Ligand, Solvent, and Deuterium Isotope Effects in Mn(III)-Based Oxidative Free-Radical Cyclizations

Barry B. Snider* and Bridget A. McCarthy

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254-9110

Received April 19, 1993•

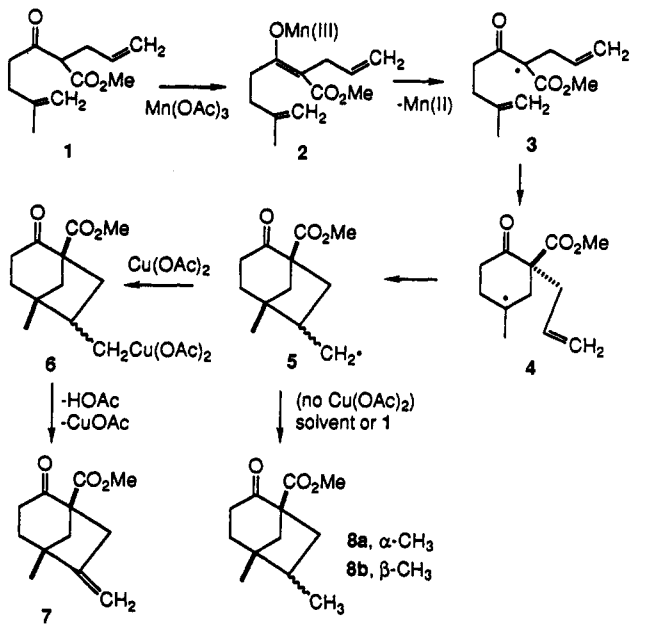
Oxidation of β-keto ester **1** with $Mn(pic)_3$ and $Cu(OAc)_2$ affords bicycloalkane **8**, not the expected alkene **7**, which is formed in high yield with $Mn(OAc)_3$ and $Cu(OAc)_2$. A series of control experiments established that the most likely explanation for this observation is that $Mn(pic)_2$, but not $Mn(OAc)_2$, reacts with the bicyclic radical **5** more rapidly than $Cu(OAc)_2$ does. These studies also indicate the potential for improved yields from oxidative free-radical cyclization of deuterated substrates. For instance, reaction of β-keto ester **1-*d*** with 2 equiv of $Mn(OAc)_3$ and no $Cu(OAc)_2$ affords 65% of **8**, whereas β-keto ester **1** provides only 22% of **8** under the same conditions. Large kinetic isotope effects change the nature of the termination step and prevent the formation of acyclic radical **3** by intermolecular hydrogen transfer. Solvent and ligand effects on the oxidation of β-keto ester **1**, malonate **14**, and acetylenic β-keto ester **25** are described.

Introduction

We have recently developed an efficient oxidative free-radical cyclization procedure using $Mn(OAc)_3$ to oxidize an unsaturated β-keto ester, 1,3-diketone, or 1,3-diester to an α-keto radical that cyclizes.[1,2] The reaction is terminated by oxidation of the cyclic radical with $Mn(OAc)_3$ or $Cu(OAc)_2$. Mono, tandem, and triple cyclizations have been carried out in high yield. The conversion of β-keto ester **1** to methylenebicyclo[3.2.1]octane **7** shown in Scheme I is a typical example of this reaction. Reaction of **1** with 2 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$ in AcOH at rt for 14 h affords 86% of **7**.[1b,f] The slow step in this process is the formation of Mn(III) enolate **2**, which rapidly loses Mn(II) to give the acyclic manganese-free free radical **3**.[1c,g] Cyclization of radical **3** affords tertiary monocyclic radical **4**, which undergoes a second cyclization to give primary bicyclic radical **5** as a ~2.5:1 mixture of *exo* and *endo* isomers. Primary radical **5** is not oxidized by Mn(III) but reacts rapidly with Cu(II) to afford the Cu(III) intermediate **6**, which rapidly loses AcOH and Cu(OAc) providing alkene **7**. Mn(III) rapidly oxidized Cu(I) to Cu(II) so that 2 equiv of Mn(III) and only a catalytic amount of Cu(II) are required.

Mn(III) oxidizes tertiary radicals rapidly, but is much less effective at oxidizing primary and secondary radicals. Oxidation of β-keto ester **1** with 2 equiv of $Mn(OAc)_3$ in AcOH without $Cu(OAc)_2$ as a cooxidant affords only 14% of alkene **7**. The major pathway is abstraction of a hydrogen atom from solvent or another molecule of **1** to afford alkanes **8a** (7%) and **8b** (17%).[1f]

Scheme I



Narasaka has recently reported that Mn(III) picolinate [$Mn(pic)_3$] in DMF is a useful reagent for the oxidation of β-keto acids to radicals, the oxidative cleavage of cyclopropanols to give β-keto radicals, and the oxidation of nitroalkanes to cation radicals.[3] In particular, he noted that β-keto acids afford different mixtures of products with $Mn(pic)_3$ and $Mn(OAc)_3$.

As part of a survey of other Mn(III) reagents and suitable solvents, we examined the oxidative cyclization of **1** with $Mn(pic)_3$.[4] To our surprise, we found that oxidation of **1** with 2 equiv of $Mn(pic)_3$ and 1 equiv of $Cu(OAc)_2$ in AcOH

(1) For previous papers in this series see: (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3569. (b) Snider, B. B.; Dombroski, M. A. *J. Org. Chem.* **1987**, *52*, 5487. (c) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137. (d) Snider, B. B.; Patricia, J. J. *J. Org. Chem.* **1989**, *54*, 38. (e) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427. (f) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (g) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607. (h) Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544. (i) Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 322.

(2) For reviews of $Mn(OAc)_3$ as an oxidant see: (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; pp 261–314. (b) Badanyan, Sh. O.; Melikyan, G. G.; Mkrtchyan, D. A. *Russ. Chem. Rev.* **1989**, *58*, 286; *Uspekhi Khimii* **1989**, *58*, 475.

(3) (a) Narasaka, K.; Miyoshi, N.; Iwakura, K.; Okauchi, T. *Chem. Lett.* **1989**, 2169. (b) Narasaka, K.; Iwakura, K.; Okauchi, T. *Chem. Lett.* **1991**, 423. (c) Iwasawa, N.; Hayakawa, S.; Isobe, K.; Narasaka, K. *Chem. Lett.* **1991**, 1193. (d) Iwasawa, N.; Hayakawa, S.; Funahashi, M.; Isobe, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 819. (e) Iwasawa, N.; Funahashi, M.; Hayakawa, S.; Narasaka, K. *Chem. Lett.* **1993**, 545.

(4) For the preparation of $Mn(pic)_2$ and $Mn(pic)_3$ see: (a) *Gmelin Handbook of Inorganic Chemistry, Mn Main Volume D4*, 8th ed.; Springer Verlag: Berlin, 1985; pp 308–312. (b) Kleinstein, A.; Webb, G. A. *J. Inorg. Nucl. Chem.* **1971**, *33*, 405. (c) Yamaguchi, H.; Sawyer, D. T. *Inorg. Chem.* **1985**, *24*, 971. (d) Richert, S.; Tsang, P. K. S.; Sawyer, D. T. *Inorg. Chem.* **1988**, *27*, 1814 and **1989**, *28*, 2471.

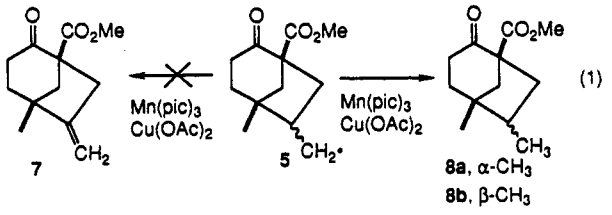
0022-3263/93/1958-6217$04.00/0

Table I. Ligand and Deuterium Isotope Effects on the Oxidative Free-Radical Cyclization of β-Keto Ester 1 with Mn(III) and Cu(II) in EtOH and AcOH

entry	solvent	substrate	Mn(III)[a] oxidant	Cu(II)[b] oxidant	additives	equiv of Mn(III) consumed[c]	7 (%)	8 (%)
1	AcOH	1	$Mn(OAc)_3$	$Cu(OAc)_2$		2	86	0
2	AcOH	1	$Mn(OAc)_3$	none			14	24
3	AcOH	1	$Mn(pic)_3$	$Cu(OAc)_2$		0.3	0	15
4	EtOH	1	$Mn(OAc)_3$	$Cu(OAc)_2$		2	71	4
5	EtOH	1	$Mn(OAc)_3$	none		0.3	2	24
6	EtOH	1	$Mn(pic)_3$	$Cu(OAc)_2$		0.22	0	22
7	AcOH	1	$Mn(OAc)_3$	$Cu(pic)_2$		2	76	4
8	EtOH	1	$Mn(OAc)_3$	$Cu(pic)_3$			38	14
9	AcOH	1	$Mn(OAc)_3$	$Cu(OAc)_2$	picH[d]	2	70	5
10	AcOH	1	$Mn(OAc)_3$	$Cu(OAc)_2$	picH[e]		9	18
11	AcOH	1	$Mn(OAc)_3$	$Cu(OAc)_2$	pyr[f]	2	80	0
12	AcOD-d_4	1	$Mn(OAc)_3$	none			5	24[g]
13	AcOD-d_4	1	$Mn(pic)_3$	$Cu(OAc)_2$			<2	24[g]
14	EtOH-d_6	1	$Mn(OAc)_3$	none			<2	25[g]
15	EtOh-d_6	1	$Mn(pic)_3$	$Cu(OAc)_2$			<2	24[g]
16	EtOH	1-d	$Mn(pic)_3$	$Cu(OAc)_2$		2	0	67[g]
17	EtOH	1-d	$Mn(OAc)_3$	none		2	<2	65[g]
18	AcOH	1-d	$Mn(pic)_3$	$Cu(OAc)_2$		2	2	60[g]
19	AcOH	1-d	$Mn(OAc)_3$	none		2	14	60[g]
20	AcOH-d_4	1-d	$Mn(pic)_3$	$Cu(OAc)_2$			<2	<5[g]
21	AcOH-d_4	1-d	$Mn(OAc)_3$	none		12	<5[g]	

[a] All reactions were carried out in 0.1 M solutions of 1 at 25 °C with 2 equiv of Mn(III) oxidant. Consumption of 1 was monitored by TLC. The reaction times are as follows: entries 1–13, <12 h, entries 14–17, 24 h; entries 13, 18–19, 48 h; entries 20–21, 65 h. [b] One equiv of Cu(II) oxidant was used. [c] If less than 2, this value was determined by titration of the remaining Mn(III) with $NaHSO_3$ after the complete consumption of 1. [d] Two equiv of picolinic acid and $Cu(OAc)_2$ were stirred 3 d at 25 °C, and $Mn(OAc)_3$ and 1 were then added. [e] Two equiv of picolinic acid and $Mn(OAc)_3$ were stirred 3 d at 25% °C, and $Cu(OAc)_2$ and 1 were then added. [f] Two equiv of pyridine. [g] No deuterium incorporation in 8.

affords none of alkene 7, the expected product, 15% of alkanes 8, and 60% of oligomeric material. $Mn(pic)_3$ appears to be suitable for the oxidation of β-keto ester 1 to afford the acyclic enol radical 3, but surprisingly, it prevents Cu(II) from oxidizing primary radical 5 to alkene 7.



In an attempt to understand this observation, we studied the oxidative cyclization of three substrates, β-keto ester 1, malonate diester 14, and acetylenic β-keto ester 25, with a variety of Mn(III) reagents in several solvents and examined the deuterium isotope effects on the rates and yields of these oxidative cyclizations.

Results and Discussion

Solvent Effects on the Oxidation of 1. AcOH is the standard solvent for $Mn(OAc)_3$ oxidative cyclizations.[1,2] We have recently shown that the use of EtOH as solvent is advantageous for acid-sensitive substrates and that EtOH is a good hydrogen donor for reduction of the cyclic primary and vinyl radicals obtained from the oxidative cyclization of 14 and 25.[1h] We began this study by surveying the use of other solvents for the oxidative cyclization of β-keto ester 1 to methylenebicyclo[3.2.1]-octane 7 with 2 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$. The reaction is fastest and proceeds in highest yield in AcOH (86%, 14 h, rt) (see Table I, entry 1). Good yields of 7 are obtained in MeOH (68%, 14 h, 60 °C), EtOH (71%, 7 h, 25 °C, entry 4), DMSO (62%, 16 h, 60 °C), dioxane (56%, 14 h, 60 °C), and CH_3CN (56%, 14 h, 60 °C). Modest yields are obtained in DMPU (36%, 41 h, 60 °C) and DMF (44%, 40 h, rt). Low yields are obtained in nitromethane (8%, 40 h, 60 °C) and THF (12%, 47 h, rt). Even with 1 equiv[5] of $Cu(OAc)_2$, bicycloalkane 8 is formed as a byproduct in DMPU (~10%), dioxane (6%), DMF (~3%), EtOH (5%), and CH_3CN (~3%); no 8 is formed in the other solvents.

As indicated above, oxidation of 1 with 2 equiv of $Mn(OAc)_3$ in AcOH without $Cu(OAc)_2$ as a cooxidant affords alkanes 8a (7%) and 8b (17%) and only 14% of alkene 7 (entry 2). Since oxidation of primary radical 5 by Mn(III) is slow and AcOH is not a good hydrogen donor, oligomerization, possibly by intermolecular addition of radical 5 to a double bond of a second molecule of 1, competes with hydrogen abstraction from the solvent or 1.

EtOH is a better hydrogen atom donor than AcOH for primary alkyl radicals.[1h,6] Oxidation of 1 with 2 equiv of $Mn(OAc)_3$ in EtOH without $Cu(OAc)_2$ as a cooxidant affords 24% of a 2.5:1 mixture of alkanes 8b and 8a, 48% of oligomeric material, and 2% of alkene 7 (entry 5). Primary radical 5 can abstract the α-hydrogen atom from another molecule of 1 to generate alkane 8 and acyclic radical 3. This process and oligomerization do not consume Mn(III). Primary radical 5 can abstract an α-hydrogen from EtOH to give alkane 8 and the α-hydroxyethyl radical (12) that is oxidized to acetaldehyde (13) by Mn(III).[7] This process will consume 2 equiv of Mn(III). Titration

(5) One equiv of $Cu(OAc)_2$ was used even though the reaction is catalytic in Cu(II) since greater amounts of 8 are formed at significantly lower (<0.1 equiv) concentrations of $Cu(OAc)_2$.

(6) The methyl radical abstracts a hydrogen atom slowly from AcOH ($k = 2 \times 10^2$ M^{-1} s^{-1}) and acetonitrile ($k = <3 \times 10^2$ M^{-1} s^{-1}) and more rapidly from the hydroxyl-bearing carbon of 2-cyanoethanol ($k = <1.6 \times 10^3$ M^{-1} s^{-1}): Gilbert, B. C.; Norman, R. O. C.; Placucci, G.; Sealy, R. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 885. The methyl radical abstracts a hydrogen atom from EtOH to give the 1-hydroxyethyl radical ($k = 5.9 \times 10^2$ M^{-1} s^{-1}): Thomas, J. K. *J. Phys. Chem.* **1967**, *71*, 1919.

(7) The 1-hydroxyethyl radical is oxidized to acetaldehyde by a variety of metals with rate constants of 10^6–10^8 M^{-1} s^{-1}: Asmus, K.-D.; Bonifacic, M. In *Landolt-Börnstein New Series, Group 2*; Fischer, H., Ed.; Springer Verlag: Berlin, 1984; Vol. 13b, pp 311–313.

of the residual Mn(III) in the EtOH reaction with sodium bisulfite solution established that 0.3 equiv of Mn(III) was consumed. This suggests that alkane 8 is formed by abstraction of a hydrogen atom from both EtOH and 1. Transfer of a hydrogen atom exclusively from EtOH would consume >0.52 equiv of Mn(III), while transfer of a hydrogen exclusively from 1 would consume no Mn(III). Alkene 7 is formed in 14% yield in AcOH without $Cu(OAc)_2$. Much less alkene 7 is formed in EtOH if $Cu(OAc)_2$ is not used as a cooxidant since EtOH is a better hydrogen donor than AcOH.

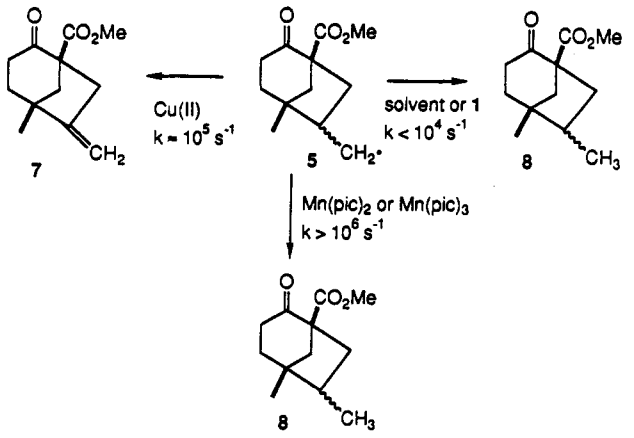
Oxidation of 1 with $Mn(pic)_3$. We next examined the reaction of 1 with 2 equiv of $Mn(pic)_3$ and 1 equiv of $Cu(OAc)_2$. Remarkably, we obtained no alkene 7 even with 1 equiv of Cu(II)! We isolated 15% of a ~2.5:1 mixture of **8b** and **8a** in AcOH (entry 3) and 22% of a similar mixture in EtOH (entry 6). The remaining material is an uncharacterizeable mixture of oligomers. Similar product mixtures are obtained with and without $Cu(OAc)_2$ and in MeOH and DMF. Apparently, use of $Mn(pic)_3$ prevents Cu(II) from oxidizing primary radical 5 to alkene 7. Titration of the reaction mixture with sodium bisulfite after the consumption of 1 indicates that 0.3 equiv of Mn(III) is consumed in AcOH and 0.22 equiv in EtOH.

Our initial thought was that the picolinate ligand exchanges from Mn(III) to Cu(II) and that $Cu(pic)_2$ does not oxidize primary radical 5. Oxidation of 1 with $Mn(OAc)_3$ and $Cu(pic)_2$[8] in AcOH affords alkene 7 in 76% yield with only 4% of 8 (entry 7). Therefore $Cu(pic)_2$ does oxidize primary radical 5, and ligand exchange[9] onto copper does not appear to be responsible for the absence of 7 with $Mn(pic)_3$. However, there is a total of 6 equiv of picolinate in entries 3 and 6 and only 2 equiv in entry 7, so that this experiment is not conclusive.

We therefore added 2 equiv of picolinic acid to $Mn(OAc)_3$ in HOAc and allowed it to equilibrate for 3 d to form a manganese picolinate species before adding $Cu(OAc)_2$ and 1 (entry 10). This reaction provides only 9% of 7 and 18% of 8. On the other hand, equilibration of 2 equiv of picolinic acid and $Cu(OAc)_2$ in HOAc for 3 d to form $Cu(pic)_2$, followed by addition of $Mn(OAc)_3$ and 1, affords 70% of 7 and only 5% of 8 (entry 9). Oxidation of 1 with $Mn(OAc)_3$ and $Cu(OAc)_2$ in AcOH containing 2 equiv of pyridine also gives 7 in high yield (entry 11). Very different results are obtained in entries 7, 9, and 10 although the gross stoichiometry is identical in all three cases. Alkene 7 is formed in high yield in entries 7 and 9, in which $Cu(pic)_2$ is either added or formed in situ, and in low yield in entry 10, in which a manganese picolinate species is formed in situ. *This conclusively establishes that picolinate does not prevent Cu(II) from oxidizing radical 5 to alkene 7.*

The pathway for formation of alkane 8 with $Mn(pic)_3$ cannot be simply the transfer of a hydrogen atom from the solvent or a second molecule of β-keto ester 1 to the bicyclic primary radical 5 (see Scheme II). The pseudo-first-order rate constant for oxidation of radical 5 to alkene 7 by 0.1 M Cu(II) is ~10^5 s^{-1} since Cu(II) reacts with primary radicals with a rate constant of ~10^6 mol^{-1} s^{-1}.[10] Since no hydrogen atom transfer is observed when Mn-

Scheme II



$(OAc)_3$ and $Cu(OAc)_2$ are used as oxidants in AcOH, hydrogen atom transfer from solvent or 1 must be much slower ($<10^3$–10^4 s^{-1}) than the reaction of 5 with Cu(II) to give Cu(III) intermediate 6. Since $Mn(OAc)_3$ and $Cu(pic)_2$ oxidizes primary radical 5 to alkene 7 in high yield, the picolinate ligand does not decrease the rate of oxidation of 5 to 7. Therefore, a manganese picolinate species must be involved in a new, faster reaction that leads from radical 5 to alkane 8 with a pseudo-first-order rate constant ≥10^6 s^{-1}.

The most likely process is the reaction of $Mn(pic)_2$ with radical 5 to give the alkylmanganese(III) picolinate 9. The manganese of 9 is coordinatively unsaturated and could bind to another molecule of β-keto ester 1 to give complex 10. A 1,5-hydrogen atom shift would generate alkane 8, $Mn(pic)_2$, and radical 3. This pathway explains the observation that the oxidation of 1 is catalytic in $Mn(pic)_3$. An alternative pathway would involve interaction of 9 with solvent, shown for EtOH, to form complex 11. A 1,4-hydrogen shift[11] would generate alkane 8, $Mn(pic)_2$, and the α-hydroxyethyl radical (12) that will be oxidized to acetaldehyde (13) by a second equivalent of Mn(III). The recent characterization of some alkylmanganese(III) complexes[12] provides some justification for this proposal.

The formation of alkene 7 will be completely suppressed if the first step in this pathway, the reaction of $Mn(pic)_2$ with 5, is irreversible and much faster than the reaction of 5 with Cu(II). The remaining steps of the pathway need not be rapid. This raises two questions: Is it reasonable to propose that $Mn(pic)_2$ reacts with a radical with a second order rate constant of 10^7–10^8 M^{-1} s^{-1}, and if so why does $Mn(OAc)_2$ not react similarly? Although little is known about the reaction of Mn(II) with radicals, the reaction of radicals with other low-valent metal salts is well known. For instance, Cu(I) reacts with some alkyl radicals 2 orders of magnitude faster than Cu(II) does.[13] Fe(II) reacts with the acetonyl radical with a rate constant of ~10^7 M^{-1} s^{-1} giving acetone and Fe(III).[14] Since Mn(III) is much more stable than Cu(III) it is reasonable for $Mn(pic)_2$ to react with radical 5 faster than Cu(II) does.

(8) For the preparation of $Cu(pic)_2$ see: Albanese, N. F.; Haendler, H. M. *Polyhedron* **1983**, *2*, 1131. Takenaka, A.; Utsumi, H.; Yamamoto, Y.; Furusaki, A.; Nitta, I. *J. Chem. Soc. Jpn., Pure Chem. Sec.* **1970**, *91*, 928.

(9) Ligand exchanges does occur during the reaction as shown by the results in entries 9 and 10. These experiments establish that this is not responsible for the absence of 7 with $Mn(pic)_3$.

(10) Kochi, J. K. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Chapter 11.

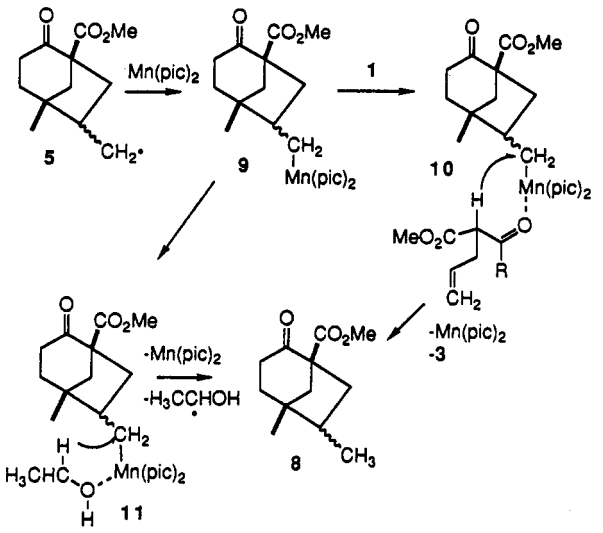
(11) Although 1,4-H shifts are rare in all carbon systems, this is not relevant to 11 which contains a Mn in the chain.

(12) Latten, J. L.; Dickson, R. S.; Deacon, G. G.; West, B. O.; Tiekink, E. R. T. *J. Organomet. Chem.* **1992**, *435*, 101.

(13) Masarwa, M.; Cohen, H.; Meyerstein, D. *Inorg. Chem.* **1991**, *30*, 1849. Masarwa, M.; Cohen, H.; Saar, J.; Meyerstein, D. *Isr. J. Chem.* **1990**, *30*, 361.

(14) Walling, C.; El-Taliawai, G. M. *J. Am. Chem. Soc.* **1973**, *95*, 844.

Scheme III

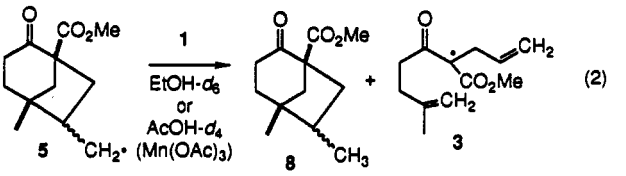


Why doesn't $Mn(OAc)_2$ behave similarly? We cannot fully answer this question but can point out several possibilities. First, the nitrogen of the picolinate will coordinate to manganese. This will perturb the oxidation potential for Mn(II).[4d] Secondly, the chelating nitrogen profoundly influences the structure of the manganese carboxylate. $Mn(pic)_3$ is an octahedral monomeric structure with three picolinates bound to manganese.[15] $Mn(OAc)_3$ is an oxo-centered trimer with seven bridging acetate ligands.[16] $Mn(OAc)_2$ also has bridging acetate ligands.[17] It is therefore possible that $Mn(pic)_2$ reacts rapidly with radical **5** while $Mn(OAc)_2$ is bridged and therefore too hindered to react rapidly with **5**.

In one special case we have observed that $Mn(OAc)_2$ will reduce radicals. Iminyl radical ($R_2C{=}N^{\bullet}$) formed by addition of a radical to a nitrile cannot be oxidized by Cu(II) or Mn(III) and appears to be reduced to the imine by $Mn(OAc)_2$ in AcOH.[1i]

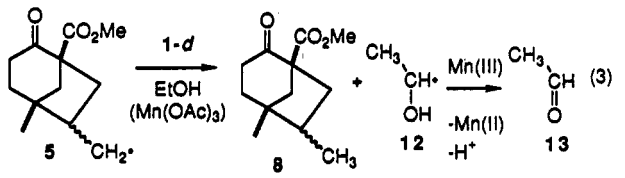
Deuterium Isotope Studies. In order to further investigate the mechanism for the formation of **8** we decided to use deuterium labelling studies to determine the source of the hydrogen atom transferred to **5**. The most likely sources are the solvent and the α-hydrogen of **1**. We examined the oxidative cyclization of **1** with either (1) 2 equiv of $Mn(OAc)_3$ and no $Cu(OAc)_2$ or (2) 2 equiv of $Mn(pic)_3$ and 1 equiv of $Cu(OAc)_2$ in AcOH-d_1, AcOH-d_4, EtOH-d_1, and EtOH-d_6 (entries 12–15). In none of these reactions is there any evidence for deuterium incorporation in the product by examination of the methyl region of the ^1H NMR spectra or the mass spectra. Incorporation of deuterium would lead to a CH_2D group in **8** that would absorb as a doublet of doublets with a small coupling to deuterium. The yield of these reactions is comparable to that obtained in undeuterated solvents. For instance, oxidation with 2 equiv of $Mn(pic)_3$ and 1 equiv of $Cu(OAc)_2$ in EtOH-d_6 affords 24% of **8** (entry 15) as opposed to 22% of **8** in EtOH (entry 6).

These results suggest that the conversion of radical **5** to the Mn(III) complex **10** and formation of alkane **8** and radical **3** in the last step is the major pathway with $Mn(pic)_3$. The observation that the oxidation is catalytic in $Mn(pic)_3$ supports this analysis. Oxidation with $Mn(OAc)_3$ and no $Cu(OAc)_2$ goes through the pathway shown in eq 2. Radical **5** abstracts the α-hydrogen from **1** to afford alkane **8** and acyclic radical **3**.



Use of β-keto ester **1**-*d* leads to very interesting and unexpected results. Oxidation of **1**-*d* with 2 equiv of $Mn(pic)_3$ and 1 equiv of $Cu(OAc)_2$ in EtOH (entry 16) was somewhat slower than the oxidation of **1** (28 h vs 14 h). More significantly, all of the Mn(III) was consumed (this is readily apparent since Mn(III) is brown and Mn(II) is almost colorless), and the yield of **8** increases from 22% with **1** to 67% with **1**-*d*. Similar results are obtained with 2 equiv of $Mn(OAc)_3$ in EtOH (entry 17), and slightly lower yields of **8** are obtained with both oxidants in AcOH (entries 18–19). In no case is there any evidence for incorporation of deuterium in alkane **8**.

These results suggest that the conversion of radical **5** to the Mn(III) complex **11** and formation of alkane **8** and the α-hydroxyethyl radical **12** in the last step is the major pathway with $Mn(pic)_3$. Oxidation with $Mn(OAc)_3$ and no Cu(II) goes through the pathway shown in eq 3. Radical



5 abstracts the α-hydrogen from EtOH to afford **8** and α-hydroxyethyl radical **12**, which is oxidized to acetaldehyde by a second equivalent of Mn(III). The observation that all of the Mn(III) was consumed in these reactions supports this analysis.

We determined the kinetic isotope effect for the oxidative cyclization of **1** by running the reaction with $Mn(OAc)_3$ and $Cu(OAc)_2$ in EtOH. This reaction gives alkene **7** in very high yield, and enolization of **1** to give **2** is the only possible pathway for consumption of **1**. β-Keto esters **1** and **1**-*d* were oxidized with 10 mol % of $Mn(OAc)_3$ and 5 mol % of $Cu(OAc)_2$, and the relative rate was approximated colorimetrically by determining the time for consumption of Mn(III). Since only 5% of the β-keto ester has been consumed this gives a pseudo-first-order rate constant. These experiments established that $k_H/k_D \approx 8.5$ for the conversion of β-keto ester **1** to manganese enolate **2**, which is the slow step in the formation of alkene **7**.[1c] Although this is a large kinetic isotope effect, it is not out of line with that for other hydrogen transfer reactions, in which tunneling may be involved.[18] k_H/k_D is approximately 25 and 8.7 for the abstraction of an α-hydrogen from CH_3OH by $(Me_3Si)_3C^{\bullet}$ and $CD_3^{\bullet}$, respectively.[18a,d]

(15) Figgis, B. N.; Raston, C. L.; Sharma, R. P.; Wbite, A. H. *Aust. J. Chem.* **1978**, *31*, 2545.
(16) Hessel, L. W.; Romers, C. *Rec. Trav. Chim.* **1969**, *88*, 545.
(17) Bertaut, E. F.; Tran, Q. D.; Burlet, P.; Burlet, P.; Thjomas, M.; Moreau, J. M. *Acta Crystallogr., Sect. B: Struct. Sci.* **1974**, *B30*, 2234.

(18) (a) Eaborn, C.; Happer, D. A. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1608. (b) Isaacs, N. S. *Physical Organic Chemistry*; Longman: Harlow, England, 1987; p 269. (c) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall: London, 1980; pp 106–140. (d) Cher, M. *J. Phys. Chem.* **1963**, *67*, 605.

The very large isotope effect with $(Me_3Si)_3C^\bullet$ is attributed to the sterically hindered radical center.[18a]

Large kinetic isotope effects due to tunneling[18] can also explain the absence of deuterium incorporation in 8 with either 1-*d* or perdeuterated solvents and the complete consumption of Mn(III) in the oxidative cyclization of 1-*d*. Alkylmanganese picolinate 9 will be converted to alkane 8 almost exclusively via complex 10 if a deuterated solvent is used because of the large isotope effect. This explains the absence of deuterium incorporation and the lack of effect of the deuterated solvent on the yield. If 1-*d* is used, alkylmanganese picolinate 9 will be converted to alkane 8 almost exclusively via complex 11 because deuterium transfer from 1-*d* is slow. This process produces the α-hydroxyethyl radical (12), which is oxidized to acetaldehyde (13) by a second equivalent of Mn(III). This explains the absence of deuterium incorporation and the consumption of 2 equiv of Mn(III) in the oxidative cyclization of 1-*d*. Similar pathways shown in eqs 2 and 3 explain the results with $Mn(OAc)_3$.

It should be possible to suppress both of these pathways if a perdeuterated solvent and 1-*d* are used. This is the case. Reaction of 1-*d* in AcOH-d_4 with either $Mn(OAc)_3$, or both $Mn(pic)_3$ and $Cu(OAc)_2$ affords mainly oligomer and less than 5% of alkane 8 (entries 20–21).

The remaining question is why does the yield of alkane 8 increase to 67% with 1-*d* from only 22% with 1? We hypothesize that radical 3 formed from manganese enolate 2 has less kinetic energy than radical 3 formed by hydrogen atom transfer through complex 10 when $Mn(pic)_3$ is used or from transfer to a hydrogen from 1 to 5 when $Mn(OAc)_3$ is used. The less energetic radicals cyclize preferentially to give cyclic radical 5. The more energetic radicals formed by hydrogen atom transfer from 1 are more likely to add intermolecularly to an alkene to initiate oligomerization.[19] Radical 3 is formed almost exclusively from manganese enolate 2 when 1-*d* is used since hydrogen atom transfer from 1-*d* is suppressed by the large deuterium isotope effect.

It is possible that the difference between the reactivity of radical 3 formed from manganese enolate 2 and hydrogen atom transfer from 1 to 5 or 9 is due to complexation of manganese to the radical formed from 2. We believe that this is not the case since numerous experiments indicate that a true free radical is formed in the $Mn(OAc)_3$ reactions.[1g]

Other Oxidants. $Mn(AcAc)_3$ and MnF_3 are two other readily available Mn(III) reagents. $Mn(AcAc)_3$ has been extensively used for oxidative coupling of phenols.[20] We briefly examined the oxidation of 1 with these reagents. Oxidation with 2 equiv of $Mn(AcAc)_3$ and 1 equiv of $Cu(OAc)_2$ affords 69% of alkene 7 in AcOH and 38% of alkene 7 and 28% of alkane 8 in EtOH. In EtOH, $Mn(AcAc)_3$ is able to partially suppress the formation of alkene 7. This is not surprising since acetylacetonate is a chelating ligand and it is reasonable to propose that $Mn(AcAc)_2$ could also react rapidly with radical 5 to give an alkylmanganese acetylacetonate analogous to 9.

Oxidation of 1 with 2 equiv of $Mn(AcAc)_3$ in EtOH affords 40–45% of alkane 8. Titration indicates that ~1.2 equiv of $Mn(AcAc)_3$ are consumed while only 0.2–0.3 equiv of $Mn(OAc)_3$ or $Mn(pic)_3$ are consumed in the analogous reaction. The somewhat improved yield and increased consumption of Mn(III) with $Mn(AcAc)_3$ is consistent with the explanation proposed above for the increase in yield of 8 from 1-*d*. Since there is no net oxidation in the conversion of 1 to alkane 8, the consumption of 1.2 equiv of Mn(III) requires that hydrogen be transferred mainly from EtOH to an alkylmanganese acetylacetonate complex analogous to 9 to generate 8 and the α-hydroxyethyl radical (12) that will be oxidized by Mn(III). Therefore as with 1-*d*, enol radical 3 is produced from manganese enolate 2 rather than by hydrogen atom transfer from 1.

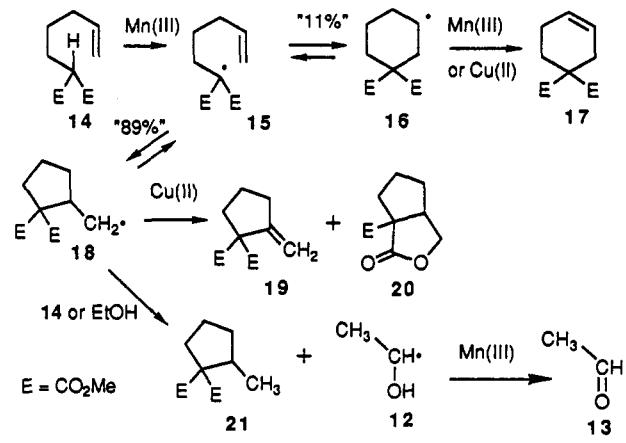
Oxidation of 1 with 2 equiv of MnF_3 and 1 equiv of $Cu(OAc)_2$ affords 86% of 7 in AcOH and 56% (66% based on recovered 1) of 7 in DMSO. MnF_3 must be the actual oxidant in DMSO. It is possible that $Mn(OAc)_3$ generated by ligand exchange is the actual oxidant in AcOH.

Table II. Solvent Effect on the Oxidative Free-Radical Cyclization of Malonate 14 with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2$.

solvent	reacn time (sp)	T (°C)	17 (%)	19[a] (%)	20[a] (%)
AcOH	28	55	7 (7)	20 (20)	48 (48)
EtOH	156	60	4 (5)	22 (30)	14 (19)
MeOH	68	70	5 (6)	35 (44)	17 (21)
DMF	67	75	5 (7)	32 (44)	17 (24)
DMSO	68	75	2 (2)	53 (71)	5 (7)
CH_3CN	112	55	3 (5)	8 (13)	38 (61)

[a] Isolated yield (yield based on recodeed 7

Scheme IV



Oxidation of Dimethyl 4-Pentenylmalonate (14). We have previously reported the oxidation of malonate 14 with 2 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$ in both EtOH and AcOH.[1h] We have now examined this reaction in DMSO, MeOH, DMF, and CH_3CN. The results for all solvents are shown in Table II. Baciocchi and Ruzzioni have recently reported analogous oxidative cyclizations of the same substrate with ceric ammonium nitrate and various Cu(II) salts in MeOH and AcOH.[21]

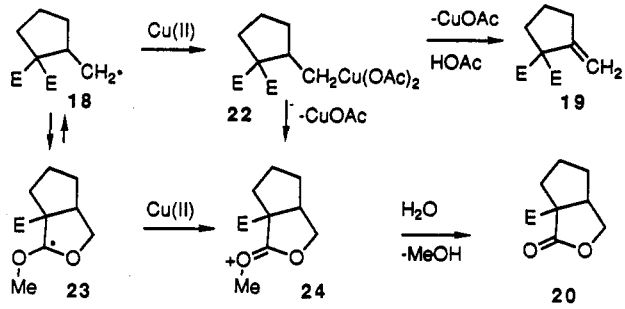
There is a remarkable solvent effects on the ratio of methylenecyclopentane 19 and lactone 20 formed by Cu(II) oxidation of cyclopentanemethyl radical 18. Oxidation of malonate 14 leads to radical 15 that cyclizes to a ≈9:1 mixture of cyclopentanemethyl radical 18 and cyclohexyl radical 16. The cyclohexyl radical 16 is oxidized to cyclohexene 17. The cyclopentanemethyl radical 18 is oxidized to a mixture of methylenecyclopentane 19 and lactone 20 in a solvent-dependent ratio. Primary radical

(19) Some examples are known in which the reactivity of a radical or diradical varies with the energy of the species. (a) White, J. M.; Sturm, G. P., Jr. *Can. J. Chem.* **1969**, *47*, 357. (b) Bergman, R. G. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Chapter 5, p 219.

(20) Dewar, M. J. S.; Nakaya, T. *J. Am. Chem. Soc.* **1968**, *90*, 7134.

(21) Baciocchi, E.; Paolobelli, A. B.; Ruzziconi, R. *Tetrahedron* **1992**, *48*, 4617.

Scheme V



18 reacts with Cu(II) to give Cu(III) intermediate 22. Loss of CuOAc and AcOH affords the expected product methylenecyclopentane 19. Displacement of CuOAc by the ester will give cation 24 that will react with water to give lactone 20. It is also possible that the radical center of 18 reacts with the ester to give the oxygen stabilized radical 23 that is oxidized by Cu(II) to cation 24.

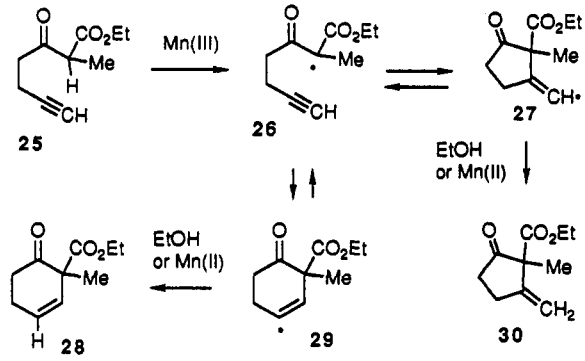
We have previously shown that lactone 20 is the major product in AcOH and methylenecyclopentane 19 is the major product in EtOH.[1h] The new results shown in Table II indicate there is even greater selectivity for methylenecyclopentane 19 in MeOH and DMF and most notably DMSO, which is the solvent of choice for the preparation of 19. CH_3CN is even more selective for lactone 20 than AcOH. The reason for these selectivities is not obvious.

Reaction of 14 with 2 equiv of $Mn(OAc)_3$ in EtOH affords 40% of alkane 21 and 15% of recovered 14.[1h] The primary cyclopentanemethyl radical 18 is not oxidized by Mn(III) but instead reacts with EtOH to give 21 and the α-hydroxyethyl radical (12) that is oxidized to acetaldehyde (13) by a second equivalent of Mn(III). This reaction consumes 2 equiv of Mn(III). A similar reaction with 14-*d* affords 50% of 21 without the incorporation of any deuterium. This confirms that the hydrogen atom transferred to radical 18 is derived from the solvent, EtOH, rather than 14.

Oxidation of malonate 14 with $Mn(pic)_3$ and $Cu(OAc)_2$ in AcOH for 42 h at 60 °C affords 56% of lactone 20, 22% of recovered malonate 14, 12% of methylcyclopentane 21, and 2% of cyclohexene 17. A similar reaction without $Cu(OAc)_2$ afforded 28% of recovered 14, 14% of methylcyclopentane 21, 2% of cyclohexene 17, and 48% of oligomeric material. Primary radical 18 is oxidized by Cu(II) to lactone 20, but not to methylenecyclopentane 19, even though $Mn(pic)_3$ is used as the oxidant. This reactivity is quite different than that observed with primary radical 5, which is not oxidized by Cu(II) when $Mn(pic)_3$ is used as the oxidant. Presumably, the proximity of the ester to the radical center in 18 and the possible intermediacy of radical 23 permit Cu(II) to oxidize 18 to lactone 20, but not methylenecyclopentane 19, in the presence of $Mn(pic)_2$ and $Mn(pic)_3$.

Oxidation of Acetylenic β-Keto Ester 25. We have previously shown that oxidative cyclization of 25 with 2 equiv of $Mn(OAc)_3$ in EtOH affords 32% of a 1.6:1 mixture of methylenecyclopentane 30 and cyclohexene 28.[1h] This process consumes 2 full equiv of Mn(III). Oxidation gives acyclic radical 26 that cyclizes to vinyl radicals 27 and 29. These radicals abstract a hydrogen atom primarily from EtOH to give the observed products and the α-hydroxyethyl radical (12) that is oxidized to acetaldehyde (13) by a second equivalent of Mn(III). The role of the solvent, EtOH, is clear from the much lower yield, 9% of a 1:6.3

Scheme VI



mixture of 30 and 28, obtained in AcOH, which is much less effective as a hydrogen atom donor. In AcOH, the yield of cyclohexene 28 is comparable to that obtained in EtOH. The yield of methylenecyclopentane 30 drops drastically. This is at least partially due to the instability of 30 under the reaction conditions. We obtain 35–40% of a 3:1 mixture of 30 and 28 if the reaction is run for a shorter time in EtOH with slightly less than 2 equiv of $Mn(OAc)_3$. A similar oxidation with $Mn(pic)_3$ in EtOH for 20 h at 60 °C affords 30% of a 3:1 mixture of 30 and 28. The total yield and selectivity increases with MnF_3. Reaction of 25 with MnF_3 in EtOH for 50 h at rt affords 44% of methylenecyclopentane 30 and 11% of cyclohexene 28.

Oxidation of 25-*d* with $Mn(OAc)_3$ in EtOH for 64 h at rt affords 38% of methylenecyclopentane 30 and 26% of cyclohexene 28. This reaction is noteworthy for the high yield of monomeric products (64% vs 35–40% from 25) and the low ratio, 1.45:1, of methylenecyclopentane 30 to cyclohexene 28. As discussed above for radical 3, the reaction is more selective when the radical 26 is formed with less kinetic energy by electron transfer from a manganese enolate rather than hydrogen transfer to a reactive vinyl radical. The increased amount of cyclohexene 28 formed from 25-*d* suggests that the cyclization of 26 formed from 25-*d* may be partially reversible.

Conclusion. The comparison of $Mn(OAc)_3$ and $Mn(pic)_3$ oxidations point out some important general features of oxidative free-radical cyclizations. A one-electron oxidant, e.g., Mn(III), Cu(II), Ce(IV), etc., is needed for both the generation of the acyclic radical and oxidation of the cyclic radical. Furthermore, the lower valent metal salt produced in the oxidation must not react rapidly with the radical intermediates. $Mn(OAc)_3$ in combination with $Cu(OAc)_2$ meets all these requirements. $Mn(OAc)_3$ generates the acyclic radical and reoxidizes CuOAc to $Cu(OAc)_2$. $Cu(OAc)_2$ reacts rapidly with the cyclic alkyl radicals; $Mn(OAc)_2$ does not. $Mn(pic)_3$ does not meet these requirements since $Mn(pic)_2$ reacts with the cyclic radical more rapidly than $Cu(OAc)_2$ does.

These studies also indicate the potential for improved yields from oxidative free-radical cyclization of deuterated substrates, most notably the conversion of 1-*d* to 8 in 67% yield as opposed to 28% yield from 1. Large kinetic isotope effects change the nature of the termination step and prevent the formation of acyclic radical 3 by intermolecular hydrogen transfer.

Experimental Section

General. $Mn(OAc)_3 \cdot 2H_2O$, $Mn(AcAc)_3$, MnF_3, $Cu(OAc)_2 \cdot H_2O$, and $Cu(OAc)_2$ were purchased from Aldrich. $Mn(pic)_3 \cdot H_2O$[4] and $Cu(pic)_2$[8] were prepared by the literature procedure. Substrates

1, 14, and 25 were prepared as previously described.[1f,h] All products have been characterized previously.[1f,h] All reactions were carried out in degassed solvent under nitrogen.

Oxidative Cyclization of 1 with $Mn(OAc)_3 \cdot 2H_2O$ in EtOH. General Workup Procedure. A solution of β-keto ester 1 (42 mg, 0.2 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (107 mg, 0.4 mmol) in 2 mL of degassed EtOH was stirred at 25 °C for 6 h. The mixture was then diluted with 10 mL of water and titrated with a standardized solution of $NaHSO_3$ to determine the amount of $Mn(OAc)_3$ remaining (0.34 mmol). The resulting solution was extracted with 3 × 10 mL of CH_2Cl_2. The combined organic extracts were washed with 10% HCl and saturated NaCl solutions and dried ($MgSO_4$). Removal of the solvent in vacuo gave 39 mg of a yellow oil. Purification by flash chromatography (9:1 hexane–EtOAc) gave 11 mg (24%) of a 2.5:1 mixture of **8b** and **8a**, respectively.

The oligomeric material can be removed from monomeric products by two different procedures. Extraction of the reaction mixture with CH_2Cl_2 gives >90% material balance containing monomeric and oligomeric material. The oligomeric material is much more polar and can easily be removed by flash chromatography. Extraction of the reaction mixture with ether gives much lower material balances containing 10–20% oligomeric material. The oligomeric material is not very ether soluble so that this procedure is more effective for isolating 80–90% pure monomeric material on a larger scale.

Oxidative Cyclization of 1 with $Mn(pic)_3 \cdot H_2O$ and $Cu(OAc)_2 \cdot H_2O$ in EtOH. A solution of β-keto ester 1 (53 mg, 0.25 mmol), $Mn(pic)_3 \cdot H_2O$ (220 mg, 0.5 mmol), and $Cu(OAc)_2 \cdot H_2O$ (50 mg, 0.25 mmol) in 2.5 mL of degassed EtOH was stirred at rt for 14 h. The mixture was then diluted with 10 mL of water and titrated with a standardized solution of $NaHSO_3$ to determine the amount of $Mn(pic)_3$ remaining (0.44 mmol). Normal workup afforded 38 mg of a yellow oil. Purification by flash chromatography (9:1 hexane–EtOAc) gave 12 mg (22%) of a 2.5:1 mixture of **8b** and **8a**, respectively.

Oxidative Cyclization of 1 with $Mn(AcAc)_3$ in EtOH. A solution of β-keto ester 1 (105 mg, 0.5 mmol) and $Mn(AcAc)_3$ (587 mg, 1.0 mmol) in 5 mL of degassed EtOH was stirred at 60 °C for 23 h. The mixture was diluted with 30 mL of water, and 10% $NaHSO_3$ was added dropwise until all residual $Mn(AcAc)_3$ was reduced. The resulting solution was then extracted with 3 × 20 mL of ether. The combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Removal of the solvent in vacuo gave 56 mg (53%) of 80% pure **8**. Flash chromatography (9:1 hexane–EtOAc) gave 42 mg (40%) of a 2.5:1 mixture of **8b** and **8a**, respectively.

The aqueous phase was then acidified with 20 mL of 10% HCl and extracted with 3 × 20 mL of CH_2Cl_2. The combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Removal of the solvent in vacuo gave 45 mg (43%) of an uncharacterizeable mixture of oligomers.

A second, identical reaction was extracted with 3 × 20 mL of CH_2Cl_2. The combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Removal of the solvent in vacuo gave 105 mg (100%) of a mixture of **8** and oligomer. Flash chromatography (9:1 hexane–EtOAc) gave 47 mg (45%) of a 2.5:1 mixture of **8b** and **8a**, respectively.

Preparation of Deuterated β-Keto Ester 1-*d*. A solution of **1** (210 mg, 1.0 mmol) and 50 mg of $NaHCO_3$ in 2 mL of 1:1 THF–D_2O was stirred at rt for 20 h. Water (10 mL) was added to the mixture, and the resulting solution was extracted with 3 × 10 mL of ether. The combined ether extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Removal of the solvent in vacuo gave 209 mg of **1-*d*** (>99% D) as shown by the absence of a peak at δ 3.58 for the α-hydrogen.

Oxidative Cyclization of 1-*d* with $Mn(pic)_3$ in EtOH. Reaction of β-keto ester **1-*d*** (21 mg, 0.1 mmol), $Mn(pic)_3 \cdot H_2O$ (88 mg, 0.2 mmol), and anhydrous $Cu(OAc)_2$ (20 mg, 0.1 mmol) in 1 mL of degassed EtOH at rt for 28 h gave 19 mg of a yellow oil after normal workup. Purification by flash chromatography (9:1 hexane–EtOAc) gave 14 mg (67%) of a 2.5:1 mixture of **8b** and **8a**, followed by 3 mg (14%) of a mixture of uncharacterizeable oligomers.

Determination of k_H/k_D for the Conversion of 1 to 7. To a stirred solution of β-keto ester **1** (42 mg, 0.2 mmol) and $Cu(OAc)_2 \cdot 2H_2O$ (2 mg, 0.001 mmol) in 1 mL of EtOH was added $Mn(OAc)_3 \cdot 2H_2O$ (5 mg, 0.002 mmol). After 14 min the color changed from brown to blue indicating that all of the $Mn(OAc)_3$ had been consumed. A solution of **1-*d*** prepared in the same manner required 120 min for the consumption of all of the $Mn(OAc)_3$.

Preparation of Deuterated Malonate 14-*d*. Deuterium exchange of a solution of malonate **22** (200 mg, 1.0 mmol) and $NaHCO_3$ (50 mg) in 2 mL of 1:1 THF–D_2O for 20 h at rt as described above for the preparation of **1-*d*** gave 200 mg of 80% enriched **14-*d***. This exchange process was repeated twice to give 197 mg of **14-*d*** (>99% *d*) as shown by the absence of a peak at δ 3.37 for the α-hydrogen.

Oxidative Cyclization of 14-*d* with $Mn(OAc)_3 \cdot 2H_2O$ in EtOH. Reaction of **14-*d*** (40 mg, 0.2 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (107 mg, 0.4 mmol) in 2 mL of degassed EtOH at 60 °C for 89 h gave 36 mg of a crude yellow oil after normal workup. Purification by flash chromatography (10:1 hexane–EtOAc) gave 20 mg (50%) of **21** followed by 9 mg (22%) of a mixture of oligomers.[1h]

Oxidative Cyclization of 14 with $Mn(Ac)_3 \cdot 2H_2O$ in DMSO. Reaction of malonate **14** (60 mg, 0.3 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (161 mg, 0.6 mmol), and $Cu(OAc)_2 \cdot H_2O$ (60 mg, 0.3 mmol) in 1.5 mL of degassed DMSO at 75 °C for 68 h gave 59 mg of a yellow oil. Purification by flash chromatography (25:1 hexane–EtOAc, followed by 2:1 hexane–EtOAc) gave 15 mg (25%) of recovered **14**, 3 mg (5%) of **17**, 32 mg (53%) of **19**, and 1 mg (2%) of **20**.

Oxidative Cyclization of Malonate 14 with $Mn(pic)_3$ and $Cu(OAc)_2$ in AcOH. Reaction of malonate **14** (25 mg, 0.125 mmol), $Mn(pic)_3 \cdot H_2O$ (110 mg, 0.25 mmol), and $Cu(OAc)_2 \cdot H_2O$ (25 mg, 0.125 mmol) in 1 mL of degassed AcOH at 60 °C for 42 h gave 24 mg of a crude yellow oil. Purification by flash chromatography (4:1 hexane–EtOAc) gave 9 mg (36%) of a 1:6:11 mixture of **17**, **21**, and recovered **14** followed by 14 mg (56%) of **20**.

Oxidative Cyclization of Malonate 14 with $Mn(pic)_3$ in AcOH. Reaction of **14** (25 mg, 0.125 mmol) and $Mn(pic)_3 \cdot H_2O$ (110 mg, 0.25 mmol) in 1 mL of degassed AcOH at 60 °C for 45 h gave 25 mg of a crude yellow oil. Purification by flash chromatography (9:1 hexane–EtOAc, followed by MeOH) gave 11 mg (44%) of a 1:6:11 mixture of **17**, **21**, and recovered **14** followed by 12 mg (48%) of a mixture of uncharacterizeable oligomers.

Oxidative Cyclization of 25 with MnF_3 in EtOH. Reaction of β-keto ester **25** (27 mg, 0.15 mmol) and MnF_3 (34 mg, 0.3 mmol) in 1.5 mL of degassed EtOH at rt for 50 h gave 27 mg of a crude yellow oil after normal workup. Purification by flash chromatography (20:1 hexane–EtOAc followed by MeOH) gave 12 mg (44%) of **30**, 3 mg (11%) of **28**, and 8 mg (29%) of uncharacterizeable oligomer.

Preparation of Deuterated β-Keto Ester 25-*d*. A solution of β-keto ester **25** (92 mg, 0.5 mmol) and $NaHCO_3$ (50 mg) in 2 mL of 1:1 THF–D_2O was stirred at rt for 20 h and worked up as described above for the preparation of **1-*d*** to give 91 mg of a 90% deuterium enriched mixture. This process was repeated once to obtain 90 mg of **25-*d*** (>99% D) as shown by the absence of a peak at δ 3.52 for the α-hydrogen.

Oxidative Cyclization of 25-*d* with $Mn(OAc)_3 \cdot 2H_2O$ in EtOH. Reaction of **25-*d*** (36 mg, 0.2 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (107 mg, 0.4 mmol) in 2 mL of degassed EtOH for 64 h at rt gave 34 mg of a crude yellow oil after normal workup. Purification by chromatography (20:1 hexane–EtOAc) gave 3 mg (8%) of recovered **25-*d***, 12 mg (33%) of **30**, and 11 mg (31%) of a 5:1 mixture of **28** and **30**, respectively.

Acknowledgment. We thank the National Institutes of Health for generous financial support.