Pergamon

Tetrahedron 54 (1998) 10641–10648

TETRAHEDRON

Mn(III)-Based Oxidative Free-Radical 6-*endo* Cyclizations of *Z*-Trisubstituted Alkenes

Barry B. Snider* and Jane Y. Kiselgof

Department of Chemistry, Brandeis University, Waltham, MA 02454-9110 (USA)

Received 14 May 1998; accepted 16 June 1998

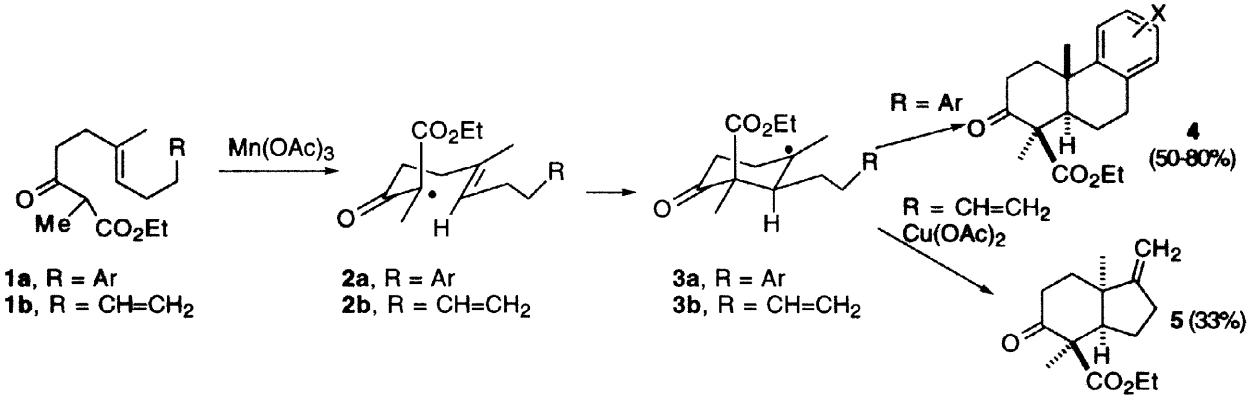
Abstract

Oxidative free-radical cyclization of *Z*-trisubstituted alkene **6a** gave the expected octahydrophenanthrenes **9** (11%) and **10** (24%), lactone **17** (10%), and octahydrophenanthrene **4** (25%), which was obtained from *E*-trisubstituted alkene **1a**. Cyclization of **6b** provided the expected hydrindane **11** (25%), cyclopentane **18b** (10%) formed by 5-*exo* cyclization, and hydrindane **5** (13%), which was obtained from *E*-trisubstituted alkene **1b**. These results provide valuable information on the mechanism of Mn(III)-based oxidative radical cyclizations and indicate the profound effect of alkene geometry on the stereochemistry of radical cyclizations.

Keywords: radicals and radical reactions; cyclization

Introduction

We have found that tandem $Mn(OAc)_3$-based oxidative free-radical cyclization[1] of unsaturated β-keto esters provides a very efficient and stereospecific route to polycyclic systems as exemplified by the synthesis of **4** from **1a**, which proceeds stereospecifically in 50-80% yield depending on the substituents on the aromatic ring.[2-7] We have established that these reactions proceed by formation of free radical **2a**, which cyclizes through a chair transition state with an axial ester to give **3a**. Tertiary radical **3a** reacts further to give **4**, either by 6-*endo* radical cyclization followed by oxidation, or by oxidation to the cation followed by Friedel-Crafts cyclization. Similarly, oxidative free-radical cyclization of **1b** with $Mn(OAc)_3$



1a, R = Ar
1b, R = CH=CH$_2$

2a, R = Ar
2b, R = CH=CH$_2$

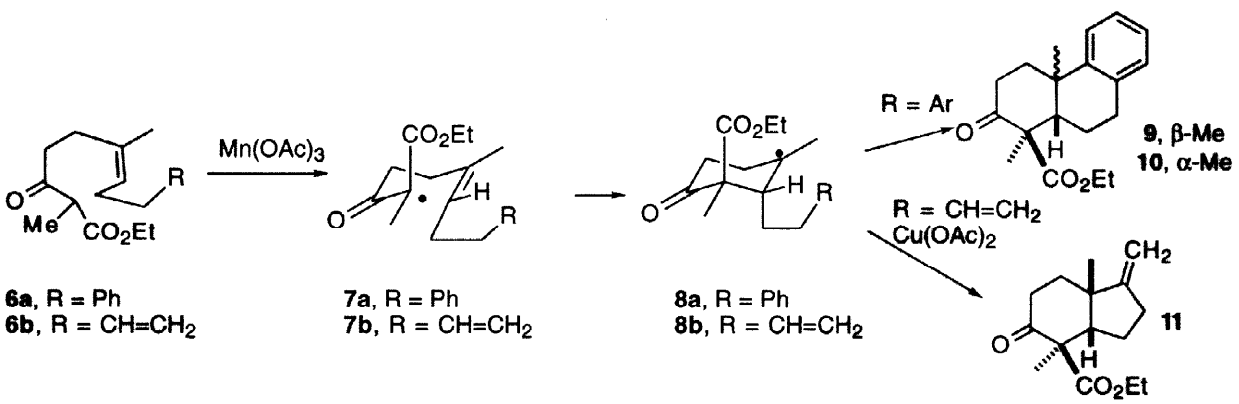
3a, R = Ar
3b, R = CH=CH$_2$

* E-Mail: snider@brandeis.edu; Fax: 781-736-2516

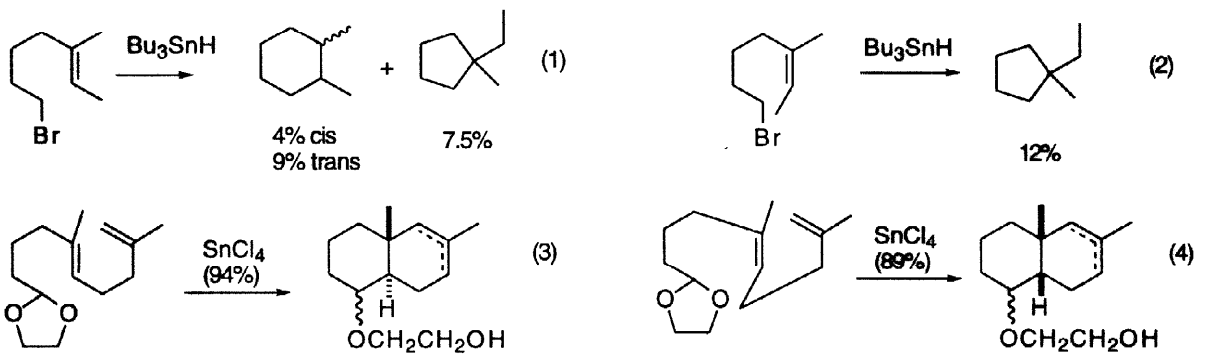
0040-4020/98/$ - see front matter
PII: S0040-4020(98)00612-7

and $Cu(OAc)_2$ affords 33% of **5** stereospecifically. Radical **2b** cyclizes through a chair transition state with an axial ester to give **3b**, which undergoes a 5-*exo* cyclization to the terminal double bond to give a *cis*-hydrindane with a primary radical, which is oxidized by Cu(II) to yield **5**.[8] Zoretic has extended this approach to triple and quadruple cyclizations.[9] *E*-Trisubstituted double bonds have been used in all of these studies, which invariably lead to the monocyclic tertiary radical with the stereochemistry shown in **3**. Further cyclization leads to *trans*-decalins such as **4** or *cis*-hydrindanes such as **5**.

We expected that use of *Z*-trisubstituted double bonds would provide a practical route to isomers of **4** and **5**. For instance, **6a** should be oxidized to radical **7a**, which should cyclize to cyclohexyl radical **8a** with an axial ester, which should cyclize to give octahydrophenanthrenes **9** and/or **10**. Similarly, **6b** should be oxidized to radical **7b**, which should cyclize to cyclohexyl radical **8b**, which should cyclize to provide hydrindane **11**.



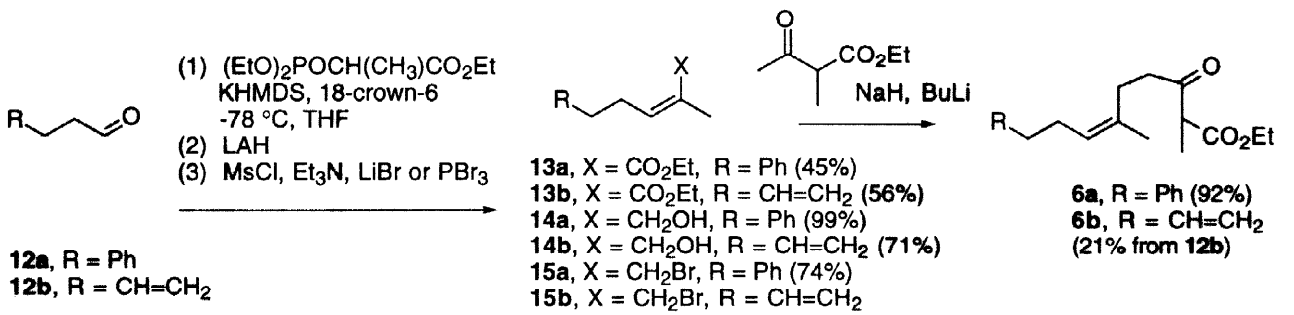
To the best of our knowledge, there is only a single study of the effect of double bond geometry on the cyclization of 5,6-disubstituted 5-hexenyl radicals.[10] Julia and co-workers reported in 1975 that reduction of 7-bromo-3-methyl-2*E*-heptene with Bu_3SnH gave 13% of the 6-*endo* cyclization products *cis*- and *trans*-1,2-dimethylcyclohexane and 7.5% of the 5-*exo* cyclization product 1-ethyl-1-methylcyclopentane and acyclic material (eq 1). On the other hand, the *Z*-isomer gave none of the 6-*endo* cyclization products and 12% of the 5-*exo* cyclization product and acyclic material (eq 2). The shift from mainly 6-*endo* cyclization with the *E*-isomer to exclusively 5-*exo* cyclization with the *Z*-isomer hinted that **6a** and **6b** might not cyclize analogously to **1a** and **1b**. In contrast, the effect of double bond geometry



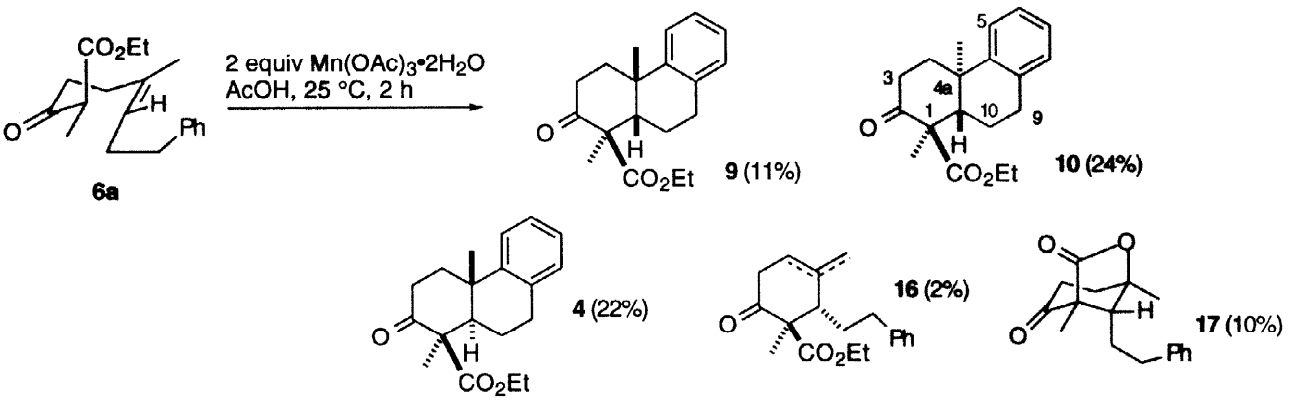
in cation-olefin cyclizations is more straightforward with *E*-double bonds leading to *trans*-decalins (eq 3) and *Z*-double bonds leading to *cis*-decalins (eq 4).[11]

Results and Discussion

The crucial step in the preparation of **6a** and **6b** was the *Z*-selective Horner-Emmons Wittig reaction using Still's procedure[12] [$(EtO)_2POCH(CH_3)CO_2Et$, KHMDS, 18-crown-6], which gave 45% of **13a** and 56% of **13b**. Reduction of **13a** with LAH gave 99% of alcohol **14a**,[13] which was treated with MsCl, Et_3N, and LiBr to give 74% of bromide **15a**. Alkylation of the dianion of ethyl methylacetoacetate with **15a** provided 92% of **6a**. Similarly, reduction of **13b** afforded 71% of alcohol **14b**,[14] which was converted to bromide **15b** with PBr_3. Because of its volatility, crude **15b** was converted to **6b** in 53% unoptimized yield.

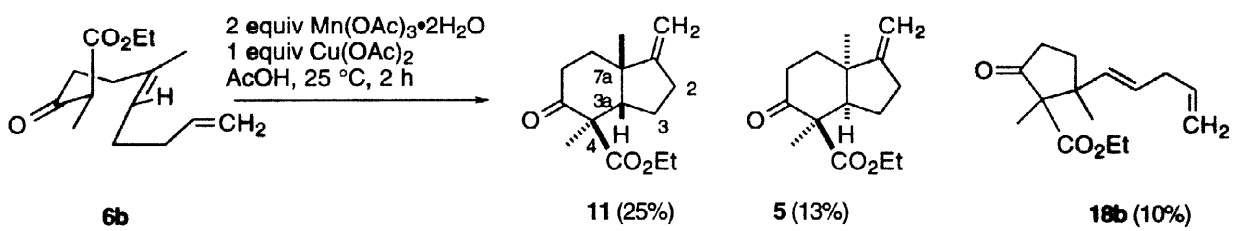


To our surprise, oxidative cyclization of **6a** with 2.3 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in AcOH at 25 °C for 2 h gave a complex mixture containing 24% of the expected product **10**, 11% of a compound tentatively assigned structure **9**, 22% of **4**, the only product from the cyclization of **1a**, 2% of alkenes **16**, and 10% of lactone **17**. The spectral data for **10** correspond closely to those reported for analogues with a methoxy group on the aromatic ring.[15,16] The stereochemistry was confirmed by NOE experiments. Irradiation of the 4a-methyl group at δ 1.35 enhanced H_{3ax} at δ 2.77, H_{10ax} at δ 1.89, H_{4eq} at δ 2.56, and H_5. Irradiation of the 1-methyl group enhanced H_{3ax} at δ 2.77 and H_{10ax} at δ 1.89. NOE enhancements cannot be observed between the two methyl groups because their absorptions are too close together. Octahydrophenanthrenes **4** and **9** were obtained as an inseparable mixture. The structure of **4** was



assigned by comparison to an authentic sample prepared from **1a**.[3] The structure of **9** was tentatively assigned based on analysis of the proton spectra of the mixture. The IR spectrum of lactone **17** exhibited carbonyl absorptions at 1787 and 1726 cm^{-1} characteristic of a γ-lactone and a cyclohexanone. The ^1H NMR spectrum indicated the absence of the ethyl group and a methyl absorption at δ 1.53 characteristic of $CH_3COC{=}O$. The axial stereochemistry of the phenylethyl side chain follows from a 1.8 Hz W coupling to the equatorial methine hydrogen. Analogous lactones are the major products in the cyclizations of related malonate esters.[3]

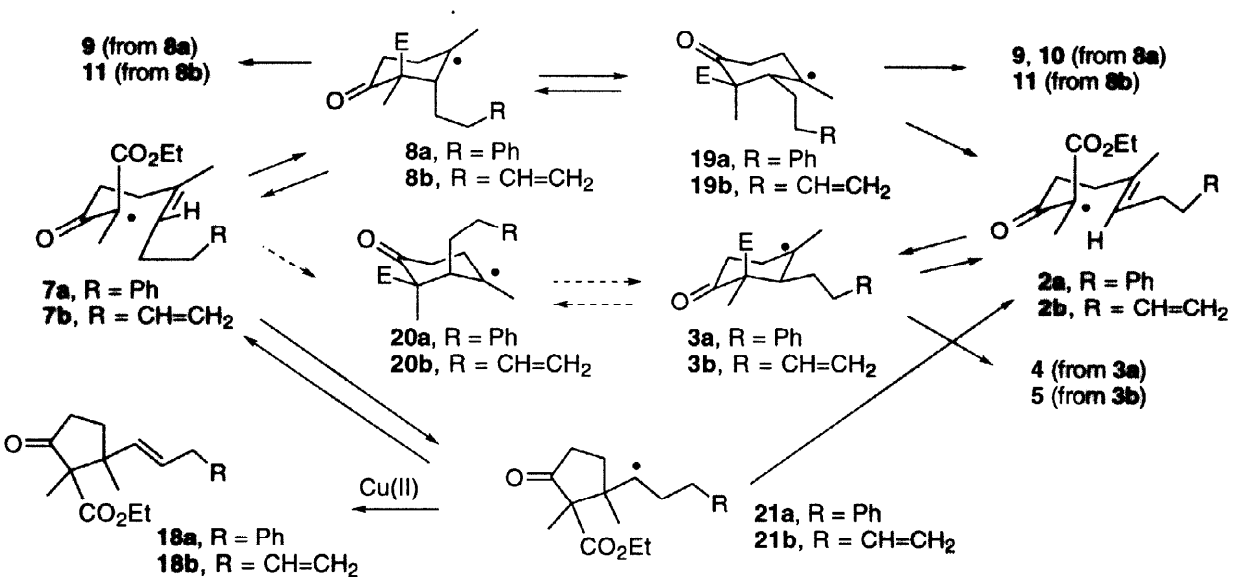
Oxidative cyclization of **6b** with 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ and 1 equiv of $Cu(OAc)_2$ in AcOH at 25 °C for 2 h also afforded a complex mixture containing 25% of the expected product **11**, 13% of **5**, the product of cyclization of **1b**, and 10% of cyclopentanone **18b**. The stereochemistry of **11** was established by NOE experiments. Irradiation of H_{3a} at δ 2.73 led to the enhancement of both the 7a- and 4-methyl groups, H_2 at δ 2.35, and H_3 at δ 1.85. This indicates that the hydrindane is *cis*-fused, and that H_{3a} and the 4-methyl group are equatorial on the cyclohexane ring as predicted by MM2 calculations. Hydrindane **5** and cyclopentanone **18b** were obtained as an inseparable mixture. The structure of **5** was assigned by comparison to an authentic sample prepared from **1b**. The characteristic 1,4-pentadienyl pattern of the side chain of **18b** was readily assigned from the ^1H NMR spectrum of the mixture; the stereochemistry about the cyclopentanone could not be assigned. Cyclopentanone **18b** is formed by 5-*exo* cyclization of **7b** to give **21b**, followed by oxidative elimination of the secondary radical by Cu(II). This is not unexpected in light of Julia's observation that reductive cyclization of 7-bromo-3-methyl-2*Z*-heptene gives only the cyclopentane (eq 2), while the *E*-isomer gives more 1,2-dimethylcyclohexane than 1-ethyl-1-methylcyclopentane (eq 1).[10] Apparently, steric interactions involving the 3-butenyl substituent on the double bond of **7b**, which is axial in the cyclohexyl radical **8b**, slow down the 6-*endo* cyclization of **7b** relative to that of **2b**, so that 5-*exo* cyclization to give **21b** occurs at a competitive rate.



6b **11** (25%) **5** (13%) **18b** (10%)

It is not clear why *Z*-radical **7** gives complex mixtures while *E*-radical **2** cyclizes stereospecifically. The most likely explanation involves ring opening of monocyclic radical **19**, which serves to isomerize *Z*-radical **7** to *E*-radical **2**. Cyclization of **7a** should give cyclohexyl radical **8a** with an axial ester. Cyclization of the axial phenylethyl group could give **9**, but approach of the phenyl group to the bottom face of the cyclohexyl radical is very hindered, so that this cyclization should be slow. Cyclohexyl radical **8a** can undergo chair-chair interconversion to give the less stable radical **19a** with an equatorial ester and an axial methyl group. Radical **19a** can cyclize to give both **9** and **10**. It can also undergo ring opening to give acyclic *E*-radical **2a**, which can then cyclize to give **3a**, which will react further to give

4. The cyclization of **3a** and **19a** should be slow since 4-phenylbutyl radicals cyclize with a rate constant of $\approx 10^3$ s^{-1}.[17] The cyclization of stabilized radicals such as **2** and **7** is known to be reversible and we have previously demonstrated that equilibration of double bond geometry can occur by ring opening of cyclic radicals in the 6-*exo* cyclization of analogous radicals to 1,2-disubstituted double bonds if the termination step is slow.[18]



Other possible explanations for the formation of **4** seem less likely. For instance, **7a** could cyclize to give monocyclic radical **20a** with an equatorial ester, which could flip to give **3a**, which will cyclize to give **4**. However, there is no apparent reason why the double bond geometry should affect the preference for an axial ester and equatorial methyl group observed in all other Mn(III)-based 6-*endo* cyclizations.[1]

The formation of **5** from **6b** probably results from a similar sequence in which monocyclic radical **8b** undergoes chair-chair interconversion to give **19b**, which opens to give acyclic radical **2b**, which cyclizes to give **5**. If this is the reaction pathway, the 5-*exo* cyclization of **8b** to **11** must be relatively slow, so that ring opening to give **2b** can occur. The formation of a 5-*exo* cyclization product (**18b**) from **6b** but not from **6a**, results from the need to use $Cu(OAc)_2$ as a co-oxidant with **6b** to oxidize the primary bicyclic radical to the exomethylene double bond of **5** and **11**. If $Cu(OAc)_2$ is not used as a co-oxidant, as in the cyclization of **6a**, any secondary cyclopentyl alkyl radical **21a** that is formed cannot be oxidized and will open to give acyclic radicals **2a** and **7a**. As expected, oxidative cyclization of **6a** with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2$ provided a few percent of **18a** as determined by the characteristic pattern of $PhCH_2CH{=}CHR$ in the ^1H NMR spectrum.

In conclusion, the mixtures of products obtained from oxidative cyclization of *Z*-trisubstituted alkenes **6a** and **6b** provide valuable information about the mechanism and relative rates of the individual steps of Mn(III)-based oxidative radical cyclizations and indicate the profound effect of alkene geometry on the stereochemistry of radical cyclization products that will be valuable in synthetic planning.

Experimental Section

General. NMR spectra were recorded in $CDCl_3$ at 300 and 400 MHz (^1H), and 75 and 100 MHz (^{13}C) unless otherwise indicated. Chemical shifts are reported in δ; coupling constants are reported in Hz. $Mn(OAc)_3 \cdot 2H_2O$ was prepared as described by Heiba and Dessau.[19]

Ethyl 2-Methyl-5-phenyl-2*Z*-pentenoate (13a). KHMDS (7.6 mL, 3.78 mmol of 0.5 M solution in toluene) was added to a solution of triethyl 2-phosphonopropionate (901 mg, 3.78 mmol) and 18-crown-6 ether (5.0 g, 18.9 mmol) in THF (76 mL) at -78 °C under nitrogen. Hydrocinnamaldehyde (**12a**) (508 mg, 3.78 mmol) was added and the reaction was stirred at -78 °C for 40 min and quenched with saturated NH_4Cl solution. The mixture was warmed to rt and extracted with ether (3 × 75 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated giving a 4:1 *Z/E* mixture of isomers. Purification by flash chromatography on silica gel (25:1 hexane/EtOAc) afforded 366 mg (45%) of pure **13a**[13] followed by the *E*-isomer: ^1H NMR 7.31-7.15 (m, 5), 5.96 (br dt, 1, *J* = 1.3, 7.1), 4.19 (q, 2, *J* = 7.1), 2.82-2.70 (m, 4), 1.89 (br s, 3), 1.3 (t, 3, *J* = 7.1); ^{13}C NMR 168.0, 141.6, 141.5, 128.4, 128.3, 127.8, 125.9, 60.1, 35.5, 31.1, 20.6, 14.3; IR (neat) 1713, 1647, 1603 cm^{-1}.

Ethyl 2-methyl-2*Z*,6-heptadienoate (13b). KHMDS (4.8 mL, 2.4 mmol of 0.5 M solution in toluene) was added to a solution of triethyl 2-phosphonopropionate (0.5 mL, 2.4 mmol) and 18-crown-6 ether (3.1 g, 12 mmol) in THF (50 mL) at -78 °C under nitrogen. 4-Pentenal (**12b**) (200 mg, 2.4 mmol) was added and the reaction was stirred at -78 °C for 40 min and quenched with saturated NH_4Cl solution. The mixture was warmed to rt and extracted with ether (3 × 100 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated giving a 5:1 *Z/E* mixture of isomers. Purification by flash chromatography on silica gel (25:1 hexane/EtOAc) afforded 224 mg (56%) of pure **13b** followed by the *E*-isomer: ^1H NMR 5.93 (tq, 1, *J* = 7.3, 1.3), 5.81 (ddt, 1, *J* = 10.2, 17.0, 6.6), 5.03 (ddd, 1, *J* = 1.3, 1.3, 17.0), 4.98 (br d, 1, *J* = 10.2), 4.20 (q, 2, *J* = 7.1), 2.56 (ddt, 2, *J* = 1.3, 7.3, 7.3), 2.17 (dtt, 2, *J* = 6.6, 1.3, 7.3), 1.90 (d, 3, *J* = 1.3), 1.30 (t, 3, *J* = 7.1); ^{13}C NMR 167.9, 141.8, 137.8, 127.5, 114.8, 59.9, 33.3, 28.7, 20.5, 14.2; IR (neat) 1715, 1641 cm^{-1}.

2-Methyl-5-phenyl-2*Z*-penten-1-ol (14a). LAH (200 mg, 5.3 mmol) was added to a solution of **13a** (366 mg, 1.68 mmol) in ether (20 mL) at 0 °C. The mixture was stirred for 2 h at room temperature and then quenched by sequential addition of H_2O (0.2 mL), 15% NaOH (0.2 mL), and H_2O (0.6 mL). Filtration and removal of the solvent afforded 292 mg (99%) of alcohol **14a**:[13] ^1H NMR 7.32-7.14 (m, 5), 5.33 (br t, 1, *J* = 7.7), 3.93 (d, 2, *J* = 6.0), 2.66 (t, 2, *J* = 7.3), 2.37 (dt, 2, *J* = 7.7, 7.3), 1.76 (d, 3, *J* = 1.1); ^{13}C NMR 141.8, 135.4, 128.7, 128.3, 127.1, 126.0, 61.5, 36.1, 29.6, 21.2; IR (CCl_4) 3622, 3570 cm^{-1}.

2-Methyl-2*Z*,6-heptadien-1-ol (14b). LAH (130 mg, 3.6 mmol) was added to a solution of **13b** (200 mg, 1.2 mmol) in ether (20 mL) at 0 °C. The reaction was stirred for 2 h at rt and quenched by sequential addition of H_2O (0.13 mL), 15% aq.NaOH (0.13 mL), and H_2O (0.4 mL). Filtration and removal of the solvent gave 152 mg of crude **14b**. Purification by flash chromatography on silica gel (4:1 hexane/EtOAc) afforded 108 mg (71%) of pure **14b**:[14] ^1H NMR 5.80 (ddt, 1, *J* = 10.2, 16.7, 6.6), 5.30 (br t, 1, *J* = 7.3), 5.02 (br d, 1, *J* = 16.7), 4.98 (br d, 1, *J* = 10.2), 4.12 (br s, 2), 2.19-2.06 (m, 4), 1.80 (s, 3) 1.39 (br s, 1); ^{13}C NMR 138.2, 134.8, 127.6, 114.9, 61.5, 33.9, 27.0, 21.2; IR (neat) 3330 cm^{-1}.

1-Bromo-2-methyl-5-phenyl-2*Z*-pentene (15a). Et_3N (0.46 mL, 3.3 mmol) was added dropwise to a solution of alcohol **14a** (292 mg, 1.66 mmol) and MsCl (0.2 mL, 2.6 mmol) in THF (10 mL) at -45 °C. The reaction was stirred for 1 h and warmed to 0 °C. A solution of LiBr (600 mg, 7.0 mmol) in THF (2 mL) was added. The reaction was stirred for 30 min and quenched with saturated NH_4Cl solution. The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with water and brine, and dried ($MgSO_4$). Removal of the solvent afforded 412 mg of crude product. Purification by flash chromatography on silica gel (25:1 hexane/EtOAc) gave 295 mg (74%) of pure **15a**: ^1H NMR 7.35-7.12 (m, 5), 5.43 (br tq, 1, *J* = 7.3, 1.3), 3.89 (s, 2), 2.69 (t, 2, *J* = 7.7), 2.38 (dt, 2, *J* = 7.3, 7.7), 1.82 (d, 3, *J* = 1.3); ^{13}C NMR 141.4, 132.2, 130.5, 128.4, 128.3, 125.9, 33.4, 32.1, 29.9, 21.9; IR (neat) 3026, 2933, 2857, 1603 cm^{-1}.

1-Bromo-2-methyl-2*Z*,6-heptadiene (15b). PBr_3 (0.6 mL, 5.9 mmol) was added in one portion to a solution of crude alcohol **14b** (prepared from 500 mg (5.95 mmol) of **12b**) and pyridine (40 μL, 0.5 mmol) in ether (20 mL) at rt. The reaction was stirred for 5 h and diluted with pentane. The organic phase was washed with saturated $NaHCO_3$ solution, water and brine, and dried ($MgSO_4$). Evaporation of the solvent afforded crude **15b** that was used without purification because of its volatility: ^1H NMR 5.86-5.75 (m, 1), 5.41-5.37 (m, 1), 5.04 (br d, 1, *J* = 17.2), 4.89 (br d, 1, *J* = 10.2), 3.98 (s, 2), 2.22-2.10 (m, 4), 1.84 (d, 1, *J* = 1.5); ^{13}C NMR

137.8, 131.9, 130.8, 115.0, 33.2, 32.2, 27.4, 21.8.

Ethyl 2,6-Dimethyl-3-oxo-9-phenyl-6Z-nonenoate (6a). Ethyl 2-methylacetoacetate (711 mg, 4.93 mmol) was added dropwise to a solution of NaH (208 mg, 5.2 mmol) and HMPA (0.52 mL, 3.0 mmol) in THF (20 mL) at 0 °C. The reaction was stirred for 1 h and then treated with *n*-BuLi (2.1 mL, 5.2 mmol of 2.5 M solution in hexane). The resulting mixture was stirred for 1 h and a solution of bromide **15a** (295 mg, 1.2 mmol) in THF (5 mL) was transferred to the reaction via cannula. The reaction mixture was stirred for 45 min, quenched with saturated NH_4Cl solution, and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water and brine, and dried ($MgSO_4$). Purification by flash chromatography on silica gel (25:1 hexane/EtOAc) gave 345 mg (92%) of pure **6a**: ^1H NMR 7.31-7.14 (m, 5), 5.21 (br t, 1, J = 7.3), 4.19 (q, 2, J = 7.1), 3.46 (q, 1, J = 7.1), 2.63 (t, 2, J = 7.8), 2.54-2.21 (m, 6), 1.65 (br s, 3), 1.32 (d, 3, J = 7.1), 1.25 (t, 3, J = 7.1); ^{13}C NMR 205.0, 170.2, 141.8, 133.9, 128.3, 128.0, 125.5, 125.3, 61.0, 52.6, 39.4, 35.9, 29.6, 25.5, 22.9, 13.8, 12.4; IR (neat) 1743, 1715 cm^{-1}.

Ethyl 2,6-Dimethyl-3-oxo-6Z,10-undecenoate (6b). Ethyl 2-methylacetoacetate (1.27 g, 8.8 mmol) was added dropwise to a solution of NaH (370 mg, 9.2 mmol) and HMPA (0.6 mL, 5.3 mmol) in THF (40 mL) in THF (20 mL) at 0 °C. The reaction was stirred for 1 h and then treated with *n*-BuLi (3.7 mL, 9.2 mmol of 2.5 M solution in hexane). The resulting mixture was stirred for 1 h and a solution of crude bromide **15b** in THF (3 mL) was transferred to the reaction via cannula. The reaction mixture was stirred for 45 min, quenched with saturated NH_4Cl solution, and extracted with ether (3 × 50 mL). The combined organic layers were washed with water and brine, and dried ($MgSO_4$). Purification by flash chromatography on silica gel (25:1 hexane/EtOAc) gave 322 mg (21% from **12b**) of pure **6b**: ^1H NMR 5.80 (ddt, 1, J = 10.2, 17.0, 6.6), 5.16 (br t, 1, J = 6.2), 5.01 (d, 1, J = 17.0), 4.95 (d, 1, J = 10.2), 4.19 (q, 2, J = 7.1), 3.52 (q, 1, J = 7.1), 2.64 (dt, 1, J = 17.4, 7.8), 2.55 (dt, 1, J = 17.4, 7.8), 2.30 (dd, 2, J = 7.8, 7.8), 2.10-2.03 (m, 4), 1.67 (s, 3), 1.34 (d, 3, J = 7.1), 1.27 (t, 3, J = 7.1); ^{13}C NMR 205.4, 170.4, 138.3, 133.7, 125.6, 114.5, 61.2, 52.8, 39.7, 33.9, 27.1, 25.7, 23.0, 14.0, 12.6; IR (neat) 1745, 1715 cm^{-1}.

Oxidative Cyclization of 6a. A solution of β-keto ester **6a** (98.5 mg, 0.33 mmol) in AcOH (3 mL) was added to a solution of $Mn(OAc)_3 \cdot 2H_2O$ (197 mg, 0.73 mmol) in AcOH (7 mL) and the resulting mixture was stirred for 2 h at rt, at which time it became clear. The reaction was diluted with water and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded 84.8 mg of crude product. Flash chromatography on silica gel (50:1 hexane/EtOAc) gave 6 mg of recovered **6a**, followed by 5 mg of a 2.3:3.6:1 mixture of **4**, **16**, and **6a**, 31 mg of a 1.8:1 mixture of **4** and **9**, 23 mg of **10**, and 9 mg of **17**. The calculated yields are 6.6 mg (7%) of recovered **6a**, 22 mg (22%) of **4**, 11 mg (11%) of **9**, 23 mg (24%) of **10**, 2.4 mg (2%) of **16**, and 8.9 mg (10%) of **17**.

Data for ethyl (1α,4aα,10aβ)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-2-oxophenanthrene-1-carboxylate (**4**) were determined from cyclization of **1a**:[3] mp 109.5-110.5; ^1H NMR 7.30-7.05 (m, 4), 4.17 (q, 2, J = 7.1), 3.13 (ddd, 1, J = 6.8, 15.1, 15.1), 2.95 (ddd, 1, J = 3.5, 3.5, 16.8), 2.83 (ddd, 1, J = 10.0, 10.0, 16.8), 2.64-2.52 (m, 2), 2.22-2.12 (m, 2), 1.85-1.75 (m, 2), 1.46 (s, 3), 1.35 (s, 3), 1.27 (t, 3, J = 7.1); ^{13}C NMR 207.9, 173.5, 146.0, 134.9, 129.2, 126.0, 126.0, 125.4, 61.2, 57.6, 53.8, 39.0, 38.0, 37.4, 31.7, 22.8, 21.3, 20.9, 13.9; IR ($CHCl_3$) 1748, 1708 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.57; H, 8.00.

Partial data for ethyl (1α,4aα,10aα)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-2-oxophenanthrene-1-carboxylate (**9**) were determined from the mixture: ^1H NMR 4.30-4.15 (m, 2), 2.78-2.71 (m, 2), 2.06-1.94 (m, 2), 1.50 (s, 3), 1.29 (s, 3), 1.28 (t, 3, J = 7.3).

Data for ethyl (1α,4aβ,10aα)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-2-oxo-phenanthrene-1-carboxylate (**10**): ^1H NMR 7.32-7.05 (m, 5), 4.27-4.10 (m, 2), 3.00-2.84 (m, 2), 2.81 (dd, 1, J = 2.2, 12.4), 2.77 (ddd, 1, J = 7.1, 11.5, 16.6), 2.66 (ddd, 1, J = 3.3, 6.6, 16.6), 2.56 (ddd, 1, J = 3.3, 7.1, 13.4), 2.05 (ddd, 1, J = 6.6, 11.5, 13.4), 1.89 (dddd, 1, J = 7.1, 11.1, 12.4, 13.2), 1.54 (dddd, 1, J = 2.2, 2.4, 6.2, 13.2), 1.45 (s, 3), 1.35 (s, 3), 1.23 (t, 3, J = 7.1); ^{13}C NMR 210.2, 172.9, 146.7, 134.7, 129.2, 126.2, 126.0, 125.2, 61.4, 60.8, 46.6, 36.7, 36.6, 35.2, 30.4, 24.3, 21.2, 16.7, 14.0; IR (neat) 1733, 1706 cm^{-1}.

Partial data for **16** were determined from the mixture: ^1H NMR (endocyclic isomer) 5.49 (m, 1), 1.86 (m, 3); (exocyclic isomer) 5.10 (br s, 1), 4.98 (br s, 1).

Data for *syn*-1,5-dimethyl-8-(2-phenylethyl)-6-oxobicyclo[3.2.1]octane-2,7-dione (**17**): ^1H NMR 7.30-7.10 (m, 5), 2.74 (ddd, 1, J = 6.2, 9.5, 13.7), 2.63 (ddd, 1, J = 7.0, 9.5, 13.7), 2.57 (ddd, 1, J = 9.0, 10.1, 17.4), 2.50 (ddd, 1, J = 1.5, 8.1, 17.4), 2.38 (ddd, 1, J = 1.8, 7.5, 7.5), 2.27 (dddd, 1, J = 1.5, 1.8, 9.0, 14.5), 2.08 (ddd, 1, J = 8.1, 10.1, 14.5), 1.67-1.55 (m, 1), 1.53 (s, 3), 1.32 (s, 3), 1.32-1.22 (m, 1); ^{13}C

NMR 201.8, 174.3, 140.2, 128.7, 128.2, 126.5, 85.2, 61.9, 56.6, 35.0, 34.1, 31.6, 28.4, 23.3, 13.4; IR (CCl_4) 1787, 1726 cm^{-1}.

Oxidative Cyclization of 6b. A solution of β-keto ester **6b** (80 mg, 0.32 mmol) in AcOH (3 mL) was added to a degassed mixture of $Mn(OAc)_3 \cdot 2H_2O$ (170 mg, 0.63 mmol) and $Cu(OAc)_2$ (58 mg, 0.32 mmol) in AcOH (5 mL). The resulting mixture was stirred for 2 h at rt. The reaction was diluted with water and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded 76 mg of crude product. Flash chromatography on silica gel (50:1 hexane/EtOAc) gave 12 mg of recovered **6b**, followed by 5 mg of a 1:6.7 mixture of **6b** and **11**, 9 mg of **11**, 6 mg of a 4:1 mixture of **11** and **5**, 19 mg of a 1:4:4.5 mixture of **11**, **18b** and **5**. The calculated yields are 13 mg (16%) of recovered **6b**, 20 mg (25%) of **11**, 10 mg (13%) of **5**[8] and 8.0 mg (10%) of **18b**.

Data for ethyl (3aα,4α,7aα)-4,7a-dimethyl-1-methylene-5-oxo-2,3,3a,4,5,6,7,7a-octahydro-1*H*-indene-4-carboxylate (**11**): ^1H NMR 4.87 (br s, 1), 4.76 (br s, 1), 4.29-4.13 (m, 2), 2.73 (dd, 1, *J* = 7.5, 12.3), 2.61 (ddd, 1, *J* = 4.8, 7.5, 16.5), 2.41-2.32 (m, 2), 2.20 (ddd, 1, *J* = 4.4, 9.0, 16.5), 1.93-1.82 (m, 2), 1.63 (ddd, 1, *J* = 4.4, 9.0, 19.2), 1.28 (t, 3, *J* = 7.1), 1.25 (s, 3), 1.24 (s, 3), 1.09-0.93 (m, 1); ^{13}C NMR 209.4, 173.5, 159.2, 103.7, 61.4, 57.3, 53.4, 43.6, 36.2, 33.4, 30.9, 27.8, 26.7, 19.6, 14.0; IR (neat) 1714, 1655 cm^{-1}.

Partial data for **18b** were determined from the mixture: ^1H NMR 5.79 (ddt, 1, *J* = 10.4, 17.1, 6.4), 5.57-5.46 (m, 2), 5.06-4.98 (m, 2), 4.15-3.95 (m, 2), 2.78 (br dd, 2, *J* = 5.5, 5.5), 2.47-2.28 (m, 2), 1.80-1.72 (m, 1), 1.40 (s, 3), 1.01 (s, 3); ^{13}C NMR 216.5, 171.0, 136.6, 134.8, 126.8, 115.3, 63.4, 60.9, 43.8, 36.7, 35.8, 31.6, 22.8, 14.1, 13.6.

Acknowledgement. We are grateful to the National Institutes of Health (GM 46470) for generous financial support.

References and Notes

1. For reviews of $Mn(OAc)_3$ as an oxidant see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Melikyan, G. G. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, **1997**; Vol. 49, Chapter 3.
2. Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.
3. Snider, B. B.; Mohan, R. M.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841.
4. Zhang, Q.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640.
5. Burnell, R. H.; Girard, M. *Synth. Commun.* **1990**, *20*, 2469.
6. Burnell, R. H.; Côte, C.; Girard, M. *J. Nat. Prod.* **1993**, *56*, 461.
7. Shishido, K.; Goto, K.; Tsuda, A.; Takaishi, Y.; Shibuya, M. *J. Chem. Soc., Chem. Commun.* **1993**, 793.
8. Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759.
9. Zoretic, P. A.; Zhang, Y.; Fang, H.; Ribeiro, A. A.; Dubay, G. *J. Org. Chem.* **1998**, *63*, 1162 and references cited therein.
10. Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737.
11. van der Gen, A.; Wiedhaup,K.; Swoboda, J. J.; Dunathan, H. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 2656.
12. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
13. Fischli, A.; Müller, P. M. *Helv. Chim Acta* **1980**, *63*, 529.
14. Cahiez, C.; Alexakis, A.; Normant, J. F. *Synthesis* **1978**, 528.
15. Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, 169.
16. Selwood, D. L.; Challand, S. R.; Champness, J. N.; Gillam, J.; Hibberd D. K.; Jandu, K. S.; Lowe, D.; Pether, M.; Selway, J.; Trantor, G. E. *J. Med. Chem.* **1993**, *36*, 3503.
17. (a) The second order rate constant for oxidation of primary radicals by $Cu(OAc)_2$ is 10^6 mol^{-1} s^{-1}: Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843. (b) The cyclization of the 4-phenylbutyl radical is 10^3 slower than oxidation by $Cu(OAc)_2$: Kochi, J. K.; Gilliom, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 5251.
18. Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607.
19. Heiba, E. I.; Dessau, R. M.; Koehl, Jr., W. J. *J. Am. Chem. Soc.* **1969**, *91*, 138.