is tentative because we could not separate it from **20** by liquid chromatography.

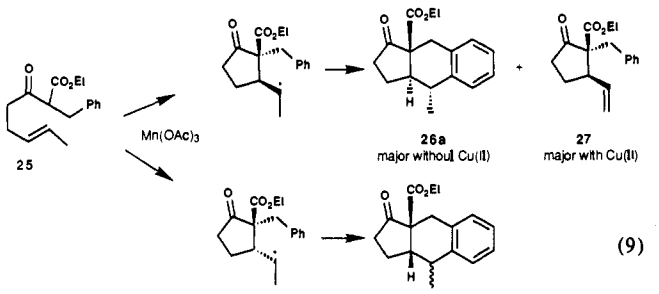
The results of the atom-transfer cyclization mesh nicely with those of the $Mn(OAc)_3$ oxidations (eq 7). Only products derived from sequential 6-endo and 5-exo cyclizations are formed, and the ratio of stereoisomers is the same in all the cases. Interestingly, we isolate only the products derived from tandem cyclizations in both the bromine and iodine atom-transfer experiments. It was already known that the second cyclization was faster than Cu(II) oxidation at 0.1 M ($k = (1–3) \times 10^6$ mol^{-1} s^{-1}),[5a] and our new results indicate that the second radical cyclization is faster than both bromine- and iodine-transfer reactions at 0.3 M. On the basis of known rate constants, we anticipate that a primary radical would abstract iodine from **18** with a rate constant $\geq 1 \times 10^9$ M^{-1} s^{-1} at 50 °C.[14] Unfortunately, there are no known rate constants for the reactions of secondary or tertiary radicals with such iodides; however, these rate constants must still be very high. One cannot escape the conclusion that the second cyclization has a very high rate constant for a radical cyclization to form a bridged ring (probably $>5 \times 10^7$ s^{-1}).

That the regio- and stereochemistry of the *second* radical cyclization is the same in the $Mn(OAc)_3$ oxidations and the atom-transfer reactions is reassuring, but it is not especially informative. It is already generally assumed that free radicals are produced *after* cyclization in the $Mn(OAc)_3$ oxidations. The identical regiochemical result in the *first* cyclization is informative, and is consistent with the intermediacy of a free acetoacetate radical in both reactions. Substrates that produce new stereocenters in the first (rather than the second) cyclization provide more information about the role of Mn in the first cyclization, and eqs 8–10 present such comparisons. $Mn(OAc)_3$ oxidation of **22** (30/1 *E*/*Z* mixture) provided **23** as an 11/1 mixture of stereoisomers in 67% yield (eq 8).[5a] Atom-transfer cyclization of bromide **24**

(8)

provided a mixture of two stereoisomeric bromides (65/35, 75% yield). Alkene **23** was isolated in 40% yield upon treatment of this bromide mixture with DBU at 120 °C. This shows that the diastereomers are bromomethyl rather than methyl epimers. We did not observe any monocyclic products, nor were there products in which the second cyclization was 6-endo, nor was the diastereomer of **23** present in detectable quantities. At this point, we do not know if the failure to detect the diastereomer of **23** in the atom-transfer reaction is due to solvent effects (higher stereoselectivity in benzene than in acetic acid), to analytical technique (authentic samples of this trace product were not available), or to loss of the product in the DBU elimination (for example, by intramolecular alkylation as in eq 7).

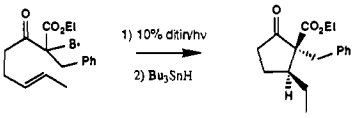
Equations 9 and 10 present the comparison of the last of the hexenyl radical substrates. In addition to the primary goal of comparing regio- and stereoselectivity in the first cyclization, a secondary goal was to learn something about the rate of a second cyclization to an aromatic ring. In the absence of Cu(II), cyclization of **25** with $Mn(OAc)_3$ gave 46% of **26a**, 16% of **26b**, and 9% of **27**.[5b] When Cu(II) was present, only 5% of **26a** and 15% of **26b** were formed, and **27** (38%) was the major product.



(9)

Cyclization gives mainly the cyclic radical with the alkyl and benzyl groups trans.[5b] This radical cyclizes primarily to the trans-fused hydrindan **26a** in the absence of Cu(II) and is oxidized primarily to **27** in the presence of Cu(II). The minor radical cyclizes to the cis-fused hydrindan **26b** in the absence or presence of Cu(II). These results were interpreted to mean that Cu(II) oxidation of the monocyclic radical (at 0.1 M) was faster than cyclization to the aromatic ring to give trans-fused **26a**. Cyclization to give **26b**, which is less strained than **26a**, occurs in the absence or presence of Cu(II). A Friedel–Crafts type cyclization to give **26** was discounted because Mn(III) does not rapidly oxidize secondary radicals to cations.

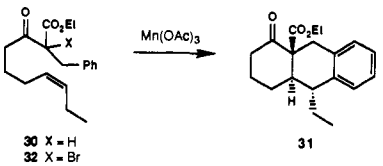
The required bromide **28** was prepared by standard bromination of **25**, and was isomerized in the usual manner. In contrast to most other atom-transfer reactions, the resulting crude reaction mixture was not especially clean. Two major products were evident in the ^{1}H NMR spectra of this mixture, but GC analysis indicated the presence of several minor products. Direct reduction of the crude reaction mixture with tributyltin hydride produced **29** as the single major product in 60% yield. Compound **29** also formed



(10)

on catalytic hydrogenation of **27** (Pd, H_2), thus confirming its structure. We did not attempt to isolate or identify any of the minor products; however, we did determine (NMR, GC) that neither **26a** nor **26b** was present in significant amounts. Once again, the results of the atom-transfer cyclization are generally consistent with the $Mn(OAc)_3$ oxidation. Product **29** has the expected stereo- and regiochemistry. In contrast to the rapid cyclizations to alkenes, the second cyclization to the aromatic ring is now slower than bromine transfer (at 0.3 M).

We selected substrate **30** to initiate studies of substituted heptenyl radicals (eq 11). Oxidation of **30** with $Mn(OAc)_3$ gave tricyclic ketone **31** whether Cu(II) was present or not.[5b] These results indicated that the second cyclization in this substrate was considerably faster than that in eq 9, and we were interested to learn its efficiency relative to bromine transfer. Unfortunately,

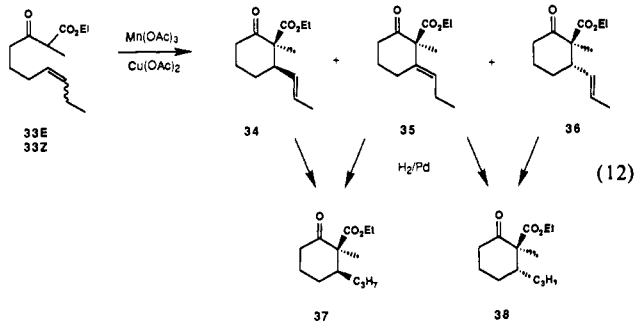


(11)

when bromide **32** was treated under the normal atom-transfer conditions, a very complex mixture of products formed. We could not discern any peaks in the crude ^{1}H NMR spectrum that could be assigned to the expected products, and further characterization was not attempted. At this point, we do not understand why there are problems in the atom-transfer reactions of benzylic acetoacetates **28** and **32**.

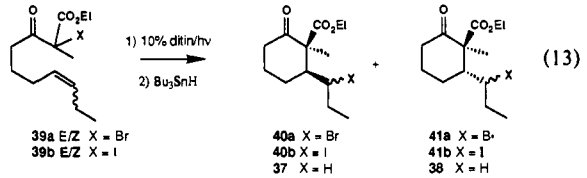
(14) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826.

We next moved to the methyl-substituted acetoacetates (eqs 12 and 13), and these substrates yielded the most interesting and informative results. $Mn(OAc)_3$ cyclizations of **33E** and **33Z** had been shown to give mixtures of products that depended on the geometry of the starting alkene. Cyclization of **33E** gave **34/35/36** in a ratio of 4.5/1/1.[4] In contrast, cyclization of **33Z** gave the same three products in a ratio of 18/4.6/1.[4] Defining the stereoselectivity in these experiments is complicated by the presence of trisubstituted olefin **35**, which could have resulted from either stereoisomer of the initial cyclization product. However, an inspection of the products implies that most of **35** must come from the same radical that leads to **34**.[4,15] Thus, the cyclization of the radical derived from **33E** is moderately stereoselective (~3/1) and that derived from **33Z** is highly stereoselective (~20/1).



(12)

The atom-transfer method is well suited for a direct analysis of stereochemistry. We prepared bromide **39aE**, and upon standard irradiation with ditin, it produced a clean mixture of four stereoisomeric bromides (4.1/1.8/1.4/1) in essentially quantitative yield (eq 13). The two major diastereomers **40a** were isolated

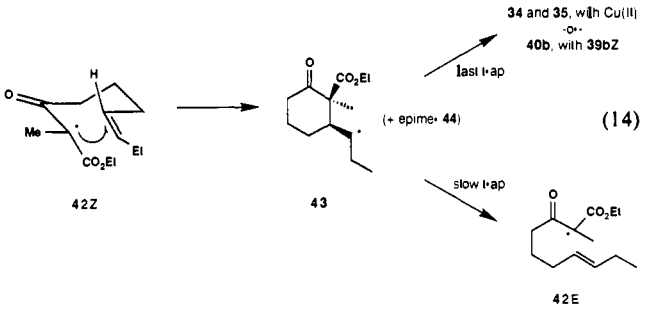


(13)

in pure form free of the two minor isomers **41a**. Tin hydride reduction of this mixture of **40a** produced only **37**, proving that **40a** and **41a** differed in configuration on the ring. Thus, the cis/trans (**40a**/**41a**) ratio in the cyclization of **39a** is 2.4/1, and this compares favorably to the estimated ratio (3/1) from the $Mn(OAc)_3$ cyclization of **33E**. However, unlike the $Mn(OAc)_3$ oxidations, the isomer **39aZ** behaved essentially the same as **39aE**. Upon isomerization, four isomers (two epimers of **40a** and two epimers of **41a**) formed in a ratio of 4.4/2.5/1.3/1. Direct tin hydride reduction of the mixture gave **37** and **38** in a ratio of 2.8/1.

The key to resolving this apparent discrepancy came when we prepared the iodide **39bZ**, and isomerized it according to the standard procedure. In this case, only two diastereomeric iodides formed (not four). Direct tin hydride reduction of this mixture gave only **37** (65% overall yield), demonstrating that these two iodides were epimers of **40b**. The different behaviors of bromide **39aZ** and iodide **39bZ** indicate that radical ring-opening reactions (reverse cyclizations) are important in the case of the bromide (see below). Thus, the kinetic cyclizations of the radicals derived from the *Z*-alkene precursors are indeed highly stereoselective.

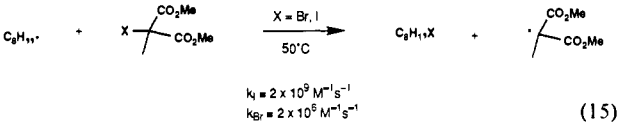
We propose the kinetic scenario outlined in eq 14 to explain these results. Radical **42Z** is formed from all the *Z* olefin precursors (**33Z**, **39aZ**, **39bZ**), and it cyclizes kinetically to give radical **43** with excellent stereoselectivity (≥95/5).[16] The features that dictate this stereochemistry have been previously discussed for the Mn(III) cyclization:[4,5] the enol radical **42Z** adopts a geometry with the ketone and the ester carbonyl groups trans, and cyclization occurs through a chairlike transition state (see **42Z**). The atom-transfer experiments presented above demonstrate that the trans geometry of the enol radical **42** is not imposed in any way by the manganese salts. It is simply the preferred geometry of the enol radical in the transition state, and probably also in the ground state. A trans orientation of the two carbonyls should minimize unfavorable dipolar interactions.



(14)

The fate of radical **43** depends on the efficiency of the radical trap in the reaction. In the presence of stoichiometric quantities of $Cu(OAc)_2$ (an excellent radical trap), **43** is rapidly oxidized to **34** and **35**. When iodide **39bZ** is the precursor, radical **43** is also trapped very efficiently by irreversible iodine transfer (a chain propagation step) to give **40b**. However, bromine transfer is typically about 1000 times slower than iodine transfer,[14] and we postulate that bromide **39aZ** is not a sufficiently good trap for **43**. Instead, **43** suffers ring opening. Although **43** might open to reform **42Z**, we postulate that most of the time it opens to form the more stable isomer **42E**. Radical **42E** then recloses to give **43** and its epimer **44** in a kinetic ratio of about 3/1. These radicals are then trapped by bromine transfer, and the result is that the *E* and *Z* bromide precursors give the same product ratio because the same radical **42E** is formed. We do not know the thermodynamic ratio of isomeric radicals **43** and **44**; however, we doubt very much that radicals **43**/**44** live sufficiently long under these conditions to reach true equilibrium. In effect, the *Z* olefin precursors are exquisitely sensitive probes for reverse radical cyclizations since only one reverse cyclization is needed to transform the product ratio observed for the *Z* olefin into that observed for the *E* olefin.

The results fix the rate for reverse cyclization of **43** to **42E** somewhere between the rate of bromine transfer (from **39a**) and iodine transfer (from **39b**) to **43**. At present, the best we can do is define a rather large window for the rate constant for ring opening of **43**. Equation 15 shows the closest known rate constants for bromine and iodine transfer.[14] We can assume that the



(15)

haloacetoacetates **39a**,**b** are roughly similar in atom-donor capabilities to the halomalonic esters. However, radical **43** is secondary, and all known rate constants have been measured with primary radicals. It is not clear whether secondary radicals will abstract halogen atoms slower (due to reduced exothermicity) or faster (due to favorable polar effects) than primary radicals. We estimate that the reverse cyclization must have a rate constant somewhere in the range of 10^5 to 10^8 s^{-1}. Since Cu(II) also traps the radical before opening, it is more likely that the actual number

(15) Cyclization of **33Z** gives a 4.1/1 mixture of (**34** + **36**)/**35**. Cyclization of **33E** gives much more **36** but gives a 5.5/1 mixture of (**34** + **36**)/**35**. Since the ratios are similar it is likely that each radical gives a ≈4–5/1 mixture of disubstituted/trisubstituted double bonds as has been observed for the parent 1-cyclohexylhexyl radical. (See: Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 1965.) The formation of a 1/1 mixture of **35**/**36** from **33E** and a 4.6/1 mixture from **33Z** indicates that most of the **35** formed from **33Z** comes from the radical precursor to **34** since the radical precursor to **36** must give a ≤1/1 ratio of **35**/**36**. This can account for, at most, 22% of the **35** formed from **33Z**.

(16) (a) It has been considered that such enol radicals may cyclize rapidly on oxygen, but that this cyclization may be reversible, with cyclization ultimately occurring on carbon. Our results rule out this possibility because radicals **42E** and **42Z** would produce the same radical if they cyclized initially on oxygen. (b) See: Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1520.

E = COR, CN, Ph

Figure 1. Ring opening of cyclopentylmethyl radicals.

is near the lower end of this range.

Even if this rate constant is at the lower end of this range, it is surprisingly high. As far as we are aware, no ring openings of cyclohexylmethyl radicals (reverse 6-exo cyclization) are known. Excluding strained cyclopropylmethyl and cyclobutylmethyl radicals, most known radical ring openings to form alkenes are of the type outlined in Figure 1. Ring opening of cyclopentylmethyl radicals to give stabilized radicals was extensively studied by Julia.[17] Typically, two stabilizing groups are present (E = carbonyl, cyano, phenyl), and both are exocyclic substituents. No accurate rate constants for such ring openings are known, but there is no reason to believe that these ring openings are relatively fast. For example, it has been estimated that the rate constant for ring opening to give a malonyl radical (Figure 1, E = CO_2R) is $<10^4$ s^{-1}.[11]

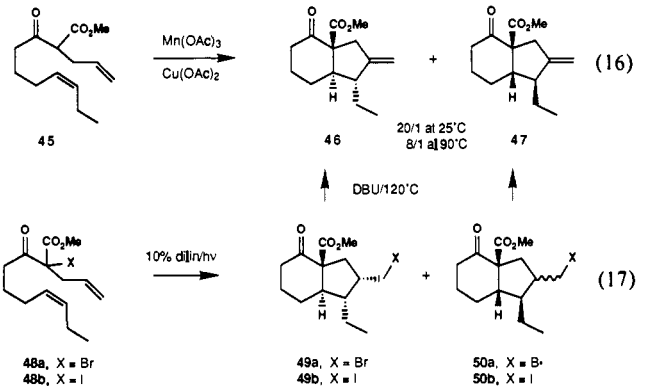
In a more related observation, Clive and Cheshire generated radical i by standard tin hydride reduction and found that it opened with C–O bond cleavage very slowly to give ii (Figure 2).[16] Radical ii is an isomer of an acetoacetate radical (the radical is only conjugated to the ketone), and we can estimate that its rate constant for formation is very slow ($k < 10^4$ s^{-1}).

Although the rapidity of the ring opening of **43** is surprising, it is even more surprising that none of the related 5-exo cyclizations of the lower homologues have yet shown any clear-cut evidence for reversibility. Because of higher ring strain, it is generally expected that ring openings of cyclopentylmethyl radicals (reverse 5-exo cyclizations) will be more rapid than those of cyclohexylmethyl radicals (reverse 6-exo cyclizations).[18] Thus, both 5-exo and 6-exo cyclizations of acetoacetates of this type should be carefully scrutinized for reversibility.

To garner further evidence for reversibility, we investigated the concentration dependence of the **37**/**38** ratio in the reduction of **40b**. The results of initial experiments with tin hydride were disappointing;[19] however, switching to the $Mn(OAc)_3$ oxidations of **33** proved very profitable. Oxidative cyclization of **33Z** with Mn(III), but without Cu(II), afforded a complex mixture of **34**–**38** (eq 12) since the secondary alkyl radicals produced in the cyclization are not oxidized rapidly by Mn(III). Oxidation of the cyclized secondary radical gives **34**–**36**, while competing abstraction of a hydrogen atom gives **37** and **38**. The mixture was most efficiently analyzed by hydrogenation (Pd/H_2), which gave an 8/1 mixture of **37** and **38**. This result contrasts to a 25/1 mixture of **34** and **36** obtained from **33** by oxidation with both Mn(III) and Cu(II). Since it is known that Cu(II) oxidizes radicals 300 times faster than Mn(III),[20] the most likely explanation for this observation is that the cyclization is partially reversible in the absence of Cu(II).

For comparison with atom-transfer cyclizations, we examined the cyclization of **33Z** at higher temperatures. Oxidative cyclization with Mn(III) and Cu(II) at 90 °C gave a 6.3/1 mixture of **34** and **36**. Oxidative cyclization with Mn(III) followed by hydrogenation gave a 2.7/1 mixture of **37** and **38**.[21] The selectivity of the cyclization at 90 °C is also lower in the absence of Cu(II). In both cases, the selectivity of the cyclization is decreased, as expected, at higher temperature.[22] From this example, it is not clear whether this is due entirely to the normal decrease in selectivity with increase in temperature or whether the cyclization is more reversible at higher temperature.

The last pair of comparison substrates is described in eqs 16 and 17. The ratio of tandem cyclization products **46** and **47** produced in the $Mn(OAc)_3$ oxidation of **45** depended on temperature. At 25 °C, the ratio of **46**/**47** was 20/1, but this ratio was reduced to 8/1 at 90 °C. These product ratios are very similar to the ratios obtained in the oxidative cyclization of **33Z** with Mn(III) and Cu(II) at both 25 and 90 °C. Is this variation due to temperature effects in a kinetic cyclization, or does reverse cyclization compete more effectively with the second cyclization at 90 °C than at 25 °C? The monocyclic radical obtained from **33Z** is oxidized by Cu(II), and the monocyclic radical obtained from **45** cyclizes to give a bicyclic system. Since the same ratios of stereoisomers are obtained in both cases, these cyclizations are probably kinetically controlled. This conclusion was confirmed by examination of the atom-transfer cyclization of **48a** and **48b**.



Bromide **48a** was prepared and isomerized at 80 °C to give a 9/1 mixture of stereoisomers **49a** and **50a** in 68% yield (the configuration of one stereocenter of **50** is not assigned). Treatment of this mixture with DBU at 120 °C gave a 10/1 mixture of **46** and **47**. Similarly, iodide **48b** gave a 10/1 mixture of **49b** and **50b** after isomerization, and a 10/1 mixture of **46**/**47** after DBU treatment. When bromide **48a** was isomerized at 5 °C, the ratio of **49a**/**50a** was now >20/1. We know from eq 15 that ring opening of the first-formed cyclic radical is faster than bromine transfer but slower than iodine transfer. That iodide **48b** and bromide **48a** gave the same bicyclic products at 80 °C (with no monocyclic product) tells us that the second cyclization in this system is faster than both bromine and iodine transfer (at 0.3 M). Thus, the second cyclization must be much faster than the reverse of the first cyclization at 80 °C. Taken together, the results indicate that the improved stereoselectivity at 5–25 °C reflects the kinetic temperature dependence of the first radical cyclization.

At present, there are only a few examples where stereoselectivities in radical cyclizations exhibit significant temperature dependences.[22] Since there are good methods to initiate radical

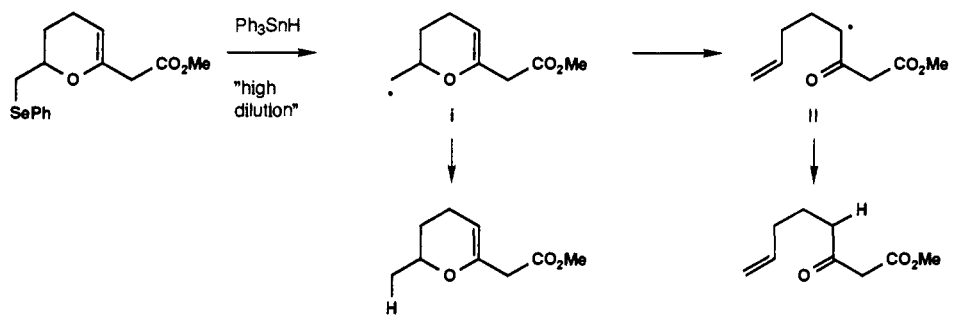


Figure 2. A reverse 6-exo cyclization.

reactions at 25 °C or lower, reduction of temperature is a simple method to increase the stereoselectivity in a radical reaction.

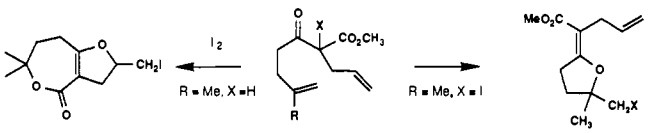
Conclusions

The primary goal of this work was to establish the nature of the reactive intermediate in the manganese(III) oxidations of tertiary acetoacetates and malonates. We can now safely conclude that free radicals such as **6b** are produced in the Mn(III) oxidations because all Mn(III) oxidative cyclizations and atom-transfer cyclizations gave comparable regio- and stereoselectivity. If Mn-complexed radicals such as **5b** are produced, they must dissociate rapidly, before cyclizations occur. We have also learned that the atom-transfer method is highly suitable for conducting cyclization reactions of acetoacetates, and that the primary products formed (halides) are often structurally complementary to those formed in Mn(III) oxidations (alkenes, lactones). Further, the tandem cyclizations to alkenes are so fast that atom transfer cannot compete, and thus the sequences are not interrupted prior to completion.

An unexpected observation in this work was the rapid ring opening of cyclohexylmethyl radical **43**. This opening, a reverse 6-exo cyclization, is considerably faster ($k > 10^5$ s^{-1}) than the sparse literature precedent would lead one to believe, and it points to a need for better understanding of the factors affecting the rates of such ring openings. A practical consequence of this rapid opening is that the radical derived from **33Z** is a very sensitive probe for reversible radical cyclizations; it takes only one ring opening to convert the stereoisomer ratio observed for **33Z** to that observed for **33E**. This stereochemical approach to the detection of reverse radical cyclizations should be general. Finally, we have learned that the stereoselectivity of these radical cyclizations is strongly influenced by temperature. Although this point seems intuitively obvious, it is only recently that temperature effects have been harnessed to insure highly stereoselective radical reactions.

Ionic Reactions of Iodoacetoacetates

As mentioned earlier, the atom-transfer cyclization of iodide **18** was initially complicated by a competing rearrangement. We observed that samples of crude, freshly prepared **18** (which contained about 5% **15**) spontaneously isomerized ($CDCl_3$ or C_6D_6, dark, 25 °C) to tetrahydrofuran **51a**, which could be isolated in yields ranging from 30 to 60% (eq 18). Tin hydride reduction



52 15 R = Me, X = H; 18 R = Me, X = I; 11 R = H, X = I 51a X = I; 51b X = H

(18)

of **51a** cleanly afforded **51b** (90%). We subsequently found that a purer sample of **18** (obtained from a very clean iodination reaction of **15**) was stable when stored at 25 °C in the dark. Photolysis of this sample provided the atom-transfer cyclization products (see eq 7) contaminated with only a trace (<5%) of **51a**. In contrast to the behavior of **15**, the related iodide **11** never exhibited a tendency to isomerize in this manner.

These results suggest that **51a** is formed by an ionic iodoenol etherification reaction. A short series of mechanistic experiments did not shed much light on the nature of the electrophilic iodine species or other requirements for the isomerization. In one experiment, the isomerization of **18** to **51a** appeared to be induced by addition of acetoacetate **15**; however, we could not reproduce this experiment. Addition of methyl acetoacetate or trifluoroacetic acid to **18** did not promote its isomerization. Addition of a catalytic amount of molecular iodine to **18** provided a 1/1 mixture of unreacted **18** and **51a** after 22 h. No further conversion to **51a** was observed up to 48 h, so this may be an equilibrium value. When **15** was treated under standard conditions for iodoenol etherification (1 equiv of I_2, C_6D_6, dark, 25 °C),[23] a completely different behavior was observed; dihydrofuran **52** formed in 85% yield. This compound presumably arises from an iodoenol etherification reaction involving the monosubstituted double bond (rather than the 1,1-disubstituted double bond), followed by HI-promoted lactonization.

While we do not fully understand the details of the conversion of **18** to **51a**, our results certainly suggest that unsaturated haloacetoacetates and related derivatives may have a useful ionic reactivity profile.

Experimental Section

Manganese(III) Cyclizations. General Methods. All reactions were carried out in flame-dried glassware unless otherwise noted. Diethyl ether was distilled from sodium/benzophenone before use. Manganese triacetate dihydrate ($Mn(OAc)_3 \cdot 2H_2O$) was purchased from Aldrich Chemical Co. and was used without further purification. All oxidative free-radical cyclizations were carried out under nitrogen and monitored by TLC or capillary GC for the disappearance of starting material. Nuclear magnetic resonance spectra were recorded on either a Varian EM-390 or a Varian XL-300 spectrometer. All NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal reference. Chemical shifts are reported in parts per million downfield from $(CH_3)_4Si$ (δ). Coupling constants are reported in hertz. IR spectra were recorded on a Perkin-Elmer 683 and are reported in cm^{-1}. Analytical GC was performed on a Perkin-Elmer 8310 fitted with a flame-ionization detector. A 25 m × 0.25 mm fused silica column containing OV-225B was used at a helium flow rate of 25 mL/min. A temperature program starting at 60 °C, increasing to 100 °C at a rate of 5 °C/min, holding at 100 °C for 10 min, increasing to 120 °C at a rate of 5 °C/min, and holding at 120 °C for 1 min was used. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI. Column chromatography was carried out on Baker silica gel deactivated with methanol. Ethyl 2-methyl-3-oxodec-(*Z*)-7-enoate (**33Z**), ethyl 6α-(*E*)-(1-propenyl)-1β-methyl-2-oxocyclohexane-1α-carboxylate (**34**), ethyl 6-(*E*)-propylidene-1β-methyl-2-oxocyclohexane-1α-carboxylate (**35**), and ethyl 6β-(*E*)-(1-propenyl)-1β-methyl-2-oxocyclohexane-1α-carboxylate (**36**) were prepared as described.[4]

Oxidative Free-Radical Cyclization of 7. Reaction of **7** (300 mg, 1.50 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (803 mg, 3.00 mmol), and $Cu(OAc)_2 \cdot H_2O$ (299 mg, 1.50 mmol) in glacial acetic acid (15 mL) at 55 °C for 43 h gave 279 mg of crude product. Flash chromatography of 243 mg (9/1 hexane/EtOAc followed by 5/1 hexane/EtOAc, deactivated silica gel) gave 100 mg of a 2/3/1 mixture of recovered **7**, **9**, and **10** (39%), followed by 124 mg of **8** (48%).

The spectral data for **9** were determined from the mixture: ^{1}H NMR δ 5.30 (t, 1, J = 2.3, =CH_2), 5.27 (t, 1, J = 2.3, =CH_2), 3.74 (s, 3, OCH_3), 2.46 (tt, 2, J = 2.3, 7.3, H4), 2.35 (t, 2, J = 6.7, H2), 1.74 (tt, 2, J = 6.7, 7.3, H3). The diethyl ester has been reported.[24]

The spectral data for **10**: ^{1}H NMR δ 5.67 (br t, 2, J = 2.0, H3 and H4), 3.72 (s, 6, OCH_3), 2.57 (br s, 2, H2), 2.20–2.00 (m, 4, H5 and H6); ^{13}C NMR δ 172.0 (OC=O × 2), 126.1 (CH=), 123.9 (=CH), 52.6 (OCH_3 × 2), 30.5 (C2), 27.5 (C5), 22.3 (C6), C1 was not observed; IR (neat) 3080, 1760, 1737, 1641 cm^{-1}. The spectral data are identical with those previously described.[25]

(17) Julia, M. *Acc. Chem. Res.* **1971**, 386.

(18) For an example, cyclopentyloxy radicals open about 50 times faster than cyclohexyloxy radicals. See: Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674; *J. Am. Chem. Soc.* **1989**, *111*, 230.

(19) Tin hydride reduction of **40b** at high concentration (0.1 M) cleanly produced **37**. Reduction of **40b** at low concentration (0.01 M or 0.001 M) gave a complex mixture of products. However, GC analysis indicated that reduced, opened product **33E** was among the components of this mixture.

(20) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524. Heiba, E. I.; Dessau, R. M. *Ibid.* **1972**, *94*, 2888.

(21) Hydrogenation of an inseparable 4.2/1 mixture of **35** and **36** gives a 3/1 mixture of **37** and **38**. Therefore hydrogenation of **35** must give a 6/1 mixture of **37** and **38**. Alkene **35** is a minor component in the **34–38** mixture. Furthermore, it gives a ratio of **37** to **38** close to that obtained from other sources. Therefore its presence does not perturb the analysis.

(22) For recent examples of temperature effects on stereoselectivity in radical addition and cyclization reactions, see: Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* **1989**, *111*, 6849. Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738 and references therein. Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *J. Am. Chem. Soc.* **1990**, *112*, 6741.

(23) (a) Iqbal, J.; Pandey, A. *Synth. Commun.* **1990**, *20*, 665. (b) Amoniolelli, R.; Bonadies, F.; Scettri, A. *Tetrahedron Lett.* **1988**, *29*, 4987. (c) Delair, T.; Doutheau, A.; Gorè, J. *Bull. Soc. Chim. Fr.* **1988**, 125. (d) For related selenoenol etherifications: Ley, S. V. *Chem. Ind.* **1985**, *4*, 101.

(24) Citterio, A.; Ceraii, A.; Sebastiano, R.; Finzi, C.; Santi, R. *Tetrahedron Lett.* **1989**, *30*, 1289.

The spectral data for **8**: ^{1}H NMR δ 4.57 (dd, 1, J = 7.8, 9.9, H4 exo), 4.08 (dd, 1, J = 2.6, 9.9, H4 endo), 3.78 (s, 3, OCH_3), 3.11 (dddd, 1, J = 2.6, 4.2, 7.8, 8.4, H3a), 2.39 (ddd, 1, J = 7.2, 9.5, 13.6, H1 endo), 2.27 (ddd, 1, J = 4.3, 6.8, 13.6, H1 exo), 2.14–2.00 (m, 1), 1.89–1.78 (m, 1), 1.73–1.56 (m, 2). The spectral data for **8** are identical with those previously described.[10]

Oxidative Free-Radical Cyclization of 25 with $Mn(OAc)_3\cdot 2H_2O$ and $Cu(OAc)_2\cdot H_2O$. Reaction of **25** (125 mg, 0.46 mmol, containing some of the Z isomer) as previously described[5b] with $Mn(OAc)_3\cdot 2H_2O$ (244 mg, 0.91 mmol) and $Cu(OAc)_2\cdot H_2O$ (91 mg, 0.46 mmol) in glacial acetic acid (5 mL) at room temperature for 14 h followed by normal workup gave 133 mg of crude product. Flash chromatography of 113 mg (20/1 hexane/ethyl acetate, deactivated silica gel) gave 40 mg of **27** (38%), followed by 22 mg (21%) of an inseparable 1/2/1 mixture of **26a** and the two cis-fused diastereomers **26b**.

The spectral data for **27**: ^{1}H NMR δ 7.29–7.20 (m, 3, ϕ-H), 7.13–7.08 (m, 1, ϕ-H), 7.11 (dd, 1, J = 1.5, 7.8, ϕ-H), 5.80 (ddd, 1, J = 7.6, 10.1, 17.4, CH=), 5.19 (ddd, 1, J = 1.3, 1.7, 10.1, =CH_2), 5.17 (dt, 1, J = 17.4, 1.5, =CH_2), 4.21 (dq, 1, J = 7.1, 10.7, OCH_2), 4.13 (dq, 1, J = 7.1, 10.7, OCH_2), 3.43 (d, 1, J = 14.1, benzylic CH_2), 3.07 (d, 1, J = 14.1), 2.79 (br ddd, 1, J = 6.5, 7.6, 11.8, H5a), 2.49 (ddd, 1, J = 5.2, 7.6, 18.9, H3), 2.13–1.98 (m, 1), 1.92–1.72 (m, 2), 1.26 (t, 3, J = 7.1, OCH_2CH_3); ^{13}C NMR δ 170.1 (OC=O), 136.4 (ϕ), 135.9 (CH=), 130.9 (2, ϕ), 128.4 (2, ϕ), 126.8 (ϕ), 117.4 (=CH_2), 64.5 (C1), 61.3 (OCH_2), 45.7 (C5), 39.0 (benzylic CH_2), 36.2 (C3), 25.4 (C4), 14.2 (OCH_2CH_3), C2 was not observed. H5a was assigned by using a single-frequency decoupling experiment. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.05; H, 7.53.

The spectral data for **26a** were determined from the mixture: ^{1}H NMR δ 7.33–7.10 (m, 4, ϕ-H), 4.03 (q, 2, J = 7.0, OCH_2), 3.45 (d, 1, J = 16.0, benzylic CH_2), 2.98 (tt, 1, J = 6.5, 6.5), 2.38 (dd, 1, J = 8.5, 9.4, H3), 2.42–2.12 (m, 4), 1.95 (dt, 1, J = 6.9, 11.5, H4 axial), 1.40 (d, 3, J = 6.6, benzylic CH_3), 1.08 (t, 3, J = 7.2, OCH_2CH_3); ^{13}C NMR δ 214.0 (C2), 169.1 (OC=O), 140.4 (ϕ), 134.8 (ϕ), 129.6 (ϕ), 126.8 (ϕ), 126.1 (ϕ), 126.1 (ϕ), 61.1 (OCH_2), 59.2 (C1), 51.2 (ring fusion H), 37.8 (benzylic CH_2), 35.7 (benzylic CH), 35.1 (C3), 23.7 (C4), 18.2 (benzylic CH_3), 13.9 (OCH_2CH_3). ^{13}C multiplicities were determined by using an APT experiment.

The spectral data for one diastereomer of **26b** were determined from the mixture: ^{1}H NMR δ 7.33–7.10 (m, 4, ϕ-H), 4.12 (q, 2, J = 6.9, OCH_2), 3.47 (d, 1, J = 15.7, benzylic CH_2), 3.08–1.25 (m, 7), 1.34 (d, 3, J = 7.1, benzylic CH_3), 1.21 (t, 3, J = 6.9, OCH_2CH_3); ^{13}C NMR δ 214.6 (C2), 171.8 (OC=O), 140.6 (ϕ), 128.5 (ϕ), 126.7 (ϕ), 126.6 (ϕ), 126.4 (ϕ), 126.1 (ϕ), 61.6 (-OCH_2), 47.6 (ring fusion H), 38.8 (benzylic CH), 38.2 (benzylic CH_2), 31.2 (C3), 26.5 (C4), 19.2 (benzylic CH_3), 13.9 (OCH_2CH_3). C1 was not observed. ^{13}C multiplicities were determined by using an APT experiment.

The spectral data for the other diastereomer of **26b** were determined from the mixture: ^{1}H NMR δ 7.33–7.10 (m, 4, ϕ-H), 4.21 (q, 2, J = 7.2, -OCH_2), 3.17 (d, 1, J = 15.4, benzylic CH_2), 3.08–1.25 (m, 7), 1.43 (d, 3, J = 7.1, benzylic CH_3), 1.28 (t, 3, J = 7.2, OCH_2CH_3); ^{13}C NMR δ 169.1 (OC=O), 140.6 (ϕ), 134.2 (ϕ), 133.5 (ϕ), 126.3 (ϕ), 61.7 (OCH_2), 38.3 (benzylic CH_2), 35.0 (C3), 32.4 (C4), 20.6 (benzylic CH_3), 14.3 (-OCH_2CH_3), 5 carbons were not observed.

Oxidative Free-Radical Cyclization of 25 with $Mn(OAc)_3\cdot 2H_2O$ Only. Compounds **27**, **26a**, and the two minor diastereomers of **26b** were prepared as described previously from $Mn(OAc)_3\cdot 2H_2O$ (244 mg, 0.91 mmol) and **25** (125 mg, 0.46 mmol) in glacial acetic acid (5 mL). The reaction mixture was stirred at room temperature for 14 h. Normal workup gave 131 mg of crude product. Flash chromatography of 113 mg (20/1 hexane/ethyl acetate, deactivated silica gel) gave 10 mg (9%) of **27**, followed by 78 mg (62%) of an inseparable 10/2.6/1 mixture of **26a** and two minor diastereomers of **26b**. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.65; H, 7.34.

Hydrogenation of Ethyl 1α-Benzyl-5β-ethenyl-2-oxocyclopentane-1β-carboxylate (27). Ethyl 1α-benzyl-5β-ethyl-2-oxocyclopentane-1β-carboxylate (**29**) was prepared as described for compound **37** from 10% palladium on carbon (~0.02 g) and **27** (0.020 g, 0.07 mmol) in ether (5 mL). The mixture was stirred under a hydrogen atmosphere for 1 h. Filtration and removal of the solvent in vacuo gave 0.021 g of **29**: ^{1}H NMR δ 7.28–7.16 (m, 3, ϕ), 7.08–7.04 (m, 1, ϕ), 7.07 (dd, 1, J = 2.0, 8.0, ϕ), 4.19 (dq, 1, J = 10.8, 7.4, OCH_2), 4.18 (dq, 1, J = 10.8, 7.4, OCH_2), 3.39 (d, 1, J = 13.9, benzylic CH_2), 3.09 (d, 1, J = 13.9, benzylic CH_2), 2.46 (ddd, 1, J = 4.2, 7.0, 17.7, H3a), 2.03–1.92 (m, 2), 1.80–1.58 (m, 3), 1.26 (t, 3, J = 7.4, OCH_2CH_3), 1.24–1.13 (m, 1), 0.94 (t, 3, J = 7.6, CH_3); ^{13}C NMR δ 170.7 (OCO), 136.8 (ϕ), 130.8 (2, ϕ), 128.3 (2, ϕ), 126.6 (ϕ), 64.4 (C1), 61.1 (OCH_2), 43.7 (C3), 39.2 (benzylic CH_2), 36.3 (C3), 25.6 (C4), 23.7 (CH_2), 14.2 (OCH_2CH_3), 12.1 (CH_3), C2 was not observed; IR (neat) 1740, 1715 cm^{-1}.

Hydrogenation of Ethyl 6α-(E)-(1-Propenyl)-1β-methyl-2-oxocyclohexane-1α-carboxylate (34). Preparation of Ethyl 6α-Propyl-1β-methyl-2-oxocyclohexane-1α-carboxylate (37). A mixture of 10% palladium on carbon (~0.02 g) in ether (5 mL) was charged with hydrogen for 5 min. Alkene **34** (0.008 g, 0.04 mmol) was added as a solution in ether (1 mL). The system was charged with hydrogen for an additional 2 min, fitted with a hydrogen reservoir, and stirred overnight. The mixture was filtered through Celite and the solvent removed in vacuo to give 0.009 g of **37**: ^{1}H NMR δ 4.14 (q, 2, J = 7.1, OCH_2), 2.72 (ddd, 1, J = 6.4, 13.5, 13.6, H3α), 2.44 (dddd, 1, J = 1.4, 2.8, 4.6, 13.6, H3β), 2.05 (ddddd, 1, J = 3.0, 3.0, 3.0, 6.0, 12.0), 1.87 (br dd, 1, J = 3.1, 13.0), 1.76 (br ddd, 1, J = 3.7, 12.1, 12.5), 1.63 (dt, 1, J = 12.5, 3.1), 1.58–1.37 (m, 4), 1.41 (br ddd, 1, J = 2.4, 4.7, 8.6), 1.34 (s, 3, C1–CH_3), 1.26 (t, 3, J = 7.1, OCH_2CH_3), 0.91 (t, 3, J = 7.1, CH_2CH_3); ^{13}C NMR δ 208.5 (C2), 171.4 (OC=O), 61.0 (C1), 60.9 (OCH_2), 48.9 (C6), 40.0 (C3), 33.2 (C4), 27.0 (C5), 25.4 (CH_2), 21.7 (CH_2), 18.8 (C1–CH_3), 14.1 (OCH_2CH_3), 14.1 (CH_3); IR (neat) 1748, 1720 cm^{-1}; t_R = 17.9. An APT experiment was used to determine ^{13}C multiplicities.

Hydrogenation of Ethyl 6-(E)-Propylidene-1β-methyl-2-oxocyclohexane-1α-carboxylate (35) and Ethyl 6β-(E)-(1-Propenyl)-1β-methyl-2-oxocyclohexane-1α-carboxylate (36). Preparation of Ethyl 6α-Propyl-1β-methyl-2-oxocyclohexane-1α-carboxylate (37) and Ethyl 6β-Propyl-1β-methyl-2-oxocyclohexane-1α-carboxylate (38). Compounds **37** and **38** were prepared as described previously for compound **37** from 10% palladium on carbon (~0.02 g) with an inseparable 4.2/1 mixture of **35** and **36** (0.033 g, 0.15 mmol) in ether (5 mL). The mixture was stirred under a hydrogen atmosphere for 2 h. Filtration and removal of the solvent in vacuo gave 0.029 g of a 3/1 mixture of **37** and **38**.

The spectral data for **38** were determined from the mixture: ^{1}H NMR δ 4.23 (dq, 1, J = 10.0, 7.1, OCH_2), 4.22 (dq, 1, J = 10.0, 7.1, OCH_2), 2.49–2.39 (m, 1), 1.98–1.10 (m, 10), 1.28 (s, 3, C1–CH_3), 1.27 (t, 3, J = 7.1, OCH_2CH_3), 0.89 (t, 3, J = 7.0, CH_2CH_3); ^{13}C NMR δ 62.1 (C1), 61.0 (OCH_2), 42.9 (C6), 38.5 (C3), 31.8 (C4), 25.3 (C5), 23.7 (CH_2), 20.6 (CH_2), 15.9 (C1–CH_3), 14.1 (OCH_2CH_3), 14.1 (CH_3); IR (neat) 1742, 1717 cm^{-1}; t_R = 19.7.

Oxidative Free-Radical Cyclizations of Ethyl 2-Methyl-3-oxodec-(Z)-7-enoate (33Z). All of the cyclizations of **33Z** listed below were run as described previously.[4,5] Reactions run with $Mn(OAc)_3\cdot 2H_2O$ without Cu(II) gave mixtures of saturated (**37**, **38**) and unsaturated (**34**–**36**) products. The crude reaction mixtures in entries 2 and 4 were hydrogenated by using the procedure described above. Crude reaction mixtures were analyzed by capillary GC by using the methods described above.

entry	conditions	ratio 34/36/35	ratio 37/38
1	2 equiv of $Mn(OAc)_3\cdot 2H_2O$ 1 equiv of $Cu(OAc)_2\cdot H_2O$ AcOH, 25 °C, 17 h	25/1/4.2	
2	2 equiv of $Mn(OAc)_3\cdot 2H_2O$ AcOH, 25 °C, 12 h		8/1
3	2 equiv of $Mn(OAc)_3\cdot 2H_2O$ 1 equiv of $Cu(OAc)_2\cdot H_2O$ AcOH, 90 °C, 5 min	6.3/1/1.5	
4	2 equiv of $Mn(OAc)_3\cdot 2H_2O$ AcOH, 90 °C, 5 min		2.7/1

Methyl 2-(2-Propenyl)-3-oxodec-(Z)-7-enoate (45). This was prepared as described previously[5] for the analogue that has methyl group rather than an ethyl group on the double bond from NaH (0.337 g of a 60% dispersion in mineral oil, 8.40 mmol), methyl 2-allylacetoacetate (1.312 g, 8.40 mmol), n-butyllithium (2.5 M in hexanes, 3.36 mL, 8.40 mmol), and 1-bromo-(Z)-3-hexene (0.458 g, 2.8 mmol). The reaction gave 1.446 g of crude product. Purification of 1.426 g by flash chromatography (silica gel, 25/1 hexane/ethyl acetate) gave 0.373 g (57%) of **45**: ^{1}H NMR δ 5.73 (ddt, 1, J = 10.2, 17.0, 7.0), 5.40 (dtt, 1, J = 10.8, 1.4, 7.1), 5.26 (dtt, 1, J = 10.8, 1.4, 7.1), 5.09 (ddd, 1, J = 1.2, 3.0, 17.0), 5.04 (ddd, 1, J = 1.2, 2.7, 10.2), 3.72 (s, 3), 3.54 (t, 1, J = 7.7), 2.62–2.42 (m, 4), 2.02 (m, 4), 1.63 (tt, 2, J = 7.1, 7.4), 0.95 (t, 3, J = 7.4); ^{13}C NMR 204.5, 169.7, 134.2, 132.7, 127.8, 117.4, 58.3, 52.3, 41.5, 32.2, 26.1, 23.3, 20.5, 14.3; IR (neat) 3079, 2955, 2925, 2860, 1740, 1715, 1640 cm^{-1}.

Methyl (1α,3aβ,7aα)-1-Ethyloctahydro-2-methylene-4-oxo-3aH-indene-3a-carboxylate (46) and Methyl (1β,3aβ,7aβ)-1-Ethyloctahydro-2-methylene-4-oxo-3aH-indene-3a-carboxylate (47). Compounds **46** and **47** were prepared as described previously for the analogue that has a methyl group rather than an ethyl group on the double bond[5] from $Mn(OAc)_3\cdot 2H_2O$ (777.5 mg, 2.90 mmol), $Cu(OAc)_2\cdot 2H_2O$ (288.6 mg, 1.40 mmol), and **45** (344.4 mg, 1.40 mmol) in glacial acetic acid (17 mL). The reaction mixture was stirred at room temperature for 13.5 h. Normal workup gave 315.8 mg (96%) of a yellow oil. Purification of

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0.294 g by flash chromatography (Baker silica gel, 10% w/w water, deactivated with methanol, 20/1 hexane/ethyl acetate) gave 0.221 g (72%) of a 25/1 mixture of **46** and **47** as a colorless oil.

The spectral data for **46** were determined from the mixture: ^{1}H NMR δ 5.02 (m, 1, =CH$_2$), 4.91 (m, 1, =CH$_2$), 3.69 (s, 3, OCH$_3$), 2.92 (m, 1, H1β), 2.83 (dddd, 1, J = 3.3, 3.3, 3.3, 16.3, H3α), 2.54 (ddd, 1, J = 1.2, 2.2, 16.6, H3β), 2.48 (ddd, 1, J = 7.0, 12.0, 14.0, C5β), 2.42 (ddd, 1, J = 3.0, 6.0, 14.0, C5α), 2.09 (m, 1, H6β), 1.95 (m, 1, H7β), 1.87 (m, 1, H7α), 1.80–1.55 (m, 3, H6α and CH$_2$), 1.59 (ddd, 1, J = 3.5, 11.5, 11.7, H7aα) 0.89 (t, 3, J = 7.4, CH$_3$); ^{13}C NMR 205.8 (C4), 171.5 (OC=O), 150.2 (C2), 107.7 (=CH$_2$), 65.4 (C3a), 55.0 (C7a), 52.1 (OCH$_3$), 45.8 (C1), 39.9 (C3), 38.0 (C5), 27.1 (C6), 24.2 (CH$_2$ or C7) 23.9 (C7 or CH$_2$), 10.0 (CH$_3$); IR (neat) 3075, 1724, 1718, 1657 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 71.14; H, 8.50.

The structural assignment of compound **46** was based on the following evidence. Decoupling of the methyl triplet at 0.89 gives a doublet at 1.62 (J = 4.1). The collapse of this multiplet to a doublet makes the proton on C7a clearly visible. The ramifications of this are discussed for compound **52** in ref 5. The assignments of the ^{13}C NMR methine (55.0, 45.8) and methyl (52.1, 10.0) resonances are based on an APT experiment.

The partial spectral data for **47** were determined from the mixture: ^{1}H NMR δ 4.99 (br s, 1, =CH$_2$), 4.83 (br s, 1, =CH$_2$), 3.73 (s, 3, OCH$_3$); ^{13}C NMR δ 107.0, 52.1, 49.7, 45.1, 40.3, 38.6, 38.0, 24.3, 10.1, 5 carbons were not observed.

Oxidative Free-Radical Cyclization of 45 at 90 °C. Mn(OAc)$_3$·2H$_2$O (344 mg, 1.25 mmol), Cu(OAc)$_2$·2H$_2$O (125 mg, 0.62 mmol), and **45** (150 mg, 0.62 mmol) in glacial acetic acid (6 mL) were stirred at 90 °C for 5 min. Normal workup gave 147 mg of an 8/1 mixture of **45** and **47**.

Atom-Transfer Cyclizations. General Methods. Proton nuclear magnetic resonance spectra were recorded on either a Bruker AC-300 300 MHz or a Bruker AM-500 500 MHz spectrometer, and all chemical shifts are reported in parts per million (ppm) relative to residual CHCl$_3$ (7.24 ppm) or residual C$_6$H$_6$ (7.20 ppm). Carbon nuclear magnetic resonance spectra were recorded on a Bruker AM-500 spectrometer at 125 MHz, and all chemical shifts are reported relative to residual CHCl$_3$ (77.09 ppm). Infrared spectra were recorded on either a Mattson Cygnus 100 or IBM IR/32 FT-IR spectrometer. Mass spectra (high resolution) were run on a Varian Match-5 DF spectrometer.

Benzene (PhH) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone. All other reagents were used as received. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed silica gel plates (Merck 60F-254), and flash chromatography was performed on Merck 60 230–400-mesh silica gel. All reactions were carried out in flame-dried flasks under a nitrogen atmosphere with positive pressure maintained throughout, unless otherwise noted.

General Procedure for Halogenation of δ-Alkenyl-β-keto Esters. Preparation of Methyl 2-Bromo-6-methyl-3-oxo-2-(2-propenyl)hept-6-enoate (19). Sodium hydride (NaH, 60% dispersion in oil, 30.2 mg, 0.754 mmol) in a 10-mL conical flask was washed with hexane (3 × 1 mL), and THF (2 mL) was added. To the stirred suspension was added dropwise via cannula a solution of methyl 6-methyl-3-oxo-2-(2-propenyl)hex-6-enoate (**15**, 74.1 mg, 0.353 mmol) in THF (2 mL). The heterogeneous mixture was stirred for 2 h, and the excess NaH was allowed to settle. The enolate solution was transferred to a dry round-bottom flask via cannula and cooled to −78 °C. A solution of *N*-bromosuccinimide (NBS, 61.7 mg, 0.346 mmol) in THF (2 mL) was added dropwise via cannula and the mixture was stirred for 10 min. A white precipitate (sodium succinimide) formed immediately upon addition of the NBS solution. The reaction mixture was diluted with ether (30 mL) and washed with water (2 × 15 mL) and brine (15 mL), and the organic phase was dried (MgSO$_4$). Filtration and solvent removal afforded **19** (98.0 mg, 96%) as a clear, colorless oil: ^{1}H NMR (300 MHz, benzene-d_6) δ 5.94–5.80 (m, 1 H), 5.02 (m, 2 H), 4.75 (br s, 2 H), 3.21 (s, 3 H), 3.11 (dd, J = 14.5, 7.0 Hz, 1 H), 3.04 (dd, J = 14.5, 7.0 Hz, 1 H), 2.95–2.76 (m, 2 H), 2.37 (t, J = 7.5 Hz, 2 H), 1.57 (s, 3 H); IR (thin film) 2957, 1734, 1653, 1437, 1232 cm^{-1}; HRMS calcd for $C_{11}H_{14}BrO_2$ (M − OCH$_3$) m/e 257.0177, obsd m/e 257.0178; LRMS m/e 257 (M − OCH$_3$), 209, 192, 177.

Methyl 2-Iodo-2-methyl-3-oxohept-6-enoate (11). Methyl 2-methyl-3-oxohept-6-enoate (100 mg, 0.59 mmol) was treated sequentially with NaH (50% dispersion in oil, 56.5 mg, 0.59 mmol) and NIS (132 mg, 0.59 mmol). The crude iodide was purified by flash chromatography (10% EtOAc/hexanes, silica gel) to give 113 mg (56%) of **11** as a yellow oil: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.80 (m, 1 H), 5.07 (dd, J = 17, 2 Hz, 1 H), 5.01 (dd, J = 10, 1 Hz, 1 H), 3.81 (s, 3 H), 3.01 (dt, J = 17, 7 Hz, 1 H), 2.88 (dt, J = 17, 7 Hz, 1 H), 2.41 (bdt, J = 7, 7 Hz, 2 H), 2.19 (s, 3 H); IR (CDCl$_3$) 3155, 3081, 2983, 2955, 1721, 1446, 1377, 1259, 1260, 1117 cm^{-1}; LRMS m/e 296, 254, 214, 182, 169, 127, 83, 55.

Methyl 2-Bromo-6-methyl-3-oxo-2-(2-propenyl)oct-6(*E*)-enoate (24). Methyl 6-methyl-3-oxo-2-(2-propenyl)oct-6-enoate (**22**), (145 mg, 0.65 mmol) was treated with NaH (60% dispersion, 34.3 mg, 0.74 mmol) and NBS (123 mg, 0.68 mmol) to afford **24** (181 mg, 92%) as a clear, colorless oil: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.92 (m, 1 H), 5.29 (br q, J = 6.3 Hz, 1 H), 5.06 (m, 2 H), 3.27 (s, 3 H), 3.16 (dd, J = 14.2, 6.6 Hz, 1 H), 3.09 (dd, J = 14.2, 6.7 Hz, 1 H), 3.00–2.77 (m, 2 H), 2.46 (t, J = 7.6 Hz, 2 H), 1.54 (d, J = 6.3 Hz, 3 H), 1.51 (s, 3 H); IR (neat) 2981, 2918, 1725, 1700, 1696, 1685, cm^{-1}; HRMS calcd for $C_{13}H_{19}O_3$ (M − Br) m/e 223, 1334, obsd m/e 223, 1334; LRMS m/e 191, 163, 141, 111.

Ethyl 2-Benzyl-2-bromo-3-oxooct-6(*E*)-enoate (28). Ethyl 2-benzyl-3-oxooct-6(*E*)-enoate (**25**, 195.6 mg, 0.713 mmol) was treated sequentially with NaH (60% dispersion in oil, 56.4 mg, 1.41 mmol) and NBS (126.0 mg, 0.708 mmol) to afford **28** (242.6 mg, 96%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.27–7.21 (m, 2 H), 7.19–7.15 (m, 3 H), 5.47–5.28 (m, 2 H), 4.24–4.13 (m, 2 H), 3.59 (d, J = 14.6 Hz, 1 H), 3.52 (d, J = 14.6 Hz, 1 H), 2.70–2.55 (m, 2 H), 2.30–2.21 (m, 2 H), 1.60 (d, J = 5.9 Hz, 3 H), 1.21 (t, J = 6.1 Hz, 3 H); IR (thin film) 3030, 2962, 2935, 1741, 1452, 1236, 1180, 964, 696 cm^{-1}; HRMS calcd for $C_{17}H_{21}O_3$ (M − Br) m/e 273.1491, obsd m/e 273.1491; LRMS m/e 273 (M − Br), 227, 177, 131, 91.

Ethyl 2-Benzyl-2-bromo-3-oxodec-7(*Z*)-enoate (32). Ethyl 2-benzyl-3-oxodec-7(*Z*)-enoate (**30**, 157.3 mg, 0.520 mmol) was treated sequentially with NaH (60% dispersion in oil, 46.3 mg, 1.15 mmol) and NBS (95.3 mg, 0.535 mmol) to afford **32** (200.0 mg, 100%) as a clear, colorless oil: ^{1}H NMR (500 MHz, benzene-d_6) δ 7.30–7.20 (m, 2 H), 7.15–7.04 (m, 3 H), 5.42 (dt, J = 10.6, 7.2 Hz, 1 H), 5.28 (dt, J = 10.6, 7.3 Hz, 1 H), 3.90–3.81 (m, 2 H), 3.78, (d, J = 14.5 Hz, 1 H), 3.73 (d, J = 14.5 Hz, 1 H), 2.70–2.56 (m, 2 H), 1.99–1.92 (m, 4 H), 1.78–1.66 (m, 2 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.81 (t, J = 7.0 Hz, 3 H); IR (thin film) 2968, 1745, 1718, 1435, 1246, 692 cm^{-1}; HRMS calcd for $C_{19}H_{25}O_3$ (M − Br) m/e 301.1804, obsd m/e 301.1804; LRMS m/e 301 (M − Br), 255, 173, 125, 91.

Ethyl 2-Bromo-2-methyl-3-oxodec-7(*Z*)-enoate (39aZ). Ethyl 2-methyl-3-oxodec-7(*Z*)-enoate (**33Z**, 50.4 mg, 0.223 mmol) was treated sequentially with NaH (60% dispersion in oil, 31.3 mg, 0.779 mmol) and NBS (43.1 mg, 0.242 mmol) to afford **39aZ** (38.5 mg, 57%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.39 (dt, J = 10.9, 7.0 Hz, 1 H), 5.26 (dt, J = 10.9, 7.1 Hz, 1 H), 4.25 (q, J = 7.0 Hz, 2 H), 2.82 (dt, J = 17.4, 7.5 Hz, 1 H), 2.66 (dt, J = 17.4, 7.2 Hz, 1 H), 2.08–1.95 (m, 4 H), 1.96 (s, 3 H), 1.72–1.63 (m, 2 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.93 (t, J = 7.4 Hz, 3 H); IR (thin film) 3030, 2962, 2935, 1741, 1452, 1236, 1180, 964, 696 cm^{-1}; HRMS calcd for $C_{13}H_{21}O_3$ (M − Br) m/e 225.1522, obsd m/e 225.1522; LRMS m/e 225 (M − Br), 179, 151, 125.

Ethyl 2-Iodo-2-methyl-3-oxodec-7(*Z*)-enoate (39bZ). Ethyl 2-methyl-3-oxodec-7(*Z*)-enoate (**33Z**, 74.0 mg, 0.327 mmol) was treated sequentially with NaH (60% dispersion in oil, 30.3 mg, 0.759 mmol) and NIS (75.3 mg, 0.334 mmol) to afford **39bZ** (100.8 mg, 87%) as a clear, pale yellow oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.43 (dt, J = 10.6, 7.1 Hz, 1 H), 5.31 (dt, J = 10.6, 7.2 Hz, 1 H), 3.87 (q, J = 7.1 Hz, 2 H), 2.86 (dt, J = 17.0, 7.5 Hz, 1 H), 2.70 (dt, J = 17.0, 7.2 Hz, 1 H), 2.13 (s, 3 H), 2.03–1.93 (m, 4 H), 1.80–1.70 (m, 2 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.86 (t, J = 7.1 Hz, 3 H).

Ethyl 2-Bromo-2-methyl-3-oxodec-7(*E*)-enoate (39aE). Ethyl 2-methyl-3-oxodec-7(*E*)-enoate (**33E**, 56.2 mg, 0.248 mmol) was treated sequentially with NaH (60% dispersion in oil, 22.9 mg, 0.573 mmol) and NBS (44.1 mg, 0.250 mmol) to afford **39aE** (60.1 mg, 80%) as a clear, colorless oil: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.45 (dt, J = 15.5, 5.9 Hz, 1 H), 5.32 (dt, J = 15.5, 6.3 Hz, 1 H), 4.25 (q, J = 7.0 Hz, 2 H), 2.80 (dt, J = 17.2, 7.2 Hz, 1 H), 2.65 (dt, J = 17.2, 6.8 Hz, 1 H), 2.00–1.94 (m, 4 H), 1.95 (s, 3 H), 1.71–1.65 (m, 2 H), 1.27 (t, J = 7.0 Hz, 3 H), 0.94 (t, J = 7.2 Hz, 3 H); IR (thin film) 2963, 2874, 1726, 1684, 1446, 1113, 1074 cm^{-1}; HRMS calcd for $C_{13}H_{21}O_3$ (M − Br) m/e 225.1493, obsd m/e 225.1493; LRMS m/e 225 (M − Br), 179, 144, 125, 97.

Methyl 2-Bromo-3-oxo-2-(2-propenyl)dec-7(*Z*)-enoate (48a). Methyl 3-oxo-2-(2-propenyl)dec-7(*Z*)-enoate (**45**, 107.6 mg, 0.452 mmol) was treated sequentially with NaH (60% dispersion in oil, 45.5 mg, 1.14 mmol) and NBS (81.1 mg, 0.455 mmol) to afford **48a** (143.0 mg, 100%) as a clear, colorless oil: ^{1}H NMR (300 MHz, benzene-d_6) δ 5.95–5.81 (m, 1 H), 5.44 (dt, J = 10.6, 7.4 Hz, 1 H), 5.31 (dt, J = 10.6, 7.1 Hz, 1 H), 5.02 (m, 2 H), 3.24 (s, 3 H), 3.12 (dd, J = 14.8, 6.9 Hz, 1 H), 3.07 (dd, J = 14.8, 7.7 Hz, 1 H), 2.79–2.54 (m, 2 H), 2.04–1.94 (m, 4 H), 1.77–1.68 (m, 2 H), 0.93 (t, J = 7.5 Hz, 3 H); IR (thin film) 2961, 1724, 1684, 1653, 1437, 1232, 1128, 925 cm^{-1}; HRMS calcd for $C_{19}H_{21}O_3$ (M − Br) m/e 237.1490, obsd m/e 237.1490; LRMS m/e 237 (M − Br), 205, 125, 107, 97.

Methyl 2-Iodo-3-oxo-2-(2-propenyl)dec-7(*Z*)-enoate (48b). Methyl 3-oxo-2-(2-propenyl)dec-7(*Z*)-enoate (**45**, 88.5 mg, 0.372 mmol) was

treated sequentially with NaH (60% dispersion in oil, 32.0 mg, 0.755 mmol) and NIS (86.2 mg, 0.383 mmol) to afford **48b** (134.2 mg, 99%) as a clear, pale yellow oil: ^{1}H NMR (300 MHz, benzene-d_6) δ 5.91–5.78 (m, 1 H), 5.44 (dt, J = 10.7, 6.8 Hz, 1 H), 5.33 (dt, J = 10.7, 7.1 Hz, 1 H), 5.04 (m, 2 H), 3.23 (s, 3 H), 3.12 (dd, J = 14.7, 6.4 Hz, 1 H), 3.03 (dd, J = 14.7, 7.4 Hz, 1 H), 2.85 (dt, J = 17.1, 7.3 Hz, 1 H), 2.67 (dt, J = 17.1, 7.2 Hz, 1 H), 2.04–1.94 (m, 4 H), 1.83–1.73 (m, 2 H), 0.93 (t, J = 7.5 Hz, 3 H).

General Procedure for the Halogen Atom Transfer Cyclization of δ-Alkenyl-β-keto Esters. General Procedure for the Removal of Tin-Containing Byproducts by DBU/I_2 Workup.[9] Preparation of Methyl 6-(Bromomethyl)-5-methyl-2-oxobicyclo[3.2.1]octane-1-carboxylate (16b,17b). Methyl 2-bromo-6-methyl-3-oxo-2-(2-propenyl)hex-6-enoate (**19**, 72.7 mg, 0.251 mmol) was dissolved in benzene-d_6 (0.9 mL) in an NMR tube, and hexamethylditin (14 μL, 0.043 mmol) was added. A septum was placed over the top of the tube, and the solution was irradiated with a 275-W sunlamp positioned about 25 cm from the tube. The reaction was warmed by the lamp, and we estimate that the temperature reached 70–80 °C. After 1 h, hexamethylditin (4 μL, 0.012 mmol) was added, and the mixture was irradiated for an additional 20 min. The reaction mixture was diluted with ether (8 mL) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 15 μL, 0.10 mmol), resulting in the formation of a heavy white precipitate. A solution of iodine in ether was added dropwise to the stirred mixture until the yellow color of I_2 persisted. The mixture was applied to a silica gel plug and eluted with ether. After solvent removal, the residue was purified by flash chromatography (15% EtOAc/hexane) to afford **16b/17b** (54.0 mg, 74%, **16b/17b** = 1.8/1 as determined by GC analysis): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 3.64 (dd, J = 9.9, 4.1 Hz, 0.64 H), 3.58 (dd, J = 10.5, 4.4 Hz, 0.36 H), 3.33 (dd, J = 10.5, 10.5 Hz, 0.36 H), 3.23 (J = 9.9, 9.9 Hz, 0.64 H), 2.62–2.31 (m, 4 H), 2.16–2.00 (m, 2 H), 1.94–1.57 (m, 3 H), 1.14 (s, 1.08 H), 1.11 (s, 1.92 H); IR (thin film) 2953, 1740, 1711, 1458, 1435, 1263 cm^{-1}; HRMS calcd for $C_{12}H_{17}BrO_3$ (M^+) m/e 288.0347, obsd m/e 288.0347; LRMS m/e 288 (M^+), 262, 260, 233, 231, 209, 181, 149.

Methyl 2-Oxo-1,5-dimethylcyclopentane-1-carboxylate (13b, 14b) and Methyl 2-Oxo-1-methylcyclohexane-1-carboxylate (12b). A flat photochemical reaction flask containing **11** (422 mg, 1.43 mmol), Me_6Sn_2 (210 μL, 0.21 mmol), and benzene (4 mL) was irradiated for 10 min. Then Bu_3SnH (458 μL, 1.70 mmol) was added and the reaction mixture was refluxed at 80 °C for 12 h. The solvent was evaporated and the product was diluted with EtOAc and filtered through silica gel. Purification by MPLC yielded an inseparable mixture of **12b** and **13b** (181 mg, 75%), **14b** (51 mg, 21%, contaminated with methyl 2-methyl-3-oxohept-7-enoate), and methyl 2-methyl-3-oxohept-7-enoate (8 mg, 3%). Compound **12b** was identical with a sample prepared by alkylation of methyl 2-oxocyclohexane-1-carboxylate. Compound **14b** was identical with the known compound.[13] Pure **13a** was isolated by crystallizing the crude mixture of iodides from hexanes. This gave pure **13a**, mp 67–68 °C, in low yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3 H), 3.42 (dd, J = 10, 4 Hz, 1 H), 2.93 (dd, J = 11, 10 Hz, 1 H), 2.68 (dd, J = 13, 9 Hz, 1 H), 2.40 (m, 3 H), 1.81 (m, 1 H), 1.55 (s, 3 H); IR ($CHCl_3$) 3684, 3019, 2400, 1754, 1732, 1520, 1458, 1435, 1379, 1320, 1215, 1173, 1076, 772, 669 cm^{-1}; LRMS m/e 265, 209, 169, 137, 109, 81, 39. Tin hydride reduction of pure **13a** produced pure **13b**, whose spectra and GC retention time were identical with that compound of the mixture with **12b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.67 (s, 3 H), 2.60 (dd, J = 9, 1 Hz, 1 H), 2.25 (m, 1 H), 2.10–1.70 (m, 2 H), 1.30 (m, 1 H), 1.27 (s, 3 H), 1.04 (d, J = 7.0 Hz, 3 H). Once all the structures of the products were confirmed, the product ratios reported in the text were obtained by GC analysis of a crude reaction mixture.

Methyl 6-(Iodomethyl)-5-methyl-2-oxobicyclo[3.2.1]octane-1-carboxylate (16c, 17c). A solution of bromides **16b** and **17b** (54.0 mg, 0.187 mmol) and sodium iodide (120.5 mg, 0.804 mmol) in acetone (3 mL) was stirred at 25 °C in the dark for 14 h. GC analysis of the reaction mixture indicated only 15% conversion. The mixture was then heated at reflux for 32 h. After cooling, the reaction mixture was diluted with ether (30 mL) and washed with water (2 × 15 mL) and then brine (15 mL), and the organic phase was dried ($MgSO_4$). After filtration and solvent evaporation, the residue was purified by flash chromatography (15% EtOAc/hexane) to provide **16c/17c** (44.4 mg, 71%, **16c/17c** = 2.4/1, ratio as determined by GC analysis): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3 H), 3.49 (dd, J = 9.5, 3.8 Hz, 0.70 H), 3.39 (dd, J = 9.4, 3.7, Hz, 0.30 H), 3.06 (dd, J = 11.9, 9.4 Hz, 0.30 H), 2.94 (11.4, 9.5 Hz, 0.70 H), 2.72–2.30 (m, 4 H), 2.18–1.55 (m, 5 H), 1.11 (s, 2.10 H), 1.09 (s, 0.90 H); IR (thin film) 2951, 1736, 1709, 1471, 1294, 1157 cm^{-1}; HRMS calcd for $C_{12}H_{17}IO_3$ (M^+) m/e 336.0264, obsd m/e 336.0264; LRMS m/e 336 (M^+), 308, 279, 260, 209, 177, 149.

Methyl 5-Methyl-6-methylene-2-oxobicyclo[3.2.1]octane-1-carboxylate (20). The iodides **16c/17c** (28.6 mg, 0.085 mmol) were dissolved in benzene-d_6 (0.8 mL) in an NMR tube, and DBU (35 μL, 0.234 mmol) was added. The tube was sealed and the solution was heated at 130 °C for 4 h. A white precipitate (ammonium hydroiodide) formed on the bottom of the tube during the reaction. After cooling, the tube was opened, and the reaction mixture was diluted with ether (15 mL) and washed with saturated aqueous NH_4Cl, water, and brine (10 mL each), and the organic phase was dried ($MgSO_4$). After filtration and solvent removal, the residue was purified by flash chromatography (20% EtOAc/hexane) to afford an inseparable mixture of **20** and **21** (3/1, 13.1 mg, 74%). Olefin **20** was identical with an authentic sample by TLC, GC, and ^{1}H NMR comparison. The structure of **21** was assigned from GC–MS (m/e = 208) and ^{1}H NMR data. Compound **21** possesses a carbomethoxy group (3.70 ppm, s) and a methyl group (1.33 ppm, s), but does not have any olefinic hydrogens.

Methyl 5,8-Dimethyl-6-methylene-2-oxobicyclo[3.2.1]octane-1-carboxylate (23). A solution of **22** (94 mg, 0.31 mmol) and hexabutylditin (16 μL, 0.045 mmol) in benzene-d_6 (1 mL) was irradiated for 2 h. Solvent evaporation and flash chromatography gave a 2/1 mixture of bromides (70 mg, 75%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz), resonances of major isomer δ 3.21 (dd, J = 10.4, 9.9 Hz, 1 H), 1.93 (d, J = 12, 1 Hz, 1 H), 1.79 (ddd, J = 13.0, 13.0, 7.21 Hz, 1 H); resonances of minor isomer δ 3.35 (dd, J = 10.9, 10.0 Hz, 1 H), 1.96 (d, J = 14.4 Hz, 1 H), 1.60 (m, 1 H); overlapping resonances δ 3.71 (s, 1 H), 3.75–3.61 (m, 1 H), 2.56–2.30 (m, 3 H), 2.30–2.10 (m, 2 H), 1.65–1.50 (m, 1 H), 1.00 (d, J = 6.4 Hz, 3 H), 0.99 (s, 3 H). The bromides were characterized by elimination. The mixture of bromides (70 mg, 0.23 mmol) with DBU (96 μL, 1 mmol) in benzene-d_6 (1 mL) was heated at 120 °C in a sealed NMR tube for 23 h. The reaction was cooled, diluted with Et_2O, and washed with 2 N HCl. Purification by flash chromatography provided alkene **23** (40%), which was identical with an authentic sample.[5a]

Ethyl 1α-Benzyl-5β-ethyl-2-oxocyclopentane-1β-carboxylate (29). A solution of ethyl 2-benzyl-2-bromo-3-oxooct-6(E)-enoate (**28**, 53.4 mg, 0.151 mmol) and hexamethylditin (12 μL, 0.036 mmol) in benzene-d_6 (0.6 mL) was irradiated for 19 h. Tri-*n*-butyltin hydride (50 μL, 0.186 mmol) and azoisobutyronitrile (AIBN, 3.8 mg, 0.023 mmol) were added to the reaction mixture, and the solution was heated at 90 °C for 2.5 h. The reaction mixture was cooled, diluted with ether (8 mL), and treated with DBU (50 μL, 0.334 mmol) and I_2 in ether, and the mixture was eluted through a silica gel plug (ether). Solvent evaporation gave a residue that was purified by flash chromatography (8% EtOAc/hexane) to afford a mixture of **29** and **25** (93/7, 29.6 mg, 66% yield of **29**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.17 (4 H, m), 7.08 (d, J = 6.6 Hz, 1 H), 4.26–4.10 (m, 2 H), 3.41 (d, J = 13.9 Hz, 1 H), 3.10 (d, J = 13.9 Hz, 1 H), 2.51–2.43 (m, 1 H), 2.01–1.90 (m, 2 H), 1.81–1.58 (m, 4 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.97 (t, J = 7.3 Hz, 3 H); IR (thin film) 2965, 1749, 1732, 1684, 1496, 1215, 1165, 704 cm^{-1}; HRMS calcd for $C_{17}H_{22}O_3$ (M^+) m/e 274.1569, obsd m/e 274.1569; LRMS m/e 274 (M^+), 229, 200, 171, 129, 91. This sample was identical with an authentic sample prepared by hydrogenation of olefin **27** by TLC, GC, and ^{1}H NMR comparison.

Ethyl 6α-Propyl-1β-methyl-2-oxocyclohexane-1α-carboxylate (37). A solution of ethyl 2-iodo-2-methyl-3-oxodec-7(Z)-enoate (**39bZ**, 100.8 mg, 0.286 mmol) and hexamethylditin (10 μL, 0.030 mmol) in benzene-d_6 (1.0 mL) was irradiated for 34 min. ^{1}H NMR analysis showed that **39bZ** was consumed, and that the iodides **40b** were the major products (2.8/1). The iodides could be separated by flash chromatography (5% EtOAc/hexane). However, in this experiment, the crude photolysis mixture was treated with tri-*n*-butyltin hydride (100 μL, 0.372 mmol) and AIBN (5.0 mg, 0.030 mmol), and the solution was heated at 80 °C for 1 h. The reaction mixture was diluted with ether (8 mL) and treated with DBU (80 μL, 0.535 mmol) and I_2 in ether, and the mixture was eluted through a silica gel plug (ether). GC analysis indicated a single reduced product, **37**. Solvent evaporation gave a residue that was purified by flash chromatography (10% EtOAc/hexane) to provide **37** (42.1 mg, 65% based on **39bZ**). This sample was identical with an authentic sample prepared by hydrogenation of olefin **34** by TLC, GC, and ^{1}H NMR comparison.

40b (major): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (d, J = 11.4 Hz, 1 H), 4.15–4.02 (m, 2 H), 2.87 (ddd, J = 14.7, 13.9, 6.6 Hz, 1 H), 2.50–2.38 (m, 2 H), 2.17–1.97 (m, 3 H), 1.68–1.52 (m, 2 H), 1.48 (s, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.31–1.20 (m, 1 H), 0.98 (t, J = 7.0 Hz, 3 H); IR (thin film) 2939, 2874, 1772, 1716, 1458, 1207, 1120 cm^{-1}.

40b (minor): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (dd, J = 7.2, 7.0 Hz, 1 H), 4.21–4.09 (m, 1 H), 3.01 (ddd, J = 15.1, 13.8, 6.7 Hz, 1 H), 2.47 (dd, J = 15.1, 4.3 Hz, 1 H), 2.18–2.02 (m, 3 H), 1.84–1.65 (m, 3 H), 1.35 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.30–1.21 (m, 1 H), 1.01 (t, J = 7.2 Hz, 3 H); IR (thin film) 2965, 2872, 1734, 1705, 1458, 1381, 1215, 1113, 1020 cm^{-1}; HRMS calcd for $C_{11}H_{16}IO_2$ (M – OEt) m/e 307.0195, obsd m/e 307.0195; LRMS m/e 307 (M – OEt), 225, 176, 151.

Methyl (1α,3aβ,7aα)-2-(Bromomethyl)-1-ethyloctahydro-4-oxo-3a*H*-indene-3a-carboxylate (49a) and Methyl (1β,3aβ,7aβ)-2-(Bromomethyl)-1-ethyloctahydro-4-oxo-3a*H*-indene-3a-carboxylate (50a). A solution of methyl 2-bromo-2-oxo-2-(3-propenyl)dec-7(*Z*)-enoate (**48a**, 55.6 mg, 0.175 mmol) and hexamethylditin (9 μL, 0.027 mmol) in benzene-d_6 (0.6 mL) was irradiated for 1 h. The solvent was evaporated and the residue was purified by flash chromatography (10% EtOAc/hexane) to afford **49a/50a** (37.6 mg, 68%, **49a/50a** = 8.5/1 as determined by GC analysis): ^{1}H NMR (300 MHz, $CDCl_3$, **49a**) δ 3.68 (s, 3 H), 3.61 (dd, *J* = 9.7, 4.0 Hz, 1 H), 3.16 (dd, *J* = 9.7, 9.7 Hz, 1 H), 2.75–2.58 (m, 1 H), 2.55–2.35 (m, 3 H), 2.23 (dd, *J* = 14.4, 8.0 Hz, 1 H), 2.04 (dd, *J* = 14.4, 7.7 Hz, 1 H), 2.10–2.00 (m, 1 H), 1.85–1.75 (m, 2 H), 1.66–1.23 (m, 4 H), 0.98 (t, *J* = 7.4 Hz, 3 H); IR (thin film) 2951, 2866, 1712, 1452, 1429, 1248, 1172, 1105, 1030 cm^{-1}; HRMS calcd for $C_{14}H_{21}BrO_3$ (M^+) *m/e* 316.0674, obsd *m/e* 316.0674; LRMS *m/e* 316 (M^+), 286, 284, 259, 257, 237, 208, 195, 177. The structure of the minor isomer **50a** was assigned by its conversion to the known olefin **47**.

Methyl (1α,3aβ,7aα)-2-(Iodomethyl)-1-ethyloctahydro-4-oxo-3a*H*-indene-3a-carboxylate (49b) and Methyl (1β,3aβ,7aβ)-2-(Iodomethyl)-1-ethyloctahydro-4-oxo-3a*H*-indene-3a-carboxylate (50b). A solution of methyl 2-iodo-3-oxo-2-(3-propenyl)dec-7(*Z*)-enoate (**48b**, 130.0 mg, 0.357 mmol) and hexamethylditin (18 μL, 0.055 mmol) in benzene-d_6 (1.2 mL) was irradiated for 24 min. The solvent was evaporated and the residue was purified by flash chromatography (10% EtOAc/hexane) to afford **49b/50b** (91.2 mg, 70%, **49b/50b** = 10 as determined by GC analysis): ^{1}H NMR (300 MHz, $CDCl_3$, **49b**) δ 3.67 (s, 3 H), 3.44 (dd, *J* = 9.2, 3.7 Hz, 1 H), 2.87 (dd, *J* = 11.7, 9.3 Hz, 1 H), 2.71–2.57 (m, 1 H), 2.53–2.31 (m, 3 H), 2.29 (dd, *J* = 14.7, 8.2 Hz, 1 H), 2.08–2.02 (m, 1 H), 1.89 (dd, *J* = 14.7, 8 Hz, 1 H), 1.82–1.70 (m, 2 H), 1.68–1.54 (m, 1 H), 1.48–1.23 (m, 3 H), 0.97 (t, *J* = 7.6 Hz, 3 H); IR (thin film) 2955, 2870, 1716, 1456, 1252, 1192 cm^{-1}; HRMS calcd for $C_{14}H_{21}IO_3$ (M^+) *m/e* 364.0535, obsd *m/e* 364.0535; LRMS *m/e* 364 (M^+), 333, 332, 305, 263, 237, 205, 177, 159. The structure of the minor isomer **50b** was assigned by its conversion to the known olefin **47**.

Methyl (1α,3aβ,7aα)-1-Ethyl-2-methyleneoctahydro-4-oxo-3a*H*-indene-3a-carboxylate (46) and Methyl (1β,3aβ,7aβ)-1-Ethyl-2-methyleneoctahydro-4-oxo-3a*H*-indene-3a-carboxylate (47). The bromides **49a/50a** (35.0 mg, 0.110 mmol) were dissolved in benzene-d_6 (0.7 mL), and DBU (46 μL, 0.307 mmol) was added. The tube was sealed, and the solution was heated at 120 °C for 4 h. After cooling, the tube was opened and the reaction mixture was applied to a silica gel plug and eluted with 30% EtOAc/hexane. Solvent removal afforded **46/47** (22.4 mg, 86%, **46/47** = 10), identical with an authentic sample prepared by Mn(III)-mediated cyclization of **45** by TLC, GC, and ^{1}H NMR comparison.

Methylenetetrahydrofurans 51a and 51b. When a sample of impure iodide **18** (containing about 15% unreacted **15**) was allowed to stand overnight in the dark at 25 °C and then purified by flash chromatography (20% EtOAc, hexane), methylenetetrahydrofuran **51a** was isolated in 40% yield as a yellow oil: ^{1}H NMR (C_6D_6, 300 MHz) δ 6.18 (m, 1 H), 5.33 (d, *J* = 17.1 Hz, 1 H), 5.13 (d, *J* = 9.8 Hz, 1 H), 3.54 (s, 3 H), 3.41 (d, *J* = 6.2 Hz, 2 H), 3.16–2.97 (m, 2 H), 2.69 (s, 2 H), 1.57 (ddd, *J* = 12.7, 9.3, 7.1 Hz, 1 H), 1.27 (ddd, *J* = 12.7, 8.2, 6.2 Hz, 1 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.97, 169.12, 136.77, 114.15, 101.08, 86.50, 51.03, 34.57, 31.55, 30.29, 25.30, 14.16; IR (neat) 2990, 1699, 1635, 1313, 1182, 1115, 960 cm^{-1}, HRMS calcd for $C_{12}H_{17}IO_3$ *m/e* 336.0200, obsd *m/e* 336.0222; LRMS *m/e* 305, 227, 209, 177, 141. Standard tin hydride reduction of **51a** produced **51b**: ^{1}HMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 4.97 (br d, *J* = 17.2 Hz, 1 H), 4.87 (br d, *J* = 9.8 Hz, 1 H), 3.66 (s, 3 H), 3.15 (d, *J* = 7.8 Hz, 2 H), 3.00 (d, *J* = 6.2 Hz, 2 H), 1.86 (t, *J* = 7.8 Hz, 2 H), 1.33 (s, 6 H); IR (neat) 2976, 1701, 1633, 1313, 1219, 1115 cm^{-1}; HRMS calcd for $C_{12}H_{18}O_3$ *m/e* 210.1256, obsd *m/e* 210.1256; LRMS *m/e* 179, 163, 154, 141, 122, 109.

Lactone Dihydrofuran 52. A solution of acetoacetate **15** (19.2 mg, 0.90 mmol) and molecular iodine (24.2 mg, 0.09 mmol) in benzene-d_6 was allowed to stand in the dark for 30 h. The mixture was diluted with Et_2O and then washed with aqueous $Na_2S_2O_3$, water, and brine. Drying and concentration provided 25.0 mg (85%) of a crude yellow oil identified as **52**. This crude product was rather pure (single peak on GC), but decomposed over several days at room temperature. Further purification was not attempted: ^{1}H NMR (300 MHz, C_6D_6) δ 4.04 (m, 1 H), 3.04 (br t, 2 H), 2.76 (m, 3 H), 2.41 (m, 1 H), 1.48 (s, 2 H), 1.34 (t, *J* = 7.2 Hz, 2 H), 1.02 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.00, 169.91, 92.50, 89.01, 75.24, 35.97, 31.85, 29.94, 27.23, 9.14; IR (neat) 2972, 1741, 1670, 1300, 1182, 987 cm^{-1}; LRMS *m/e* 322 (M^+) 279, 253, 195, 177, 145, 125.

Evidence for Hydrophobic Interaction between Calicheamicin and DNA

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Abstract: A hydrophobic interaction has been shown to be an important factor in the calicheamicin/DNA association. This is based on the effect of various inorganic salts on the rate of cleavage of covalently closed-circular form I DNA and the temperature dependence of the calicheamicin/DNA interaction. The strongly hydrated Na_2SO_4 increased the rate of cleavage by decreasing the solubility of the very lipophilic calicheamicin, thus strengthening the hydrophobic association with the DNA. The weakly hydrated $NaClO_4$ had the opposite effect since it increased the solubility of calicheamicin in the aqueous solution. The enthalpy change ($\Delta H°_{obs}$) for calicheamicin/DNA binding is temperature-dependent, and the negative heat capacity change (ΔC_p = −1.21 kcal mol^{-1} K^{-1}) is consistent with the hydrophobic nature of DNA/calicheamicin interaction.

Introduction

Recent studies have shown the diyne–ene-containing antitumor antibiotics calicheamicin[1] (**1**) and esperamicin[2] to be potent minor-groove DNA-cleaving agents.[3,4] For a molecule of only 1367 Da, calicheamicin shows remarkable double-strand cleavage specificity with principal sites at the 5′ penultimate pyrimidine in 5′TCCT, C*T*CT, and A*C*CT tracts and two nucleotides toward

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