Mn(III)-Based Oxidative Fragmentation–Cyclization Reactions of Unsaturated Cyclobutanols

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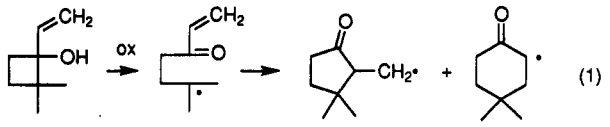
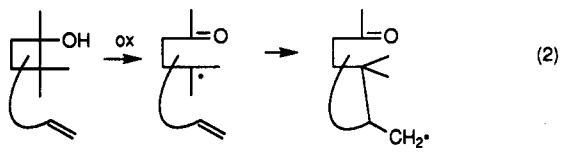
Allylic cyclobutanols **1**, **10**, **21**, **27**, **32**, **39**, **51**, and **58** are oxidatively fragmented by $Mn(OAc)_3 \cdot 2H_2O$ in EtOH to give tertiary radicals as shown in eq 1. These tertiary radicals undergo both 6-*endo*-cyclization to the α,β-unsaturated ketone to afford α-keto radicals and 5-*exo*-cyclization to provide β-keto cyclopentylmethyl radicals. The α-keto radicals produced by 6-*endo*-cyclization are reduced to ketones or dimerize. The β-keto radicals formed by 5-*exo*-cyclization are oxidized by $Cu(OAc)_2$ to yield methylenecyclopentanones and rearrange to give 3-oxocyclohexyl radicals that are oxidized by $Cu(OAc)_2$ to afford cyclohexenones. Acetylenic cyclobutanols **47**, **49**, and **65** are oxidatively fragmented by $Mn(OAc)_3 \cdot 2H_2O$ in EtOH to provide tertiary radicals that cyclize to give α-keto vinyl radicals, which abstract a hydrogen atom to yield methylenecyclopentanones. Pentenylcyclobutanol **75** is oxidatively fragmented by $Mn(OAc)_3 \cdot 2H_2O$ to afford tertiary radical **74**, which cyclizes to furnish cyclopentylmethyl radicals **77** and **78**, which are oxidized by $Cu(OAc)_2$ to methylenecyclopentanes **76** and **79**.

Introduction

The one-electron oxidation of cyclobutanols to give γ-keto radicals is well-known. We wanted to develop procedures that would permit the acyclic γ-keto radical to be trapped by cyclization to a proximate double bond to give a new cyclic structure. The double bond could be conjugated to the ketone produced in the fragmentation as shown in eq 1 or attached to the cyclobutane fragment by a tether as shown in eq 2. We have developed a class of oxidative free-radical cyclizations initiated by oxidation of 1,3-dicarbonyl compounds to an α-keto radical by $Mn(OAc)_3$ and terminated by oxidation of an alkyl radical to an alkene by $Cu(OAc)_2$.[1] We anticipated that $Mn(OAc)_3$ would oxidatively cleave unsaturated cyclobutanols to give γ-keto radicals that would cyclize and that $Cu(OAc)_2$ would oxidize the cyclic radicals shown in eqs 1 and 2 to alkenes.



(1)



(2)

Relief of ring strain makes fragmentation of cyclobutyl-containing radicals a facile process. Many examples of the oxidative fragmentation of cyclobutanols have been reported. Reaction of cyclobutanol with ceric ammonium nitrate affords the γ-keto radical that is trapped primarily as the nitrate ester.[2] Oxidation of 1-vinylcyclobutanol with $HgO-I_2$ leads to the γ-keto radical that is trapped as the iodide.[3] Dowd has examined the addition of radicals to cyclobutanones to give cyclobutyloxy radicals that fragment.[4] Oxidation of cyclobutanones with $VO(OEt)Cl_2$ affords γ-carbalkoxy radicals that add to electron-deficient alkenes.[5] Cyclobutylcarbinyl radicals fragment readily to give 4-pentenyl radicals.[6,7] The iminyl radicals derived from cyclobutanones fragment to give γ-nitrile radicals.[8]

Ring opening reactions of cyclopropylcarbinyl radicals are also very facile.[9] While this work was in progress, Narasaka reported an elegant study on the oxidative fragmentation of cyclopropanols with Mn(III) picolinate to give β-keto radicals that add inter- and intramolecularly to alkenes.[10] We reported that oxidation of cyclopropyl silyl ethers with cupric tetrafluoroborate affords radicals that add to alkenes[11] and Booker-Milburn reported similar reactions with $FeCl_3$.[12]

Results and Discussion

Oxidative Fragmentation of 1. Initial experiments were carried out with vinylcyclobutanol **1**, which was

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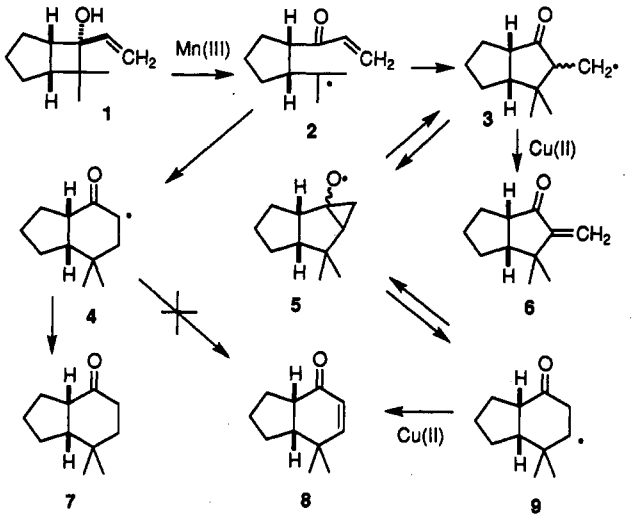
readily prepared by addition of vinyllithium to the *exo* face[13] of 7,7-dimethylbicyclo[3.2.0]heptan-6-one.[14] Oxidation of **1** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in EtOH for 3 h at 25 °C affords 83% of methylenecyclopentanone **6** and a trace (<1%) of cyclohexenone **8**. The first step in the conversion of **1** to **6** presumably is the formation of the Mn(III) alkoxide, which fragments, with relief of ring strain, to give the more stable tertiary radical **2** and Mn(II). We do not believe that an alkoxy radical is an intermediate since preliminary experiments indicate that cyclohexanols do not react under these conditions. $Mn(OAc)_3$ differs from the stronger oxidant $Pb(OAc)_4$ that oxidizes a wide variety of alcohols to alkoxy radicals.[15]



5-*Exo*-cyclization of radical **2** will give cyclopentylmethyl radical **3** as a mixture of stereoisomers, both of which will be oxidized to **6** by $Cu(OAc)_2$. Intermolecular additions of alkyl radicals to conjugated enones occurs preferentially on the β-carbon to give the α-keto radical. As has been previously observed,[16] the inherent preference for 5-*exo*-cyclization overcomes the electronic preference for addition to the β-carbon.

A priori, there are two possible pathways for the formation of cyclohexenone **8**. The obvious pathway involves 6-*endo*-cyclization of radical **2** to give α-keto radical **4** that could be oxidized to afford cyclohexenone **8**. However, α-keto radicals are easily reduced by low valent metals, e.g., Fe(II),[17] and not easily oxidized. If **4** were formed, we would expect that reduction to the enolate by Mn(II) and protonation to give cyclohexanone **7** would also occur. The second, less obvious pathway to **8** involves the rearrangement of β-keto radical **3** to β-keto radical **9** by addition of the radical to the carbonyl group to form a cyclopropyloxy radical. This pathway is well precedented by the recent studies of Dowd and Beckwith.[18,19]

If both **6** and **8** are formed from cyclopentylmethyl radical **3**, the ratio of the two products should depend on the concentration of Cu(II). A greater percentage of cyclohexenone **8** should be formed at low Cu(II) concentration, since the oxidation of **3** to give **6** will be slower, while the rearrangement of **3** to radical **9** will occur at the same rate. Reaction of **1** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and only 0.1 equiv of $Cu(OAc)_2$ provides 75% of a 9:1 mixture of **6** and **8**. Since the yield of **8** increases from <1% with 1.0 equiv of Cu(II) to 7.5% with 0.1 equiv of Cu(II), **8** is formed from rearrangement of **3** to β-keto radical **9**, which is then oxidized, rather than from oxidation of α-keto radical **4**. Oxidation of **1** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ without $Cu(OAc)_2$ for 4 h at 25 °C gives no **6** and only 5% of **8**. As expected, Mn(III) does not oxidize primary radical **3** and is not effective for the oxidation of secondary radical **9**.

Methylenecyclopentanones have been prepared from 1-vinylcyclobutanols by Pd[20] and Hg-catalyzed[21] ring expansion reactions. The Mn(III) reaction described here is mechanistically distinct since it involves a fragmentation–cyclization sequence to achieve a net ring expansion.

We briefly explored the reaction of **1** with other oxidants that can generate alkoxy radicals.[22c] Initial results with ceric ammonium nitrate,[2] $Pb(OAc)_4$,[15] and (diacetoxyiodo)-benzene–iodine, which has been used with good success in alkoxy radical fragmentation and transannular cyclization reactions related to those described here,[22] were not promising. Oxidation of **1** with 2 equiv of $Mn(pic)_3$ and 1 equiv of $Cu(OAc)_2$ in DMF[10] gives 17% of cyclohexenone **8** and no methylenecyclopentanone **6**. We have found that oxidation of radicals to alkenes does not occur readily with $Mn(pic)_3$ and $Cu(OAc)_2$, apparently due to the rapid reaction of the radical with a manganese picolinate species.[23]

Oxidative Fragmentation of 10. Oxidation of propenylcyclobutanol **10** was examined to unambiguously determine the mechanism of cyclohexenone formation. Reaction of **10** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 0.1 equiv of $Cu(OAc)_2$ in EtOH for 30 min at reflux affords 10% of ethylidenecyclopentanone **18**, 11% of cyclohexenone **20**, and 56% of an 11:5:4 inseparable mixture of ethylidenecyclopentanone **19** and vinylcyclopentanones **16** and **17** (stereochemistry unassigned). Conjugation of the double bonds of **16** and **17** in the crude product mixture with Et_3N in ether followed by purification provides 34% of **18**, 29% of **19**, and 10% of **20**. Ethylidenecyclopentanes **18** and **19** do not interconvert on treatment with Et_3N in ether. Since the yield of **18** increases from 10% to 34% by conjugation of the double bonds of **16** and **17**, while the yield of **19** is essentially unchanged (≈31% (55% × 56%) vs 29%), **16** and **17** must isomerize mainly to the *Z*-enone **18** and *E*-enone **19** must therefore be formed directly by Cu(II) oxidation of **13**.

The structure of cyclohexenone **20** was assigned on the basis of the absorption of the alkene hydrogen at δ 6.30,

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(20) (a) de Almeida Barbosa, L.-C.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 177. (b) Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, *26*, 2503.

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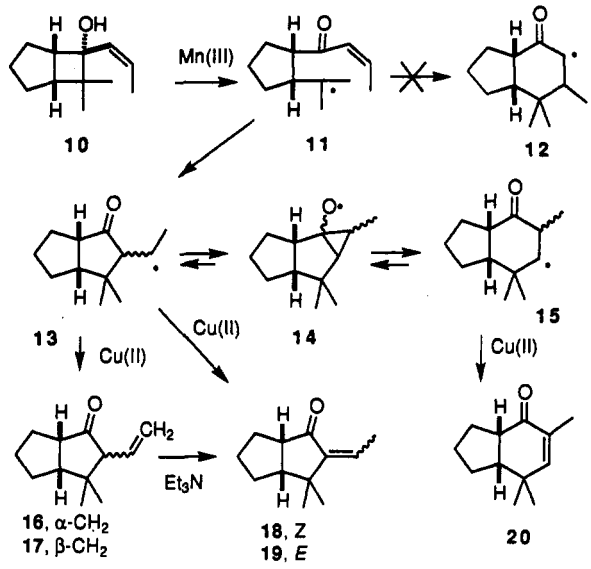
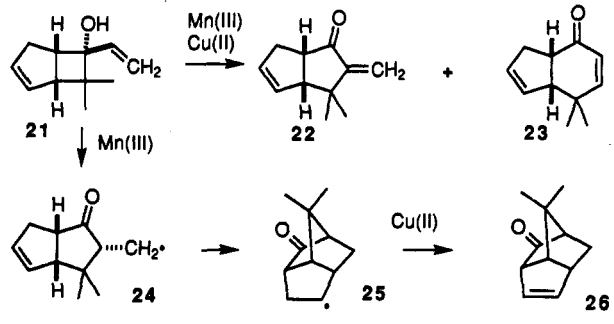
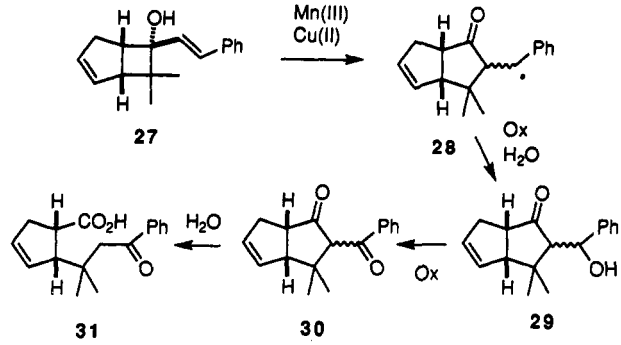
a value identical to that of 2,4,4-trimethyl-2-cyclohexenone (δ 6.30)[24] and quite different from that of 3,4,4-trimethylcyclohexenone (δ 5.75).[25] Cyclohexenone **20** is formed by 5-*exo*-cyclization of **11** to give **13**, rearrangement via cyclopropyloxy radical **14** to cyclohexyl radical **15**, and oxidation by Cu(II). 6-*Endo*-cyclization of **11** would have given α-keto radical **12**, which would have given a 3-methylcyclohex-2-enone if it had been oxidized.



Oxidative Fragmentation of 21. A tandem cyclization is observed in the oxidative fragmentation–cyclization of **21**, which is readily available from addition of vinyllithium to the *exo* face[13] of 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one.[14] Oxidation of **21** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in EtOH for 1 h at reflux affords 22% of methylenecyclopentanone **22**, 1.5% of cyclohexenone **23**, and 44% of tricyclic enone **26**.[26] Unsaturated *endo*-cyclopentylmethyl radical **24** undergoes a rapid 5-*exo*-cyclization to give tricyclic radical **25** that is oxidized to **26** by Cu(II).



Oxidative Fragmentation of 27. An alternate termination process converts benzylic cyclopentylmethyl radical **28** to keto acid **31**. Oxidation of **27** with 4 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in EtOH for 12 h at 25 °C affords 25% of keto acid **31**. Fragmentation and cyclization as discussed above leads to benzylic radical **28**. Benzylic radicals are readily oxidized by Mn(III) or Cu(II) to cations, which react with water to give alcohol **29**. Oxidation of **29** by Mn(III) affords ketone **30**, which undergoes a retro-Dieckmann cyclization to give keto acid **31**.



Oxidative Fragmentation of 32. Oxidation of cyclohexenyl alcohol **32** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in EtOH for 11 h at 25 °C provides 14% of enone **34**, 21% of ketone **37**, and 22% and 18% of the diastereomeric dimers **35** and **36**, respectively. Similar mixtures of products were formed when 1 equiv of $Cu(OAc)_2$ is used as a co-oxidant. The tertiary radical formed from fragmentation of **32** undergoes exclusively 6-*endo*-cyclization to give α-keto radical **33**. Radical cyclization to 1-cyclohexenyl ketones has been shown to give 6-*endo*- rather than 5-*exo*-cyclization.[27] Examination of models suggests that proper overlap of the radical with the enone double bond will give the *syn* isomer **33** shown. Oxidation of α-keto radical **33** will give enone **34**, while hydrogen transfer or reduction by Mn(II) and protonation will give saturated ketone **37**. Hydrogenation of **34** affords a 3:1 mixture of **37** and **38**. Hydrogenation should occur predominantly from the less hindered β-face. Therefore the isomer formed from reduction of radical **33** and the major isomer from hydrogenation of enone **34** is tentatively assigned structure **37**. The structure of dimer **35** was established by X-ray crystallography.[28] The spectral data for the two dimers are very similar and structure **36** was tentatively assigned to the other diastereomer. α-Keto radical **33** is racemic and would be expected to form both diastereomeric dimers. Dimerization of α-keto radicals by C–C bond formation to give 1,4-diketones is well-known.[29] C–O bond formation is less common[1c] but is reasonable for very highly substituted, hindered α-keto radicals such as **33**.

Oxidative Fragmentation of 39. Addition of vinyllithium to spiro[3.5]nonan-2-one[30] affords 88% of **39**. Oxidation of **39** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in EtOH at reflux for 40 min affords 6% of methylenecyclopentanone **41**, 24% of cyclohexanone **42**,[31] 30% of cyclohexenone **44**,[32] 11% of the less polar dimer **46a**, and 10% of the more polar dimer **46b**. A similar reaction using only 0.1 equiv of $Cu(OAc)_2$ affords only

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(28) X-ray data, analyses, and experimental details are available from the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(29) (a) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 649 and 2912. (b) Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* **1977**, 3741. (c) Frazier, R. H., Jr.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408.
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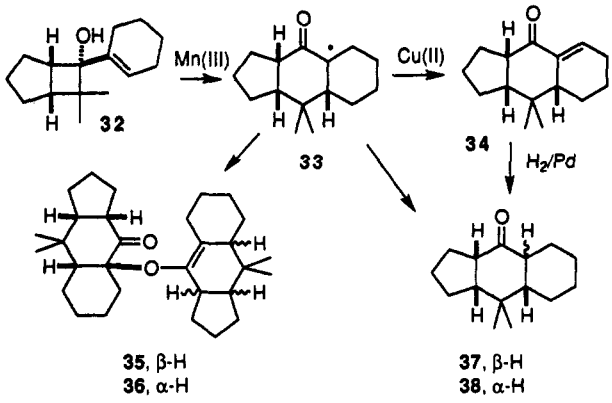
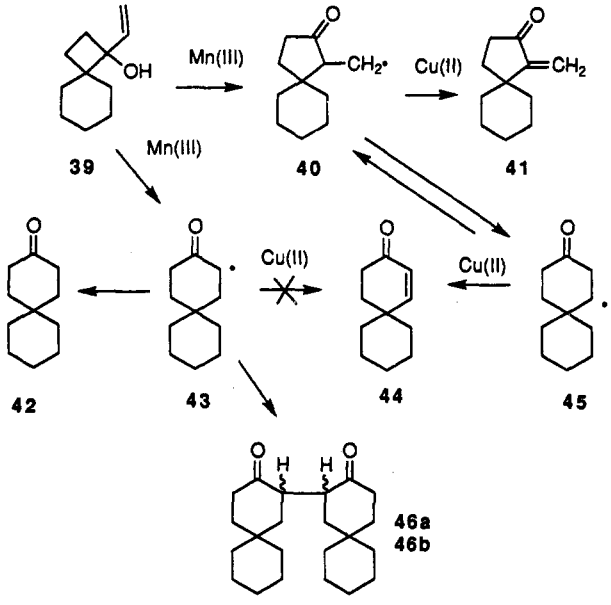
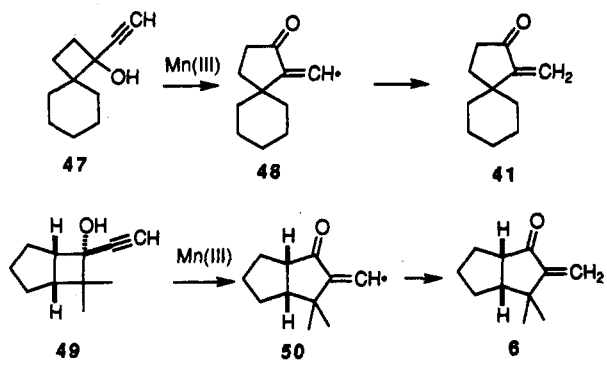


2.5% of **41**, 23% of **42**, 34% of **44**, and 21% of dimers **46a** and **46b**. The same amount of cyclohexanone **42** and dimers **46a** and **46b** are formed at both copper concentrations, suggesting that α-keto radical **43** is not oxidized to cyclohexenone **44**. The total yield of **41** and **44** is constant since both are derived from a common intermediate, cyclopentylmethyl radical **40**, although as expected, more methylenecyclopentanone **41** is formed at higher Cu(II) concentration. Oxidation of **39** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ without $Cu(OAc)_2$ in EtOH at reflux for 30 min affords 14% of cyclohexanone **42**, 11% of cyclohexenone **44**, 10% of **46a**, and 10% of **46b**. Oxidation of **39** with 2 equiv of $Mn(pic)_3$ in DMF affords 14% of **42**, 6% of **44**, and 28% of dimers **46a** and **46b**.

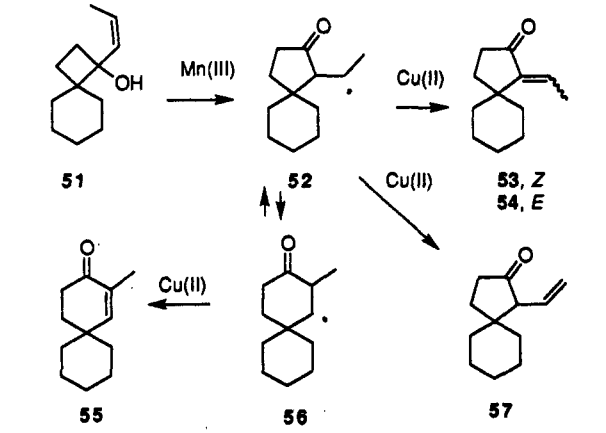


α-Keto radical **43** is converted to cyclohexanone **42** either by hydrogen abstraction or by reduction with Mn(II) and protonation. Radical **43** also dimerizes to give a mixture of diastereomers **46a** and **46b** in a process that may be metal mediated. Secondary α-keto radical **43** gives exclusively C–C dimers unlike the more hindered tertiary α-keto radical **33**, which gives C–O dimers **35** and **36**. The structures of **46a** and **46b** were confirmed by conversion of each isomer to an equilibrium mixture with K_2CO_3 in MeOH and preparation of an authentic sample by oxidation of the lithium enolate of cyclohexanone **42** with $CuCl_2$.[29a] We also established that cyclohexanone **42** is stable under the conditions used to oxidize cyclobutanol **39**, indicating that dimers **46a** and **46b** are primary products formed from α-keto radical **43** rather than secondary products formed by further oxidation of **42** with $Mn(OAc)_3 \cdot 2H_2O$ or $Cu(OAc)_2$.

Although methylenecyclopentanone **41** is a minor product from **39**, it is available in 45% yield by oxidative fragmentation–cyclization of propargylic alcohol **47** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in EtOH at 25 °C for 12 h. Fragmentation and addition of the tertiary radical to the ynone provides vinyl radical **48**, which does not rearrange and is not oxidized but rather rapidly extracts a hydrogen atom to give **41**. The procedure is general, since the analogous reaction of propargylic alcohol **49** affords 68% of **6**.



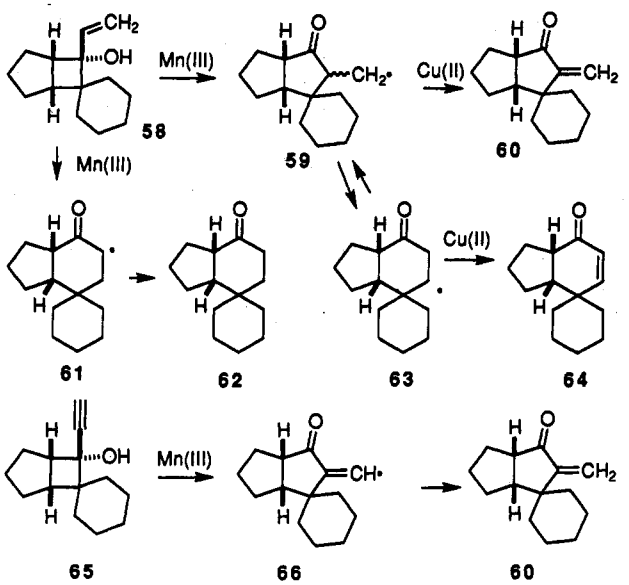
Oxidative Fragmentation of 51. Oxidative fragmentation–cyclization of **51** was examined to determine the effect of the methyl group on the regioselectivity of the radical cyclization. The β-methyl group should retard 6-*endo*-cyclization and accelerate 5-*exo*-cyclization. As expected, all the products obtained from **51** result from initial 5-*exo*-cyclization. Oxidation of **51** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 0.1 equiv of $Cu(OAc)_2$ affords 8% of (*Z*)-ethylidenecyclopentanone **53**, 22% of (*E*)-ethylidenecyclopentanone **54**, 24% of 2-methylcyclohexenone **55**, and 1% of vinylcyclopentanone **57**. As discussed previously for **20**, the formation of a 2-methylcyclohexenone requires the formation and rearrangement of a cyclopentylmethyl radical.



The cyclization of the radical produced from **39** gives very different mixtures of products than the cyclization of radical **2**, produced from cyclobutanol **1**, even though both cyclizations are additions of tertiary radicals to unsubstituted α,β-unsaturated enones. Radical **2** undergoes exclusively 5-*exo*-cyclization to give **3** while the radical from **39** undergoes 40% 6-*endo*-cyclization to give α-keto radical **43**. Furthermore, cyclopentylmethyl radical **3** is oxidized to methylenecyclopentanone **6** much faster than it rearranges while cyclopentylmethyl radical **40** rearranges

to cyclohexyl radical **45** much faster than it is oxidized. There are two structural differences between cyclobutanols **39** and **1**. The cyclobutane ring of **1** is fused to a cyclopentane and the *gem*-dimethyl groups of **1** have been replaced with a spiro cyclohexane in **39**. To determine which of these features is responsible for the change in regioselectivity of the radical cyclization, we examined the oxidative fragmentation–cyclization of vinylcyclobutanol **58**, which has the fused cyclopentane of **1** and the spiro cyclohexane of **39**.

Oxidative Fragmentation of 58. Addition of vinyllithium to the cyclobutanone precursor[33] affords 76% of **58**. Reaction of **58** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in EtOH at reflux for 40 min affords a 58:23:19 mixture of **60**, **62**, and **64** as determined by GC analysis. A similar reaction with only 0.1 equiv of $Cu(OAc)_2$ provides a 34:26:40 mixture of **60** (22%), **62** (17%), and **64** (26%), which were isolated in the yields indicated. Dimers analogous to **46** are probably formed but were not characterized due to their structural complexity. Hydrogenation of **64** affords 99% of **62**, confirming the structure assignments. Oxidation of **58** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ without $Cu(OAc)_2$ affords a trace of **60**, 12% of **62**, and 8% of **64**. Oxidation of propargylic alcohol **65** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in EtOH at reflux provides 40% of methylenecyclopentanone **60** uncontaminated with **62** or **64**.



The formation of the same percentage of **62** with 0.1 (25%) and 1 equiv (23%) of $Cu(OAc)_2$ indicates that α-keto radical **61** is reduced to **62** and is not oxidized to **64**. Enones **60** and **64** are both formed from cyclopentylmethyl radical **58**, since the total percentage of the two products does not change with varying Cu(II) concentration. As expected, methylenecyclopentanone **60** is the major product (58%) when 1.0 equiv of Cu(II) is used, while the rearranged product cyclohexenone **64** predominates (40%) when only 0.1 equiv of Cu(II) is used.

The radical from **1** cyclizes exclusively 5-*exo*. The radical from **58**, in which the *gem*-dimethyl groups have been replaced by a bulkier spiro cyclohexane, cyclizes 75–77% 5-*exo*. Steric effects may be responsible for this change in selectivity. Examination of models suggests that the cyclohexyl radical formed from **58** is more hindered than tertiary radical **2** and that the transition state for 5-*exo*-cyclization is more hindered than the transition state for 6-*endo*-cyclization. The cyclohexyl radical formed from **39** cyclizes 60% 5-*exo*, suggesting that the fused cyclopentane ring of **58** does not have a major effect on the initial radical cyclization.

Cyclopentylmethyl radical **3** gives a 9:1 ratio of methylenecyclopentanone **6** to cyclohexenone **8** when 0.1 equiv of Cu(II) is used. Under these conditions, cyclopentylmethyl radical **59** affords a 0.85:1 ratio of methylenecyclopentanone **60** to cyclohexenone **64**. Therefore replacement of the *gem*-dimethyl group of **3** with the spiro cyclohexane of **59** facilitates isomerization to the β-keto cyclohexyl radical. With 0.1 equiv of Cu(II), cyclopentylmethyl radical **40** affords a 0.07:1 ratio of methylenecyclopentanone **41** to cyclohexenone **44**. Since the only difference between **59** and **40** is the fused cyclopentane ring, this ring may retard the isomerization to β-keto cyclohexyl radical **63** or facilitate oxidation to methylenecyclopentanone **60**. More complete analysis is not possible since the equilibration of radicals such as **59** and **63** is reversible so that both kinetic and thermodynamic factors need to be considered. The markedly different ratios of products obtained from **1**, **39**, and **58** demonstrate that small changes in the structure of the cyclobutanol can have a major effect on the reaction pathway.

Oxidative Fragmentation of 75. We next turned to examples of the type shown in eq 2 in which the double bond is not conjugated to the ketone produced in the fragmentation. Cyclobutanol **75** was prepared in three steps from 6-heptenoic acid (**67**). Alkylation of the dianion of **67** with 5-iodo-1-pentene yields 79% of acid **68**, which is converted to acid chloride **69** with oxalyl chloride. Addition of the acid chloride to Et_3N in toluene at reflux generates the ketene, which undergoes an intramolecular [2 + 2] cycloaddition[34] providing 67% of cyclobutanone **70**. Addition of methyllithium from the *exo* face[13] affords 73% of **75**.

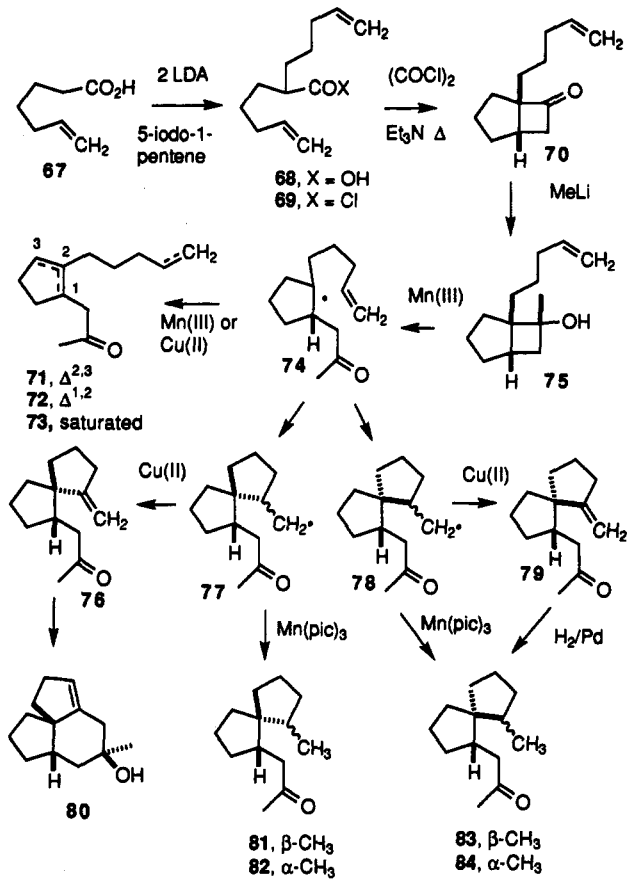
Oxidation of **75** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in EtOH at 25 °C for 4 h affords 1.5% of **76** and 69% of an 1:1:8 mixture of **71**, **72**, and **79**. Oxidative fragmentation leads to tertiary radical **74**. 5-*Exo*-cyclization gives a mixture of the four cyclopentylmethyl radicals **77** and **78**. Cyclization occurs preferentially from the less hindered face to give **78**, which is oxidized by Cu(II) to give the observed major product **79**. Cyclization from the more hindered face gives **77**, which is oxidized to the minor product **76**. The minor enone **76** undergoes an intramolecular ene reaction on standing in $CDCl_3$ for 2 d to give homoallylic alcohol **80**. This establishes the relative stereochemistry of **76** and **79** since only isomer **76**, with the double bond and the acetone side chain cis, can undergo an intramolecular ene reaction.[35]

We examined the oxidation of **75** with other oxidants under a variety of other conditions. Oxidation under Narasaka's conditions with 2 equiv of $Mn(pic)_3$ and 1 equiv of $Cu(OAc)_2$ in DMF at 25 °C for 5 h affords 62% of a 5:5:8:8:10:24 mixture of **71**, **72**, **83**, **81** or **82**, **82**, or **81**, and

(33) Brady, W. T.; Ting, P. L. *J. Org. Chem.* **1974**, *39*, 763.

(34) Snider, B. B.; Allentoff, A. J.; Walner, M. B. *Tetrahedron* **1990**, *46*, 8031.

(35) Using MODEL version 2.96 and MMX obtained from Prof Kosta Steliou, University of Montreal, we calculated ΔH_f and ΔS_f for **76**, **79**, **80**, and the ene adduct from **79**. From these we calculate $\Delta H = -11.2$ kcal/mol and $\Delta S = -22$ eu for the ene reaction of **76** to give **80** and $\Delta H = +1.0$ kcal/mol and $\Delta S = -22$ eu for the ene reaction of **79** to give the ene adduct. At room temperature, $\Delta G = -4.6$ and +7 kcal/mol for the ene reactions of **76** and **79**, respectively.



84, respectively. As noted above, oxidation of primary radicals to alkenes by Cu(II) does not occur readily when $Mn(pic)_3$ is used. This appears to be due to the rapid reaction of the radical with a manganese picolinate species.[23] The structures of **83** and **84** were established by hydrogenation of the 1:1:8 mixture of **71**, **72**, and **79** to give a 3:2:10 mixture of **73**, **83**, and **84**, respectively. Hydrogenation of the double bond of **79** should occur with modest preference from the somewhat less hindered β-face to give **84** as the major product. Uncharacterizable mixtures were obtained from oxidation of **75** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and no $Cu(OAc)_2$ in EtOH, with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2$ in AcOH, and with 2 equiv of $Mn(pic)_3$ in EtOH with or without $Cu(OAc)_2$. Oxidation of **75** by ceric ammonium nitrate, $NaHCO_3$, and $Cu(OAc)_2$ in CH_3CN affords a 1:1 mixture of **71** and **72** in modest yield.

The formation of the monocyclic unsaturated ketones **71** and **72** was unexpected. Unsaturated ketones resulting from oxidation of the tertiary radicals, e.g., **2** and **11**, formed in the oxidative fragmentation were not isolated from any of the other cyclizations. The other cyclizations are probably faster than that of **74**, since the nucleophilic tertiary radicals are adding to electron-deficient α,β-unsaturated ketones in all other examples. It is also possible that oxidation products analogous to **71** and **72** are formed but react further since they are vinyl ketones.

All the examples described above involve fragmentation of a cyclobutanol to give a tertiary 5-hexenyl radical that undergoes 5-*exo*- or 6-*endo*-cyclization. We examined the oxidative fragmentation–cyclization of homoallylic alcohols **85** and **86** to determine whether the slower 6-*exo*- or 7-*endo*-cyclization could compete with oxidation of the tertiary radical. A complex mixture of products is obtained in preliminary experiments, suggesting that oxidation of the tertiary radical formed in the fragmentation is faster than 6-*exo*- or 7-*endo*-cyclization. Initial trial experiments with cyclobutanols that would fragment to secondary radicals were not promising. For instance, a complex mixture is obtained from vinylcyclobutanol **87**.[20b]

Conclusion. Allylic cyclobutanols are oxidatively fragmented by $Mn(OAc)_3 \cdot 2H_2O$ in EtOH to give tertiary radicals as shown in eq 1. These tertiary radicals undergo both 6-*endo*-cyclization to the α,β-unsaturated ketone to afford α-keto radicals and 5-*exo*-cyclization to provide β-keto cyclopentylmethyl radicals. The α-keto radicals produced by 6-*endo*-cyclization are reduced to ketones or dimerize. The β-keto radicals formed by 5-*exo*-cyclization are oxidized by $Cu(OAc)_2$ to yield methylenecyclopentanones and rearrange to give 3-oxocyclohexyl radicals that are oxidized by $Cu(OAc)_2$ to afford cyclohexenones. Acetylenic cyclobutanols are oxidatively fragmented by $Mn(OAc)_3 \cdot 2H_2O$ in EtOH to provide tertiary radicals that cyclize to give α-keto vinyl radicals, which abstract a hydrogen atom to yield methylenecyclopentanones.

Experimental Section

NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ and coupling constants in hertz. Combustion analyses were performed by Spang Microanalytical Laboratory. $Mn(OAc)_3 \cdot 2H_2O$ (97% pure) and $Cu(OAc)_2$ (98% pure) were purchased from Aldrich. All alkylations and oxidative cyclizations were run under N_2 in flame-dried glassware. Reagents were added by syringe or cannula.

Preparation of 1. Vinyllithium (1.85 mL of 1.65 M in THF, 3.05 mmol) was added dropwise to a solution of 7,7-dimethylbicyclo[3.2.0]heptan-6-one[14] (281 mg, 2.03 mmol) in THF (10 mL) at −78 °C. The reaction was stirred for 15 min at −78 °C and quenched by slow addition of saturated NH_4Cl solution (10 mL). Water was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 333 mg of crude **1**. Flash chromatography (95:5 hexanes/EtOAc) provided 326 mg (97%) of **1**: ^1H NMR 6.09 (dd, 1, J = 10.7, 17.3), 5.17 (dd, 1, J = 1.5, 17.3), 5.05 (dd, 1, J = 1.5, 10.7), 2.83 (ddd, 1, J = 1.5, 8.0, 8.3), 2.14 (ddd, 1, J = 2.3, 8.3, 8.5), 1.89–1.64 (m, 4), 1.49–1.35 (m, 2), 1.03 (s, 3), 0.88 (s, 3); ^{13}C NMR 143.2, 111.5, 77.0, 45.8, 44.4, 42.3, 28.7, 28.5, 27.7, 25.9, 17.2; IR (neat) 3473, 3083, 2952, 2862, 1634, 1465, 1446, 1414, 1382, 1364, 1209, 1170, 999, 983, 917. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.58; H, 11.08.

Oxidation of 1. $Cu(OAc)_2$ (147 mg, 0.79 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (439 mg, 1.59 mmol) were degassed in vacuo. EtOH (14 mL) was added and the mixture was stirred for 10 min and treated with a solution of cyclobutanol **1** (120 mg, 0.72 mmol) in EtOH (4 mL) via a cannula. The solution was stirred for 3 h at rt and H_2O (15 mL) was added. The mixture was extracted with ether (25 and 3 × 10 mL). The combined ether layers were washed with brine (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to give 126 mg of crude **6**. Flash chromatography (9:1 pentane/ether) gave 99 mg (83%) of **6**: ^1H NMR 5.99 (d, 1, J = 0.7), 5.21 (d, 1, J = 0.7), 2.83 (ddd, 1, J = 10.8, 7.6, 3.7), 2.25 (ddd, 1, J = 11.2, 7.9, 6.6), 2.15–2.01 (m, 1), 1.87–1.65 (m, 3), 1.55–1.40 (m, 1), 1.22 (s, 3), 1.17 (s, 3), 1.01–0.85 (m, 1); ^{13}C NMR 211.2, 154.0, 116.4, 52.3, 51.0, 40.3, 31.9, 29.8, 27.9, 26.3, 23.8; IR (neat) 2957, 2869, 1723, 1637, 1449, 1406, 1365, 1302, 1290, 1276, 1165, 1084, 937. Anal. Calcd for $C_{11}H_{16}O$: C, 79.46; H, 10.91. Found: C, 79.58; H, 11.08.

Oxidation of 1 with $Mn(pic)_3$ and $Cu(OAc)_2$. Alcohol 1 (100 mg, 0.60 mmol) was dissolved in DMF (5 mL). $Cu(OAc)_2$ (110 mg, 0.60 mmol) was added. $Mn(pic)_3$ (553 mg, 1.26 mmol) in DMF (10 mL) was added dropwise over 15 min. The reaction was complete within 45 min. Workup and purification as described above gave 22 mg of unidentifiable material and 17 mg (17%) of **8**: ^1H NMR 6.54 (dd, 1, J = 2.2, 10.1), 5.84 (d, 1, J = 10.1), 2.75 (ddd, 1, J = 1.5, 6.5, 6.5), 2.40–2.29 (m, 1), 2.10 (dddd, 1, J = 2.0, 6.5, 6.5, 13.1), 1.80–1.68 (m, 2), 1.65–1.48 (m, 2), 1.37–1.25 (m, 1), 1.27 (s, 3), 1.14 (s, 3); ^{13}C NMR 201.4, 157.3, 126.0, 51.2, 47.4, 34.7, 30.3, 27.5, 27.2, 27.0, 22.4; IR (neat) 2960, 2871, 1731, 1673, 1470, 1451, 1376, 1225, 1122.

Preparation of 10. *t*-BuLi (3.83 mL of 1.7 M in pentane, 6.51 mmol) was added dropwise to a solution of 1-bromopropene (411 mg, 3.26 mmol, 77% *cis*, 23% *trans*) in THF (9 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and at rt for 15 min and recooled to −78 °C. 7,7-Dimethylbicyclo[3.2.0]-heptan-6-one (300 mg, 2.17 mmol) in THF (2 mL) was added and the solution was stirred for 30 min. The reaction mixture was quenched by dropwise addition of saturated NH_4Cl and H_2O. Workup as described above followed by flash chromatography (99:1 hexanes/EtOAc) gave 140 mg (36%) of pure **10** followed by 98 mg (25%, 80% pure) of the *trans* isomer of **10**.

Data for 10: ^1H NMR 5.68 (dq, 1, J = 11.2, 1.6), 5.53 (dq, 1, J = 11.2, 7.0), 2.81 (dd, 1, J = 8.3, 8.3), 2.10 (ddd, 1, J = 2.4, 8.3, 8.3), 1.96–1.86 (m, 2), 1.75–1.60 (m, 2), 1.74 (dd, 3, J = 1.6, 7.0), 1.51–1.32 (m, 2), 1.30 (s, 1), 1.07 (s, 3), 0.92 (s, 3); ^{13}C NMR 136.5, 127.5, 76.4, 47.7, 46.1, 42.1, 29.2, 28.4, 27.9, 26.2, 17.6, 15.1; IR (neat) 3493, 2950, 2862, 1644, 1446, 1382, 1364, 1010, 984, 926.

Oxidation of 10. $Mn(OAc)_3 \cdot 2H_2O$ (591 mg, 2.14 mmol) in EtOH (15 mL) was added dropwise over 15 min to a solution of cyclobutanol **10** (183 mg, 1.02 mmol) and $Cu(OAc)_2$ (19 mg, 0.10 mmol) in EtOH (15 mL) at reflux. The solution was stirred for 15 min and worked up as described above to give 185 mg of crude product. A portion of this crude material (133 mg) was purified by flash chromatography (99:1 hexanes/EtOAc) to give 13 mg (10%) of **18**, followed by 15 mg (11%) of **20**, and 73 mg (56%) of a 55:25:20 mixture of **19**, **16** or **17**, and **17** or **16**, respectively.

The remainder of the crude product (52 mg) was dissolved in ether (2 mL) and Et_3N (1 mL). The solution was stirred for 1 d at rt and concentrated in vacuo. Flash chromatography (99:1 hexanes/EtOAc) provided **18** (17 mg, 34%), followed by **20** (5 mg, 10%) and **19** (15 mg, 29%). Isomerization of the above mixture of **19**, **16**, and **17** (6 mg) under identical conditions provided a quantitative yield of a ≈1:1 mixture of **18** and **19**. Both pure **18** and pure **19** were stable under these reaction conditions. A similar oxidation of the *trans* isomer of **10** (80% pure) gave a mixture of the same products in the same ratio as obtained from **10** as determined by analysis of the ^1H NMR spectrum.

Data for 16 and 17: ^1H NMR (major) 5.70 (ddd, 1, J = 8.8, 10.3, 17.1), 5.25 (dd, 1, J = 2.0, 10.3), 5.10 (ddd, 1, J = 0.8, 2.0, 17.1), 1.12 (s, 3), 0.76 (s, 3); (minor) 5.64 (ddd, 1, J = 8.5, 10.3, 17.1), 5.32 (dd, 1, J = 2.0, 10.3), 5.14 (ddd, 1, J = 0.8, 2.0, 17.1), 1.08 (s, 3), 0.92 (s, 3); ^{13}C NMR (both) 221.5, 219.3, 132.1, 131.2, 120.6, 119.6, 66.3, 60.9, 52.5, 51.5, 51.3, 40.9, 39.8, 30.3, 29.7 (2 C), 28.9, 27.6 (2 C), 27.5, 26.7, 25.8, 23.8, 19.7; IR (neat) 1737.

Data for 18: ^1H NMR 5.93 (q, 1, J = 7.4), 2.76 (ddd, 1, J = 3.6, 9.4, 9.4), 2.20–2.10 (m, 1), 2.13 (d, 3, J = 7.4), 2.09–1.94 (m, 1), 1.87–1.62 (m, 3), 1.52–1.37 (m, 1), 1.14 (s, 3), 1.13 (s, 3), 1.10–0.90 (m, 1); ^{13}C NMR 212.7, 144.7, 134.4, 52.1, 51.6, 40.7, 32.6, 29.7, 27.9, 26.3, 24.4, 14.3; IR (neat) 2955, 2869, 1711, 1640, 1448, 1365, 1345, 1092.

Data for 19: ^1H NMR 6.66 (q, 1, J = 7.6), 2.75 (ddd, 1, J = 3.5, 9.4, 9.4), 2.14 (ddd, 1, J = 6.6, 7.2, 11.3), 2.09–1.61 (m, 3), 1.90 (d, 3, J = 7.6), 1.58–1.40 (m, 1), 1.38 (s, 3), 1.24 (s, 3), 1.04–0.88 (m, 1); ^{13}C NMR 210.5, 144.9, 133.4, 53.7, 51.0, 40.3, 29.8, 29.6, 27.4, 26.0, 24.8, 13.6; IR (neat) 2955, 2870, 1717, 1642, 1467, 1448, 1259, 1158, 1141.

Data for 20: ^1H NMR 6.30 (br s, 1), 2.74 (dd, 1, J = 7.6, 7.6), 2.38–2.27 (m, 1), 2.15–2.01 (m, 1), 1.88–1.47 (m, 3), 1.74 (d, 3, J = 1.3), 1.36–1.10 (m, 2), 1.23 (s, 3), 1.10 (s, 3); ^{13}C NMR 201.6, 152.7, 131.7, 51.4, 47.5, 34.2, 30.6, 28.1, 27.7, 27.2, 22.5, 16.2; IR (neat) 2957, 2871, 1667, 1470, 1449, 1364, 1070, 1022, 884.

Preparation of 21. Addition of vinyllithium (4.00 mL of 1.65 M in THF, 6.60 mmol) dropwise to a solution of 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one[14] (600 mg, 4.41 mmol) in THF (22 mL) at −78 °C as described above for the preparation of **1** followed by flash chromatography (9:1 hexanes/EtOAc) provided 660 mg (91%) of **21**: ^1H NMR 5.95 (br d, 1, J = 5.6), 5.94 (dd, 1, J = 10.7, 17.3), 5.84 (dddd, 1, J = 2.2, 2.2, 2.2, 5.6), 5.21 (dd, 1, J = 1.7, 17.3), 5.09 (dd, 1, J = 1.7, 10.7), 3.14 (br dd, 1, J = 8.1, 8), 2.82–2.76 (m, 1), 2.52 (br d, 1, J = 17.3), 2.36 (ddddd, 1, J = 2.4, 2.2, 2.2, 8.1, 17.3), 1.86 (br s, 1), 1.13 (s, 3), 0.88 (s, 3); ^{13}C NMR 140.4, 134.6, 133.4, 113.0, 79.3, 53.9, 47.2, 41.4, 31.4, 27.4, 17.7; IR (neat) 3500, 3060, 2960, 2930, 2910, 2870, 1640, 1615, 1465, 1450, 1420, 1370, 1350, 1120, 1070, 1000, 920, 730. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.37; H, 9.78.

Oxidation of 21 with $Mn(OAc)_3$ and $Cu(OAc)_2$. Reaction of $Cu(OAc)_2$ (124 mg, 0.67 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (370 mg, 1.34 mmol), and alcohol **21** (100 mg, 0.61 mmol) in EtOH (15 mL) for 5 h at rt as described above for the oxidation of **1** gave 98 mg of crude product. Flash chromatography (49:1 hexanes/EtOAc) provided 65 mg (65%) of a 36:64 mixture (as determined by integration of the NMR spectrum) of **22** and **26**, followed by 1.2 mg (1%) of **23**.

An identical reaction carried out for 1 h at reflux gave 70% of a 4:6 mixture of **22** and **26** and 1.5% of **23**. Flash chromatography of the mixture (99:1 hexanes/EtOAc) afforded 22 mg (22%) of **22** and 42 mg (42%) of **26**.

Data for 22: ^1H NMR 5.96 (d, 1, J = 0.8), 5.74 (dddd, 1, J = 5.7, 2, 2, 2), 5.69 (dddd, 1, J = 5.7, 2, 2, 2), 5.17 (d, 1, J = 0.8), 3.11 (m, 1), 2.94 (ddd, 1, J = 1.7, 7.8, 8.3), 2.70 (br d, 1, J = 16.6), 2.65–2.55 (m, 1), 1.31 (s, 3), 1.19 (s, 3); ^{13}C NMR 211.4, 154.2, 132.7, 131.1, 116.3, 58.0, 48.4, 41.7, 36.9, 32.1, 24.4; IR (neat) 3070, 2970, 2940, 2870, 1730, 1645, 1470, 1450, 1370, 1315, 1275, 1160, 1085, 940, 755, 665. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.38; H, 8.82.

Data for 23: ^1H NMR 6.62 (dd, 1, J = 1.0, 10.1), 5.92 (d, 1, J = 10.1), 5.86 (dddd, 1, J = 2.4, 2.3, 2.3, 5.8), 5.76 (ddd, 1, J = 1.8, 1.8, 1.8, 5.8), 3.05–2.95 (m, 2), 2.74 (br d, J = 17), 2.63 (d of m, 1, J = 17), 1.24 (s, 3), 1.17 (s, 3); IR (neat) 2960, 2926, 2869, 1728, 1664, 1466, 1377, 1286, 1126, 834, 744.

Data for 26: ^1H NMR 6.21 (dd, 1, J = 3.2, 5.4), 5.85 (dd, 1, J = 3.2, 5.4), 2.96–2.84 (m, 3), 2.34 (br d, 1, J = 4.7), 2.26 (br ddd, 1, J = 4.7, 8.7, 12.7), 1.60 (dd, 1, J = 1.7, 12.7), 1.14 (s, 3), 1.09 (s, 3); ^{13}C NMR 215.5, 142.2, 131.0, 64.4, 63.2, 56.4, 43.7, 42.2, 38.1, 23.0, 21.0; IR (neat) 3063, 2958, 2876, 1745, 1599, 1459, 1392, 1373, 1270, 1238, 1154, 1074, 867, 845, 762, 723. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.19; H, 8.55.

Preparation of 27. *trans*-β-Bromostyrene (500 mg, 2.73 mmol) was dissolved in THF (14.0 mL). The solution was cooled to −78 °C and *tert*-butyllithium (3.29 mL of 1.7 M in pentane, 5.60 mmol) was added dropwise. The reaction mixture was stirred 15 min at −78 °C and 30 min at 0 °C and then recooled to −78 °C, providing a solution of β-styryllithium.

7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-one[14] (372 mg, 2.73 mmol) in THF (1.0 mL) was added. The reaction was stirred for 1 h at −78 °C and worked up as described for the preparation of **1**. Flash chromatography (24:1 hexanes/EtOAc) provided 369 mg (56%) of pure **27**: ^1H NMR 7.39 (ddd, 2, J = 1.5, 1.5, 7), 7.30 (ddd, 2, J = 1.5, 7, 7), 7.20 (dddd, 1, J = 1.5, 1.5, 7, 7), 6.58 (d, 1, J = 15.1), 6.33 (d, 1, J = 15.1), 5.97 (dddd, 1, J = 2, 2, 2, 5.6), 5.85 (dddd, 1, J = 2.3, 2.3, 2.3, 5.6), 3.24 (dd, 1, J = 7.0, 7.0), 2.88–2.81 (m, 1), 2.56 (br d, 1, J = 17.3), 2.40 (ddddd, 1, J = 2.3, 2.3, 2.3, 8.0, 17.3), 1.98 (br s, 1); ^{13}C NMR 137.2, 134.6, 133.4, 132.2, 128.4, 128.0, 127.2, 126.4, 79.3, 54.0, 48.1, 42.2, 31.5, 27.5, 17.8; IR (neat) 3480, 3050, 2980, 2900, 1710, 1600, 1500, 1465, 1450, 1070, 970, 740, 690. Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.90; H, 8.25.

Oxidation of 27. $Cu(OAc)_2$ (93 mg, 0.50 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (532 mg, 1.92 mmol) were added sequentially to cyclobutanol **27** (110 mg, 0.46 mmol) in EtOH (11.5 mL). The mixture was stirred at rt overnight and worked up as described above, providing 104 mg of crude **31**. Flash chromatography (5:1 hexanes/EtOAc) provided 31 mg (25%) of pure **31**: ^1H NMR 7.92 (ddd, 2, J = 1.5, 1.5, 7.5), 7.56–7.39 (m, 3), 5.94 (br d, 1, J = 5.8), 5.78 (br d, 1, J = 5.8), 3.35–3.29 (m, 1), 3.24 (ddd, 1, J = 7.6, 8.4, 8.4), 3.19 (d, 1, J = 15.2), 2.93 (d, 1, J = 15.2), 2.75 (ddddd, 1, J = 2.4, 2.4, 2.4, 8.4, 16.4), 2.43 (br dd, 1, J = 7.6, 16.4), 1.10 (s, 3), 1.07 (s, 3); ^{13}C NMR 200.7, 181.5, 138.5, 132.7, 131.2,

131.1, 128.5, 128.1, 58.3, 46.1, 45.6, 37.9, 35.7, 26.6, 25.7; IR (neat) 3600–2500, 1750–1650, 1600, 1585, 1450, 1220, 1180, 1010, 750, 690, 560. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.70; H, 7.58.

Preparation of 32. The tosylhydrazone of cyclohexanone (1.06 g, 3.98 mmol) was dissolved in a solution of 10% TMEDA in ether (10 mL). The mixture was cooled to −78 °C and *n*-BuLi (5.07 mL of 2.5M in hexanes, 12.67 mmol) was added dropwise. The reaction was stirred for 30 min at −78 °C, 2 h at 0 °C, and 15 min at rt and recooled to −78 °C, giving a solution of 1-cyclohexenyllithium.

7,7-Dimethylbicyclo[3.2.0]heptan-6-one (500 mg, 3.62 mmol) in ether (2 mL) was added, and the reaction was stirred for 30 min at −78 °C and worked up as described for the preparation of **1**, giving, after flash chromatography (199:1 hexanes/EtOAc), 420 mg (53%) of pure **32**: ^{1}H NMR 5.62 (br s, 1), 3.10 (ddd, 1, J = 1.7, 8.4, 8.4), 2.20–1.33 (m, 15), 1.24 (br s, 1), 0.98 (s, 3), 0.95 (s, 3); ^{13}C NMR 140.9, 121.8, 80.7, 46.1, 41.5, 40.2, 28.9, 28.0, 27.6, 25.8, 25.6, 25.2, 22.6, 22.5, 17.9; IR (neat) 3472, 2932, 2858, 1462, 1447, 1016, 978. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.60; H, 11.15.

Oxidation of 32. Cyclobutanol **32** (100 mg, 0.45 mmol) in EtOH (2.0 mL) was added to a solution of $Cu(OAc)_2$ (92 mg, 0.50 mmol) and $Mn(OAc)_3{\cdot}2H_2O$ (276 mg, 1.00 mmol) in EtOH (9.4 mL). The reaction was stirred at rt for 11 h and worked up as described above to give 99 mg of crude product. Flash chromatography (199:1 hexanes/EtOAc) provided 20 mg (20%) of **35**, followed by 24 mg (24%) of **36**, 23 mg (23%) of **37**, and 15 mg (15%) of **34**.

A similar reaction without $Cu(OAc)_2$ yielded 22 mg (22%) of **35**, 18 mg (18%) of **36**, 21 mg (21%) of **37**, and 14 mg (14%) of **34**.

Data for 34: ^{1}H NMR 6.94–6.90 (m, 1), 2.68 (ddd, 1, J = 8.6, 8.6, 12.2), 2.46–2.36 (m, 1), 2.35–2.26 (m, 1), 2.25–2.19 (m, 1), 2.14 (dddd, 1, J = 2.8, 5.6, 5.6, 12.2), 2.09–1.61 (m, 6), 1.58–1.10 (m, 4), 0.98 (s, 3), 0.49 (s, 3); ^{13}C NMR 203.2, 137.4, 135.5, 51.3, 48.9, 46.4, 35.1, 28.6, 27.9, 26.8, 25.7, 25.5, 22.9, 21.7, 16.3; IR (neat) 2956, 2870, 1692, 1622, 1462, 1450, 1391, 1369, 1194.

The structure of **35** was determined by X-ray crystallography:[28] mp 137–138 °C (hexane); ^{1}H NMR 3.76 (ddd, 1, J = 3.9, 8.2, 9.7), 3.06 (br d, 1, J = 12.4), 2.35–2.25 (m, 2), 2.24–2.13 (m, 1), 2.07 (br dd, 1, J = 4.5, 10.5), 1.96–1.09 (m, 28), 1.42 (s, 3), 0.97 (s, 3), 0.92 (br s, 6); ^{13}C NMR 213.8, 143.6, 125.4, 83.2, 56.1, 55.3, 52.3, 49.4, 45.9, 38.9, 34.8, 34.4, 33.0, 32.8, 31.5, 30.8, 30.0, 29.7, 29.2, 28.9, 28.2 (2 C), 26.7, 26.3, 25.9 (2 C), 25.3, 23.7, 23.5, 23.1; IR (KBr) 2954, 2865, 1712, 1673, 1470, 1446, 1397, 1361, 1171, 1074, 858, 740.

Data for 36: ^{1}H NMR 3.25 (ddd, 1, J = 7.6, 7.6, 11.5), 2.94 (br d, 1, J = 11.8), 2.64–2.59 (m, 1), 2.40–2.32 (m, 1), 2.28 (dd, 1, J = 6.6, 6.6), 2.07 (ddd, 1, J = 5, 5, 14), 1.97–1.89 (m, 1), 1.87–1.15 (m, 27), 1.12 (s, 3), 0.89 (s, 3), 0.87 (s, 3), 0.69 (s, 3); ^{13}C NMR 213.5, 145.7, 124.9, 83.1, 55.2, 54.6, 51.8, 49.2, 47.4, 40.7, 35.3, 32.8, 32.0, 31.1, 30.8, 30.4, 30.3, 29.2, 28.5, 28.0, 27.9 (2 C), 25.8, 25.5, 25.4, 24.6, 23.9, 22.5, 21.5, 21.1; IR (neat) 2952, 2867, 1713, 1660, 1616, 1447, 1391, 1367, 1169, 1153, 1125, 1080, 738. Anal. Calcd for $C_{30}H_{46}O_2$: C, 82.14; H, 10.57. Found: C, 82.12; H, 10.58.

Data for 37: ^{1}H NMR 2.98 (br s, 1), 2.73 (br dd, 1, J = 8, 8), 2.45–2.34 (m, 1), 2.18 (br d, 1, J = 13.3), 2.14–2.04 (m, 1), 1.82–0.93 (m, 13), 1.36 (s, 3), 1.04 (s, 3); ^{13}C NMR 213.9, 55.4, 52.3, 49.6, 45.2, 34.6, 32.9, 28.9, 27.6, 27.1, 26.0, 25.9, 23.8, 23.3, 22.3; IR (neat) 2941, 2868, 1707, 1447, 1367, 1091, 890. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 82.08; H, 11.26.

Hydrogenation of 34. A solution of enone **34** (15 mg) in ether (3.0 mL) containing 10% Pd/C (3.0 mg) was stirred overnight under 1 atm of H_2. The solution was filtered through silica gel and concentrated in vacuo. Flash chromatography (99:1 hexanes/EtOAc) gave 11 mg (73%) of **37** followed 4 mg (27%) of **38**: ^{1}H NMR 2.70 (ddd, 1, J = 8.6, 8.6, 11.8), 2.22 (ddd, 1, J = 7.0, 9.7, 11.8), 2.11–2.04 (m, 1), 1.91–1.10 (m, 15), 0.97 (s, 3), 0.61 (s, 3); ^{13}C NMR 218.4, 52.9, 50.8, 50.0, 49.2, 34.4, 30.3, 28.2, 27.5, 26.8, 26.6, 26.5, 25.9, 25.6, 17.4; IR (neat) 2936, 2855, 1704, 1465, 1448, 1390, 1368, 1196, 1182.

Preparation of 39. Vinyllithium (1.72 mL of 1.65 M in THF, 2.84 mmol) was added dropwise to a solution of spiro[3.5]nonan-1-one[30] (262 mg, 1.90 mmol) in THF (10 mL) at −78 °C. The mixture was stirred at −78 °C for 15 min and worked up as described above for **1**. Flash chromatography (49:1 hexanes/EtOAc) gave 278 mg (88%) of pure **39**: mp 40–41 °C; ^{1}H NMR 6.07 (dd, 1, J = 10.7, 17.3), 5.25 (dd, 1, J = 1.5, 17.3), 5.13 (dd, 1, J = 1.5, 10.7), 2.16 (ddd, 1, J = 4.3, 8.8, 11.8), 1.98 (ddd, 1, J = 8.4, 9.9, 11.8), 1.77–1.60 (m, 4), 1.58–1.35 (m, 6), 1.30–1.12 (m, 3); ^{13}C NMR 140.7, 111.7, 78.3, 47.8, 34.3, 31.1, 31.0, 26.1, 25.1, 22.8, 22.5; IR (KBr) 3259, 2925, 2851, 1638, 1447, 1237, 1153, 1140, 1040, 1028, 1005, 914. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.19; H, 10.97.

Oxidation of 39. $Mn(OAc)_3{\cdot}2H_2O$ (279 mg, 1.01 mmol) in EtOH (8 mL) was added dropwise to a solution of cyclobutanol **39** (80 mg, 0.48 mmol) and $Cu(OAc)_2$ (9.0 mg, 0.048 mmol, 0.1 equiv) in EtOH (2 mL) at rt. The reaction was stirred for 10 h and worked up as previously described to afford 79 mg of crude product. Flash chromatography (99:1 hexanes/EtOAc) provided 15 mg (19%) of **42**, followed by 16 mg (20%) of **44** and 13 mg (16%) of a 1:1 mixture of **46a** and **46b**.

$Mn(OAc)_3{\cdot}2H_4O$ (140 mg, 0.50 mmol) in EtOH (4 mL) was added dropwise over 15 min to a solution of cyclobutanol **39** (40 mg, 0.24 mmol) and $Cu(OAc)_2$ (4.4 mg, 0.024 mmol, 0.1 equiv) in EtOH (2 mL) at reflux. The reaction was stirred 40 min and worked up as described above, giving 41 mg of crude product. Flash chromatography provided 25 mg (62%) of a 4:38:58 mixture of **41**, **42**, and **44**, respectively, followed by 8.2 mg (21%) of a 1:1 mixture of **46a** and **46b**.

An identical reaction using 44 mg (1 equiv) of $Cu(OAc)_2$ afforded 23 mg (57%) of a 10:40:50 mixture of **41**, **42**, and **44**, respectively, followed by 4.5 mg (11%) of **46a** and 5 mg (12%) of **46b**.

Data for 44: ^{1}H NMR and IR spectra are identical to those described in the literature;[32] ^{13}C NMR 200.1, 159.1, 127.3, 35.9, 35.5, 33.7, 32.8, 25.9, 21.6.

Data for the less polar dimer 46a: ^{1}H NMR 3.03 (br d, 2, J = 14.6), 2.48 (ddd, 2, J = 5.9, 13.4, 14.6), 2.23 (ddd, 2, J = 3.2, 4.8, 14.6), 1.98–1.87 (m, 4), 1.81–1.12 (m, 24); ^{13}C NMR 212.7, 43.3, 40.3, 38.7, 37.6, 37.1, 33.0, 32.3, 26.7, 22.2, 21.8; IR (neat) 2922, 2852, 1704, 1454, 1140, 962, 738; MS m/z (rel intensity) 330 (M^+, 13.2), 287 (3), 217 (4), 166 (61), 165 (100), 137 (24).

Data for the more polar dimer 46b: ^{1}H NMR 2.78–2.68 (m, 2), 2.44–2.26 (m, 4), 1.93–1.82 (m, 2), 1.80–1.73 (m, 2), 1.60–1.28 (m, 24); ^{13}C NMR 211.7, 45.5, 40.3, 38.1, 36.9, 35.0, 32.7, 32.3, 26.7, 22.1, 21.9; IR (neat) 2921, 2851, 1710, 1452, 1142, 961, 736.

Oxidation of 39 with $Mn(Pic)_3$ in DMF. $Mn(pic)_3$ (79 mg, 0.18 mmol) in DMF (1.75 mL) was added dropwise to a solution of cyclobutanol **39** (15 mg, 0.09 mmol) in DMF (0.5 mL). The reaction was stirred at rt overnight, water (2 mL) was added, and the solution was extracted with ether (3 × 4 mL). The combined organic layers were washed with brine (2 × 2 mL), dried ($MgSO_4$), and concentrated in vacuo to give 16 mg of crude product. Flash chromatography (99:1 hexanes/EtOAc) afforded 3 mg (20%) of a 70:30 mixture of **42** and **44**, followed by 4 mg (28%) of a 1:1 mixture of **46a** and **46b**.

Hydrogenation of 44. A solution of enone **44** (10 mg, 0.061 mmol) in ether (2 mL) was stirred under 1 atm of H_2 with 10% Pd/C (2 mg) overnight, filtered through silica gel, and concentrated in vacuo, giving 10 mg (99%) of pure **42**: the ^{1}H NMR spectrum is identical to that described in the literature;[31] ^{13}C NMR 213.0, 37.2, 36.1, 35.8, 32.0, 26.6, 21.9; IR (neat) 2926, 2853, 1716, 1454.

Preparation of 47. Lithium acetylide–ethylenediamine complex (356 mg, 90% pure, 3.27 mmol) was added at 0 °C to a solution of spiro[3.5]nonan-1-one[30] (150 mg, 1.09 mmol) in THF (6 mL). The reaction was stirred 1 h at rt and quenched with ice. The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, providing 201 mg of crude **47**. Flash chromatography (49:1 hexanes/EtOAc) gave 95 mg (53%) of pure **47**: ^{1}H NMR 2.58 (s, 1), 2.33 (ddd, 1, J = 4.8, 9.0, 11.9), 2.14 (ddd, 1, J = 8.2, 9.8, 11.9), 1.97 (br s, 1), 1.77–1.20 (m, 12); ^{13}C NMR 85.5, 73.8, 72.8, 47.4, 35.2, 33.4, 30.6, 26.0, 25.5, 22.8, 22.4; IR (neat) 3408, 3306, 2929, 2852, 2109, 1757, 1446, 1234, 1171, 1112, 1062, 997, 919, 623.

Oxidation of 47. $Mn(OAc)_3{\cdot}2H_2O$ (116 mg, 0.42 mmol) in EtOH (3 mL) was added dropwise to a solution of cyclobutanol **47** (33 mg, 0.20 mmol) in EtOH (2 mL). The mixture was stirred

at rt overnight and worked up as described above to give 35 mg of crude **41**. Flash chromatography (99:1 hexanes/EtOAc) gave 15 mg (45%) of **41**: ^{1}H NMR 6.00 (d, 1, J = 0.8), 5.23 (d, 1, J = 0.8), 2.34 (dd, 2, J = 8, 8), 1.86 (dd, 2, J = 8, 8), 1.73–1.26 (m, 10); ^{13}C NMR 208.5, 155.0, 116.1, 43.5, 37.1, 35.4, 29.3, 25.8, 22.4; IR (neat) 2927, 2855, 1725, 1634, 1450, 1405, 1246, 1095, 950, 898.

Preparation of 49. A solution of 7,7-dimethylbicyclo[3.2.0]-hept-6-one[14] (200 mg, 1.45 mmol) in 2 mL of THF was added to a suspension of lithium acetylide–ethylenediamine complex (444 mg, 90% pure, 4.34 mmol) in THF (9 mL) at −78 °C. The reaction was stirred 30 min at 0 °C and worked up as described above for **47** to give 229 mg of crude **49**. Flash chromatography (49:1 hexanes/EtOAc) gave 69 mg of unreacted cyclobutanone followed by 115 mg (48%) of pure **49**: ^{1}H NMR 2.97 (dd, 1, J = 8, 8), 2.58 (s, 1), 2.21 (ddd, 1, J = 1.6, 8, 8), 1.97–1.90 (m, 1), 1.88–1.63 (m, 3), 1.48–1.33 (m, 2), 1.27 (s, 3), 0.89 (s, 3); ^{13}C NMR 86.8, 73.5, 71.9, 47.4, 46.1, 41.7, 30.0, 28.2, 27.6, 25.9, 16.5; IR (neat) 3526, 3306, 2955, 2862, 1464, 1445, 1092, 1022.

Oxidation of 49. $Mn(OAc)_3 \cdot 2H_2O$ (304 mg, 1.10 mmol) in EtOH (6 mL) was added dropwise to a solution of cyclobutanol **49** (85 mg, 0.52 mmol) in EtOH (7 mL). The mixture was stirred at rt overnight, worked up as described above, and purified by flash chromatography to give 58 mg (68%) of **6**.

Preparation of 51. *t*-BuLi (2.56 mL of 1.7 M in THF, 4.36 mmol) was added dropwise to a solution of *cis*-1-bromopropene (275 mg, 2.18 mmol, 77% *cis*, 23% *trans*) in THF (4 mL) at −78 °C. The solution was stirred at −78 °C for 90 min and spiro-[3.5]nonan-2-one[30] (150 mg, 1.09 mmol) in THF (1.5 mL) was added. The reaction was stirred for 30 min and worked up as described above to give 161 mg of crude **51**. Flash chromatography (99:1 hexanes/EtOAc) provided 85 mg (43%) of **51** followed by 25 mg (13%) of the *trans* isomer of **51**.

Data for 51: ^{1}H NMR 5.64 (d, 1, J = 11.5), 5.59 (dq, 1, J = 11.5, 5.5), 2.20 (ddd, 1, J = 5.7, 9.0, 11.8), 2.04 (ddd, 1, J = 7.0, 9.5, 11.8), 1.85–1.70 (m, 2), 1.79 (d, 3, J = 5.5), 1.66–1.08 (m, 11); ^{13}C NMR 132.9, 127.7, 78.5, 48.4, 34.2, 34.1, 31.2, 26.2, 25.7, 22.8, 22.4, 15.0; IR (neat) 3453, 3012, 2926, 2852, 1447.

Oxidation of 51. $Mn(OAc)_3 \cdot 2H_2O$ (209 mg, 0.76 mmol) in EtOH (7 mL) was added dropwise over 15 min to a solution of cyclobutanol **51** (65 mg, 0.36 mmol) and $Cu(OAc)_2$ (6.7 mg, 0.036 mmol) in EtOH (2 mL) at reflux. The solution was heated at reflux for 30 min and worked up as described above to give 67 mg of crude product. Flash chromatography (99:1 hexanes/EtOAc) gave 5 mg (8%) of pure **53**, followed by 16 mg (25%) of a 95:5 mixture of **55** and **57** and 14 mg (22%) of **54**. A similar oxidation of the *trans* isomer of **51** gave a more complex mixture of products.

Data for 53: ^{1}H NMR 5.96 (q, 1, J = 7.4), 2.27 (dd, 2, J = 8, 8), 2.15 (d, 3, J = 7.4), 1.80 (dd, 2, J = 8, 8), 1.75–1.10 (m, 10); ^{13}C NMR 210.2, 146.0, 134.2, 44.1, 37.6, 36.6, 28.8, 22.6, 14.4; IR (neat) 2926, 2854, 1714, 1637, 1450, 1374, 1344.

Data for 54: ^{1}H NMR 6.66 (q, 1, J = 7.7), 2.30 (dd, 2, J = 8.1, 8.1), 1.96 (d, 3, J = 7.7), 1.86 (dd, 2, J = 8.1, 8.1), 1.84–1.40 (m, 9), 1.35–1.17 (m, 1); ^{13}C NMR 207.6, 145.5, 133.1, 44.0, 35.6, 35.0, 29.2, 25.8, 22.3, 14.0; IR (neat) 2926, 2857, 1720, 1639, 1448, 1208.

Data for 55: ^{1}H NMR 6.58 (br s, 1), 2.42 (dd, 2, J = 6.9, 6.9), 1.87 (ddd, 2, J = 0.8, 6.9, 6.9), 1.76 (d, 3, J = 1.4), 1.60–1.40 (m, 10); ^{13}C NMR 200.3, 154.4, 133.0, 36.2, 35.5, 33.8, 32.9, 26.0, 21.7, 16.2; IR (neat) 2925, 2856, 1742, 1674, 1452.

Data for 57: 5.64 (ddd, 1, J = 8.8, 10.3, 17.0), 5.31 (dd, 1, J = 2.0, 10.3), 5.13 (ddd, 1, J = 0.9, 2.0, 17.0), 2.57 (br d, 1, J = 8.8).

Preparation of 58. Vinyllithium (2.24 mL of 1.65 M in THF, 3.69 mmol) was added dropwise to a solution of spiro[bicyclo-[3.2.0]heptane-6,1′-cyclohexan]-7-one[33] (439 mg, 2.46 mmol) in THF (12 mL) at −78 °C. The reaction was stirred for 15 min and worked up as described for the preparation of **1** to give 520 mg of crude **58**. Flash chromatography (97:3 hexanes/EtOAc) provided 386 mg (76%) of pure **58**: ^{1}H NMR 6.12 (dd, 1, J = 10.7, 17.3), 5.15 (dd, 1, J = 1.5, 17.3), 5.05 (dd, 1, J = 1.5, 10.7), 2.78 (ddd, 1, J = 1.7, 8.3, 8.3), 2.19 (ddd, 1, J = 2.9, 8.3, 8.3), 1.97–1.10 (m, 16); ^{13}C NMR 143.2, 111.4, 77.7, 45.8, 44.4, 43.9, 37.2, 29.0, 27.6, 26.1, 26.0, 25.8, 23.6, 22.7; IR (neat) 3600, 3484, 3082, 2923, 2852, 1633, 1447, 998, 915. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.13; H, 10.34.

Oxidation of 58. $Mn(OAc)_3 \cdot 2H_2O$ (197 mg, 0.71 mmol) in EtOH (4.0 mL) was added dropwise over 30 min to a solution of cyclobutanol **58** (70 mg, 0.34 mmol) and $Cu(OAc)_2$ (6.3 mg, 0.034 mmol) in EtOH (4.5 mL) at reflux. The solution was heated for 10 min, cooled to rt, and worked up as described above to provide 74 mg of a 34:26:40 mixture of **60**, **62**, and **64**, respectively, as determined by GC analysis. Flash chromatography (99:1 hexanes/EtOAc) gave 15 mg (22%) of **60**, followed by 12 mg (17%) of **62** and 18 mg (26%) of **64**.

The above reaction repeated with 1.0 equiv of $Cu(OAc)_2$ provided 75 mg of crude product. GC analysis indicated that **60**, **62**, and **64** were present in a 58:23:19 ratio, respectively.

Data for 60: ^{1}H NMR 6.01 (s, 1), 5.21 (d, 1, J = 0.9), 2.77 (ddd, 1, J = 3.9, 9.0, 9.0), 2.61 (ddd, 1, J = 6.6, 8.3, 14.9), 2.12–1.99 (m, 1), 1.87–1.15 (m, 14), 0.91 (ddd, 1, J = 7.0, 11.2, 13.9); ^{13}C NMR 211.8, 154.3, 117.2, 50.5, 46.2, 44.1, 39.3, 32.7, 28.6, 27.6, 26.2, 25.7, 22.7, 22.6; IR (neat) 2930, 2855, 1722, 1634, 1448, 1085, 936, 902.

Data for 64: ^{1}H NMR 6.71 (dd, 1, J = 2.0, 10.2), 5.87 (d, 1, J = 10.2), 2.73 (dd, 1, J = 6.5, 6.7), 2.37–2.27 (m, 1), 1.82–1.39 (m, 15), 1.34–1.19 (m, 1); ^{13}C NMR 202.0, 156.8, 148.4, 47.4, 46.9, 38.5, 37.6, 35.2, 27.8, 25.8, 25.7, 22.3, 22.2, 21.0; IR (neat) 2929, 2860, 1732, 1673, 1450, 1227, 1127.

Hydrogenation of 64. A solution of enone **64** (14 mg, 0.069 mmol) in ether (1.0 mL) containing 10% Pd/C (1.0 mg) was stirred for 1 h under 1 atm of H_2. Filtration through silica provided 14 mg (99%) of **62**: ^{1}H NMR 2.68 (ddd, 1, J = 1, 6, 6), 2.45 (dddd, 1, J = 0.8, 6.6, 14.9, 14.9), 2.32 (ddd, 1, J = 2, 8, 8), 2.21 (ddd, 1, J = 2.9, 4.7, 14.9), 1.87–1.03 (m, 18); ^{13}C NMR 213.8, 51.9, 49.6, 37.1, 36.8, 35.4, 33.8, 31.9, 26.5, 25.0, 24.2, 21.8 (2 C), 21.7; IR (neat) 2927, 2861, 1710, 1456, 1148, 1134. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.19; H, 10.40.

Preparation of 65. Lithium acetylide–ethylenediamine complex (258 mg, of 90% pure, 2.37 mmol) was added to a solution of spiro[bicyclo[3.2.0]heptane-6,1′-cyclohexan]-7-one[33] (140 mg, 0.79 mmol) in THF (4.0 mL) at −78 °C. The mixture was stirred at 0 °C for 30 min and worked up as described above for the preparation of **47**. Flash chromatography (99:1 hexanes/EtOAc) gave 92 mg (57%) of **65**: ^{1}H NMR 2.93 (ddd, 1, J = 1.6, 8.3, 8.3), 2.56 (s, 1), 2.24 (ddd, 1, J = 2.0, 8.3, 8.3), 1.97–1.87 (m, 1), 1.86–1.18 (m, 16); ^{13}C NMR 87.0, 73.3, 72.3, 47.3, 44.8, 44.7, 38.3, 28.7, 27.5, 26.0, 25.9, 25.7, 23.5, 22.8; IR (neat) 3521, 3305, 2925, 2853, 2104, 1464, 1447, 1103, 1010, 646, 620.

Oxidation of 65. $Mn(OAc)_3 \cdot 2H_2O$ (114 mg, 0.41 mmol) in EtOH (3.0 mL) was added dropwise over 10 min to a solution of cyclobutanol **65** (40 mg, 0.20 mmol) and in EtOH (1.9 mL) at reflux. The solution was heated for 20 min and worked up as described above to give 41 mg of crude **60**. Flash chromatography (99:1 hexanes/EtOAc) gave 16 mg (40%) of **60**.

Preparation of 68. THF (5 mL) and diisopropylamine (0.69 mL, 4.95 mmol) were added to a flame-dried flask. The mixture was cooled to 0 °C and *n*-BuLi (1.98 mL of 2.5 M in hexanes, 4.95 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min. Acid **67** (288 mg, 2.25 mmol) in 2 mL of THF and DMPU (0.54 mL, 4.50 mmol) were then added. The solution was stirred for 1 h at 25 °C and recooled to 0 °C. 5-Iodo-1-pentene (441 mg, 2.25 mmol) in 2 mL of THF was added rapidly and the reaction was stirred at rt for 2 h. The reaction mixture was acidified with 10% HCl (10 mL) and extracted with ether (4 × 10 mL). The combined ether layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give 403 mg of crude **68**. Flash chromatography (90:10:1 hexanes/EtOAc/HOAc) provided 328 mg (74%) of **68**: ^{1}H NMR 5.79 (ddt, 2, J = 17.0, 10.2, 6.7), 5.01 (br d, 2, J = 10.2), 4.96 (br d, 2, J = 17.0), 2.39–2.32 (m, 1), 2.06 (dt, 4, J = 7.0, 7.0), 1.71–1.37 (m, 8); ^{13}C NMR 182.7, 138.3, 114.7, 45.2, 33.6, 31.5, 26.5; IR (neat) 3077, 2940, 2861, 1704, 1641, 1459, 1416, 1286, 1233, 993, 911. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.38.

Preparation of 70. Acid **68** (300 mg, 1.53 mmol) was dissolved in benzene (5 mL) and oxalyl chloride (0.67 mL, 0.97 g, 7.65 mmol) was added dropwise. The reaction mixture was stirred at rt for 2 h and heated at reflux for 30 min. Excess oxalyl chloride and solvent were removed in vacuo. Crude acid chloride **69** in toluene (5 mL) was added to a solution of Et_3N (1.28 mL, 9.2 mmol) in toluene (20 mL) at reflux. The solution was heated at reflux for 15 h, cooled, and washed with H_2O (20 mL). The aqueous layer was back extracted with ether. The combined

organic layers were dried ($MgSO_4$) and concentrated in vacuo, giving crude **70** (261 mg). Flash chromatography (19:1 hexanes/EtOAc) provided 184 mg (67%) of pure **70**: ^{1}H NMR 5.78 (tdd, 1, J = 6.7, 10.2, 17.0), 4.99 (br d, 1, J = 17.0), 4.95 (br d, 1, J = 10.2), 3.11 (dd, 1, J = 9.6, 18.3), 2.60–2.50 (m, 1), 2.43 (dd, 1, J = 4.6, 18.3), 2.09–1.98 (m, 3), 1.95–1.75 (m, 3), 1.73–1.49 (m, 4), 1.43–1.30 (m, 2); ^{13}C NMR 218.1, 138.4, 114.7, 75.8, 49.2, 35.3, 34.1, 34.0, 32.7, 32.6, 25.0, 24.9; IR (neat) 3070, 2930, 2850, 1775, 1640, 1460, 1450, 1440, 1385, 1060, 985, 905. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.99; H, 10.26.

Preparation of Cyclobutanol 75. Cyclobutanone **70** (560 mg, 3.14 mmol) in THF (16 mL) was cooled to −78 °C and MeLi (3.14 mL of 1.5 M in ether, 4.71 mmol) was added dropwise. The reaction was stirred for 15 min and quenched slowly by dropwise addition of saturated NH_4Cl (20 mL). CH_2Cl_2 (30 mL) was added and the layers were separated. The aqueous layer was further extracted (CH_2Cl_2, 3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, giving 581 mg of crude **75**. Flash chromatography (19:1 hexanes/EtOAc) provided 443 mg (73%) of pure **75**: ^{1}H NMR 5.80 (tdd, 1, J = 6.7, 10.2, 17.0), 5.00 (ddd, 1, J = 1.5, 3.7, 17.0), 4.93 (br d, 1, J = 10.2), 2.09–1.86 (m, 4), 1.84–1.76 (m, 2), 1.63–1.24 (m, 9), 1.35 (s, CH_3); ^{13}C NMR 138.9, 114.4, 72.4, 56.9, 39.5, 36.9, 35.9, 34.6, 31.7, 31.0, 26.2, 26.1, 24.8; IR (neat) 3390, 3070, 2930, 2850, 1640, 1460, 1445, 1370, 1220, 1190, 1110, 1085, 980, 940, 900. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.24; H, 11.45.

Oxidation of Cyclobutanol 75. Cyclobutanol **75** (170 mg, 0.88 mmol) in EtOH (3 mL) was added to a solution of $Cu(OAc)_2$ (178 mg, 0.96 mmol) and $Mn(OAc)_3{\cdot}2H_2O$ (532 mg, 1.93 mmol) in EtOH (6 mL). The reaction mixture was stirred at rt for 4 h and worked up as described above to give 166 mg of crude product. Flash chromatography (49:1 hexanes/EtOAc) provided 2.5 mg (1.5%) of **76** and 116 mg (69%) of an 8:1:1 mixture of **79**, **71**, and **72**, respectively, as determined by analysis of the ^{1}H NMR spectra. Upon standing in $CDCl_3$ for 2 days, **76** isomerized to **80**.

Partial data for 71: ^{1}H NMR 5.81 (tdd, 1, J = 6.7, 10.3, 17.1), 5.04 (br s, 1), 5.01 (br d, 1, J = 17.1), 4.96 (br d, 1, J = 10.3), 2.65 (dd, 1, J = 3.9, 16.4).

Partial data for 72: ^{1}H NMR 5.81 (tdd, 1, J = 6.7, 10.3, 17.1), 5.01 (br d, 1, J = 17.1), 4.96 (br d, 1, J = 10.3), 3.14 (br s, 2).

Partial data for 76: ^{1}H NMR 4.93 (br s, 1), 4.68 (br s, 1), 2.45 (br d, 1, J = 11.6), 2.37–2.12 (m, 3), 2.10 (s, 3), 2.09–1.95 (m, 1), 1.82–1.45 (m, 9), 1.35–1.20 (m, 1).

Data for 79: ^{1}H NMR 4.91 (dd, 1, J = 2.0, 2.0), 4.81 (dd, 1, J = 2.0, 2.4), 2.43 (br d, 1, J = 14), 2.33–2.14 (m, 3), 2.13 (s, 3), 2.07–1.97 (m, 1), 1.77–1.53 (m, 6), 1.50–1.31 (m, 3), 1.28–1.10 (m, 1); ^{13}C NMR 209.2, 158.1, 103.2, 55.8, 44.8, 43.7, 41.5, 34.2, 32.6, 30.1 (2 C), 23.0, 21.4; IR (neat) 3068, 2951, 2871, 1713, 1648, 1449, 1434, 1355, 1156, 878. Anal. Calcd for $C_{13}H_{20}O$ (**79**, **71** and **72**): C, 81.20; H, 10.48. Found: C, 81.28; H, 10.54.

Data for 80: ^{1}H NMR 5.49 (dd, 1, J = 2, 2), 2.37–2.15 (m, 4), 1.92–1.65 (m, 5), 1.63–1.47 (m, 5), 1.45–1.30 (m, 2), 1.24 (s, 3); ^{13}C NMR 144.0 (C), 125.7 (CH), 71.1 (C), 56.2 (C), 46.1, 42.7, 39.4, 39.1, 30.9, 30.14, 30.08, 29.6, 22.0; IR (neat) 3452, 2949, 2867, 1711, 1452, 1371, 1266, 1108, 1071, 917, 784.

Hydrogenation of 79, 71, and 72 (25 mg, 0.13 mmol) in ethanol (1.0 mL) over Pd/C (2 mg, 10%) under 1 atm of hydrogen for 15 h gave 25.0 mg (99%) of an inseparable 10:2:3 mixture of **84**, **83**, and **73**, respectively.

Partial data for 73: ^{1}H NMR 2.14 (s, 3); ^{13}C NMR 15.8.

Partial data for 83: ^{1}H NMR 2.95 (dd, 1, J = 4.2, 15.9), 2.14 (s, 3), 0.90 (d, 3, J = 7.0).

Data for 84: ^{1}H NMR 2.44 (dd, 1, J = 3.2, 15.5), 2.22 (dd, 1, J = 10.2, 15.5), 2.15 (s, 3), 0.86 (d, 3, J = 6.8); ^{13}C NMR 209.6, 44.9, 39.5, 38.6, 33.0, 32.4, 31.15, 31.12, 30.3, 21.6, 21.5, 14.1 (the quarternary carbon was not observed); IR (neat) 2952, 2870, 1716.

Oxidation of 75 by Mn(pic)$_3$ in DMF. $Cu(OAc)_2$ (58 mg, 0.31 mmol) and $Mn(pic)_3$ (286 mg, 0.65 mmol) were added to a solution of alcohol **75** (50 mg, 0.26 mmol) in DMF (6.5 mL). The reaction was stirred at rt for 5 h and then was quenched by addition of a solution of 10% $NaHSO_3$ (10 mL). The resulting solution was extracted with ether (4 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 48 mg of crude product. Flash chromatography (49:1 hexanes/EtOAc) provided 31 mg (62%) of a 5:5:8:8:10:24 mixture of **71**, **72**, **83**, **81** or **82**, **82** or **81**, and **84**, respectively.

Partial data for 81 and 82: ^{1}H NMR 0.82 (d, 3, J = 7.1), 0.81 (d, 3, J = 7.1).

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Supplementary Material Available: ORTEP drawing of **35** and ^{1}H and ^{13}C NMR spectra of compounds **8**, **10**, **18**, **19**, **20**, **23** (^{1}H only), **34**, **38**, **41**, **46a**, **46b**, **47**, **49**, **51**, **53**, **54**, **55**, **60**, **64**, **65**, **76** (^{1}H only), and **80** (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.