Manganese(III)-Based Oxidative Free-Radical Tandem and Triple Cyclizations

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Abstract: Tandem oxidative free-radical cyclization of **1a** with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ in acetic acid at 25 °C gives bicyclo[3.2.1]octane **7a** in 86% yield. Oxidation of the β-ketoester gives the enol radical **2a** which undergoes 6-endo cyclization to give tertiary radical **3a**. A second cyclization gives a mixture of primary radicals **5a** which is oxidized directly to alkene **7a** by $Cu(OAc)_2 \cdot H_2O$. This reaction has been used to prepare bicyclo[3.2.1]octanones **7b-e**. Introduction of methyl substituents on the chain leads selectively to **18a-c** with an axial methyl group establishing that the (*E*)-enol radical **15** is formed selectively. Oxidation of **25** leads selectively to the exo-radical **26** which undergoes an oxidative elimination with $Cu(OAc)_2 \cdot H_2O$ with high selectivity for the Hofmann isomer **28**. *trans*-Hydrindanone **52** is formed selectively from *Z* isomer **47a**. *cis*-Hydrindanones **69a-c** are formed selectively from dienes **65a-c**. Triple oxidative cyclizations can also be carried out efficiently. Trienes **38** and **58** are converted to tricyclics **41a** (39%) and **61** (60%), respectively.

Free-radical cyclizations of alkenes have recently been developed into a valuable method for the synthesis of cyclic compounds.[1] Tandem and triple free-radical cyclizations offer a particularly attractive route to polycyclic compounds from dienes and trienes. Free-radical cyclizations have most frequently been initiated by reduction of a halide to a radical with R_3SnH and terminated by reduction of the cyclic radical with R_3SnH to a hydrocarbon. This approach is limited since a relatively unfunctionalized product resulting from a net two-electron reduction is produced. Oxidative free-radical cyclization in which the initial radical is generated oxidatively and/or the cyclic radical is oxidized to terminate the reaction have considerable synthetic potential since more highly functionalized products can be prepared from simpler precursors. Although some early examples are known,[2] it is only recently that several classes of such reactions have been developed.[1g,3,4]

Heiba and Dessau[6a,d] and Bush and Finkbeiner[7] originally demonstrated that acetic acid is oxidized by $Mn(OAc)_3 \cdot 2H_2O$[5] in acetic acid at reflux to the carboxymethyl radical which adds to alkenes to give a radical which is oxidized by a second equivalent of $Mn(OAc)_3 \cdot 2H_2O$ to give a γ-lactone. The mechanism of this reaction has been extensively explored and further synthetic applications developed by Heiba and Dessau,[6] Kooyman,[8] Nikishin and Vinogradov,[9] McQuillin,[10] Fristad,[11] Corey,[12] and others.[12] More recently, Heiba and Dessau[6e] and Nikishin and Vinogradov[9e,f,h-k,m] have shown that $Mn(OAc)_3 \cdot 2H_2O$ mediated oxidative addition of β-dicarbonyl compounds to alkenes occurs efficiently at 25-70 °C.

We have found that oxidation of unsaturated β-ketoesters with manganese(III) is an efficient method for initiation of oxidative free-radical cyclizations.[13,14] In the preceding paper in this series

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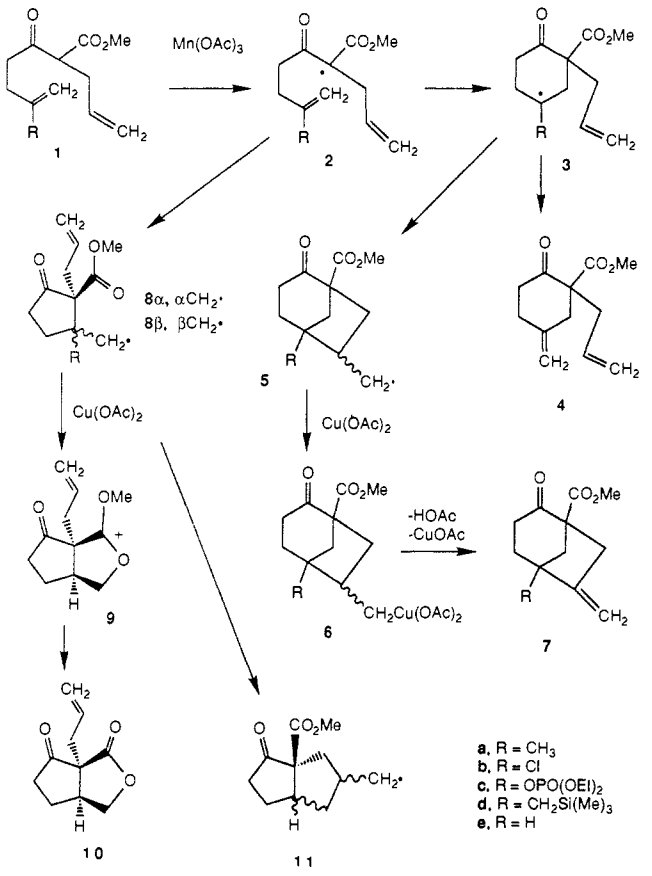
Scheme I



our studies of the initiation, cyclization, and termination of monocyclization reactions are fully described.[13h] We report here our studies of tandem and triple oxidative free-radical cyclizations.

Results and Discussion

Formation of Bicyclo[3.2.1]octanes. We report here a new class of oxidative cyclizations in which two or three sequential cyclizations to double bonds generate a bicyclic cyclopentanemethyl radical which is then oxidized to generate a methylenecyclopentane or vinylcyclopentane.[15] Alkylation of the dianion[16] of methyl allylacetoacetate[17] with methallyl chloride gives diene **1a** in 42% yield. Reaction of β-ketoester **1a**, as a 0.1 M solution in acetic acid, with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ for 26 h at room temperature gives an 86% yield of **7a**.

Oxidation of the β-ketoester of **1a** by $Mn(OAc)_3 \cdot 2H_2O$ gives the radical **2a**, possibly as a manganese complex.[13d] Cyclization gives exclusively the tertiary cyclohexyl radical **3a**.[1] The primary cyclopentanemethyl radical **8a** is not formed. There are several reasons for the selective formation of **3a**. Carbonyl-substituted radicals are electrophilic and should show a greater preference for the formation of a tertiary radical than a normal, nucleophilic alkyl radical. Steric interactions favor the formation of **3a** since formation of **8a** would require the formation of a bond between two fully substituted carbons, a process shown to be slow in elegant kinetic studies by Beckwith.[1d,e,18] Finally, Curran[1g,19] and Clive[20] have shown that the presence of a carbonyl group in the forming ring favors the production of the 6-endo product.

Monocyclic radical **3a**, a normal alkyl radical unperturbed by stabilizing groups or manganese, cyclizes, as expected,[1,18] to give exclusively the cyclopentanemethyl radical **5a**. Cyclopentanemethyl radical **5a** undergoes the expected reaction[21] with $Cu(OAc)_2 \cdot H_2O$ to give organocopper intermediate **6a** which undergoes facile β-hydride elimination to give **7a**. The use of $Cu(OAc)_2 \cdot H_2O$ is crucial to the success of this reaction. The unsaturated product **7a** is formed in only ≈14% yield in the absence of $Cu(OAc)_2 \cdot H_2O$. The major products are oligomer and a mixture of saturated products formed from **5a** by abstraction of a hydrogen atom from the medium.

The success of this reaction depends upon the fact that the cyclizations of **2a** to give **3a** and **3a** to give **5a** are faster than the oxidation of either **2a** or **3a** by $Mn(OAc)_3 \cdot 2H_2O$ or $Cu(OAc)_2 \cdot H_2O$. Oxidation of electron-deficient radical **2a** does not occur since it would give an enol cation. Oxidation of alkyl radicals by $Mn(OAc)_3 \cdot 2H_2O$ is slow. Tertiary radicals are oxidized to cations; primary and secondary radicals usually abstract a hydrogen atom faster than they are oxidized. Use of $Cu(OAc)_2 \cdot H_2O$ as a co-oxidant in $Mn(OAc)_3 \cdot 2H_2O$ oxidations has been developed by Heiba and Dessau[6] and Nikishin and Vinogradov[9] to insure oxidative termination. $Cu(OAc)_2 \cdot H_2O$ is a thermodynamically weak oxidant that nevertheless reacts very rapidly with radicals to give copper(III) intermediates such as **6a** that react further to give alkenes such as **7a**. The CuOAc produced in the oxidation is reoxidized by $Mn(OAc)_3 \cdot 2H_2O$.

A priori, it was not clear that cyclization of **3a** to **5a** would be faster than oxidation to give either **4** or isomers with an endocyclic double bond. Oxidation of primary radicals to alkenes by $Cu(OAc)_2 \cdot H_2O$ occurs with a rate constant of $1-3 \times 10^6$ M^{-1} s^{-1}.[21c,d,22-25] Cyclization of the 5-hexenyl radical to cyclopentanemethyl radical occurs with a rate constant of 10^5. Therefore oxidation of **3a** by 10^{-1} M cupric ion could have been expected to compete very effectively with cyclization to **5a**. The absence of **4** even in the presence of 10^{-1} M cupric ion implies that the unimolecular rate constant for cyclization of **3a** is significantly greater than the bimolecular rate constant for oxidation of **3a** by cupric ion. A more complete analysis is precluded by the lack of rate data for the oxidation of tertiary radicals by cupric ion and for the cyclization of radicals to form bridged rings such as **5a**.

Radical cyclizations are compatible with a wide variety of functional groups. Alkylation of the dianion[16] of methyl allylacetoacetate[17] with 2,3-dichloropropene, 3-chloro-2-((diethylphosphoryl)oxy)propene,[26] and 2-chloromethyl-3-(trimethyl-

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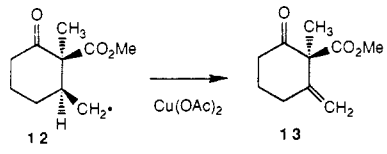
Scheme II



silyl)propene gives **1b**, **1c**, and **1d** in 83%, 55%, and 38% yield, respectively. Oxidative cyclization of **1b** and **1c**, as described above for **1a**, gives **7b** and **7c** in 72% and 77% yield, respectively. The preparation of **7c** in two steps provides a very effective route to a fully functionalized CD ring system of gibberellic acid containing a ketone and an ester which could be used to elaborate the B ring.[27] Oxidative cyclization of **1d** gives a mixture of the expected product **7d** (30%), monocyclic diene **4** (11%), and desilylated product **7a**. The monocyclic product **4** is formed by oxidation of **3d** to the cation followed by desilylation. Oxidation of **3d** is accelerated by the presence of the cation-stabilizing β-trimethylsilyl group. The desilylated product **7a** is probably formed by protodesilylation of **1d** to give **1a** which then undergoes a normal oxidative cyclization.

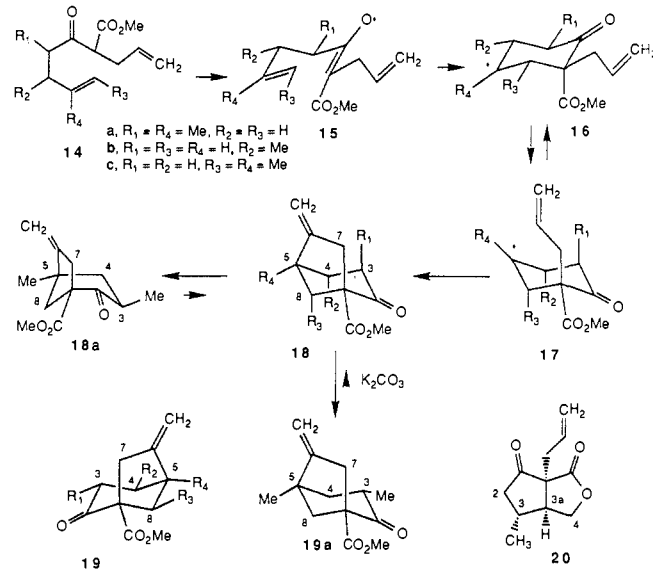
β-Ketoester **1e**[28] was prepared in 44% yield by the alkylation of the dianion[16] of methyl allylacetoacetate[17] with allyl bromide. Reaction of **1e** as described above for 5 h at 25 °C gives **7e** (43%) and **10** (16%). As we have previously reported,[13c] oxidative cyclization to an unsubstituted terminal double bond gives an ≈9:4 mixture of secondary cyclohexyl radical **3e** and primary cyclopentanemethyl radical **8βe**. Radical **3e** is converted to **7e** as described above for **3a**. Addition of the radical center in **8βe** to the double bond will be very slow since a trans fused bicyclo[3.3.0]octane would be formed.[18c] Presumably, the radical center reacts with cupric ion to give an intermediate that reacts with the carbonyl group to give cation **9** which is hydrolyzed to give **10**.[29]

Fristad has shown that the carboxylic acid is involved in the oxidation of γ-carboxypropyl radicals to γ-lactones by Mn(III).[11d] The carbocation is not an intermediate since Mn(III) oxidizes secondary radicals very slowly. On the other hand, esters do not generally assist the oxidation of proximate radicals by Mn(III).[6,11] However, the carbomethoxy group in **8βe** must be involved in the oxidation step since oxidation of an isolated primary radical by cupric ion should give a methylenecyclopentane. The formation of **10** suggests that the proximity of the ester carbonyl and radical center in **8βe** facilitates the formation of **9**. Oxidation of the closely related radical **12** with Cu(II) gives mainly **13**; only a small amount of the corresponding lactone is formed.

Mixtures of stereoisomers have been obtained in analogous oxidative cyclizations that give cyclopentanemethyl radicals.[13c,h] The cyclization of **2e** should have given 60–80% of **8βe** and 20–40% of **8αe**. Radical **8αe** should have cyclized rapidly to give *cis*-**11**. Oxidation would give the isolable methylenecyclopentane which was not observed. This suggests that **8αe** was not formed; it is possible that **8αe** was formed and converted to uncharacterized products.

Determination of Enol Radical Geometry. Methyl groups were introduced into the substrate in an attempt to determine the geometry of the transition state leading to **3a**. Alkylation of methyl 4,6-dimethyl-3-oxo-6-heptenoate[13f] and methyl 5-methyl-3-oxo-6-heptenoate[13f] with allyl bromide affords **14a** (56%) and **14b** (50%). β-Ketoester **14c** (42%) was prepared by alkylation of the dianion[16] of methyl allylacetoacetate with (*E*)-1-bromo-2-methyl-2-butene. Cyclization of all three substrates leads predominantly to **18** with an axial methyl group.

Scheme III



Oxidative cyclization of **14a** gives a 5:1 mixture of **18a** and **19a**. Chromatographic purification results in partial equilibration to give a 2:1 mixture of **18a** and **19a** in 57% yield. Further equilibration with potassium carbonate in methanol converts the mixture to pure **19a**. (Adduct **19a** formed by equilibration of **18a** must be the enantiomer of **19a** formed directly by cyclization of **14a**. This cannot be detected since the starting material is racemic.) The stereochemistry of **18a** and **19a** can be convincingly assigned based on their relative stability. Molecular mechanics calculations[30] indicate that **19a** is more stable than the boat conformer of **18a** by 2.2 kcal/mol which in turn is more stable than the chair conformer of **18a** by 0.3 kcal/mol.

The stereochemistry and conformational assignment of **18a** and **19a** can be confirmed by analysis of the ^{1}H and ^{13}C NMR spectra. The axial, endo methine H3 in **19a** is coupled to exo- and endo-H4 with J = 12.3 and 7.8 Hz, respectively, as expected for axial–axial and axial–equatorial couplings.[30] The ^{13}C NMR spectrum shows shifts from that of **7a** expected for the introduction of an equatorial methyl group: C1 (−0.1), C3 (3.8), C4 (9.7), C5 (0.5), and C8 (0.7). The exo-methine H3 in **18a** is coupled to exo- and endo-H4 with J = 10.5 and 5.4 Hz which is not consistent with equatorial–axial and equatorial–equatorial couplings in the chair conformer but is entirely consistent with expected coupling constants of 9.6 and 7.4 Hz expected for the boat conformer.[30] The ^{13}C spectrum of **18a** is not consistent with that calculated for the chair conformer with use of the spectrum of **7a** and the expected shifts of an axial methyl group. However, the ^{13}C NMR spectrum of *endo*-3-methylbicyclo[3.2.1]octane is also not consistent with that expected for the chair conformer which led Lippmaa and coworkers to propose that it exists predominantly in the boat conformation.[31]

Oxidative cyclization of **14b** gives an inseparable 5:1 mixture of **18b** and **19b** in 51% yield and **20** in 15% yield. The structure of the major isomer **18b** was assigned based on analysis of the ^{1}H and ^{13}C NMR spectra. Decoupling of the methyl group at δ 1.10 indicated that the methine proton H4 was coupled to H3-endo with J = 8.2 Hz, to H3-exo with J = 2.8 Hz, to H5 with J = 2.8 Hz, and to H8 by a four-bond W coupling of 1.5 Hz. These vicinal coupling constants and the long-range coupling constant are only consistent with an equatorial H4. The ^{13}C NMR

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(30) MMX (obtained from Serena Software, 489 Serena Lane, Bloomington, IN 47401) was used on a VAX 8650. Updated versions of MODEL (obtained from Prof. Midland, University of California, Riverside, and Prof. Steliou, University of Montreal) were used for structure input and analysis. NMR coupling constants were calculated using MODEL on structures minimized with MMX.
(31) Lippmaa, E.; Pehk, T.; Belikova, N. A.; Bobyleva, A. A.; Kalinichenko, A. N.; Ordubadi, M. D.; Platé, A. F. *Org. Magn. Reson.* **1976**, *8*, 74.

spectrum of **18b** shows shifts from that of **7a** expected for the introduction of an axial methyl group: C3 (3.2), C4 (4.3), C5 (6.1), and C8 (-4.1). The ^{13}C NMR spectrum of **19b** shows shifts from that of **7a** expected for the introduction of an equatorial methyl group: C3 (8.3), C4 (4.0), C5 (6.2), and C8 (-0.1). The shielding of C8 by the axial methyl group in **18b** but not by the equatorial methyl group in **19b** is particularly significant.

The stereochemistry of **20** follows from the ^1H NMR absorption of H3 at δ 2.11 (dddq, 1, J = 6.1, 10.8, 10.9, 6.6). These coupling constants are consistent only with the exo isomer **20**. Furthermore, C4 in **20** absorbs at δ 70.1 only 0.8 ppm upfield from C4 in **7a**. In the endo isomer, C4 should be shifted upfield by several ppm by the γ gauche effect.[32]

Oxidative cyclization of **14c** gives an 11:1 mixture of **18c** and **19c** in 67% yield. The structure of **18c** follows from the ^1H NMR absorption of H8 at δ 2.21 (dq, 1, J = 2.0, 7.0 Hz). The unexpected coupling constant of 2.0 Hz is a four-bond W coupling with H4-endo indicating that H8 is equatorial. The ^{13}C NMR spectra confirms the stereochemical assignment. C4 is shifted upfield to δ 34.3 by the axial methyl group in **18c** from δ 40.3 in **7a** and δ 40.0 in **19c**. The axial methyl group in **18c** absorbs at δ 9.9, while the equatorial methyl group in **19c** absorbs at δ 12.8. C7 is shifted upfield to δ 36.9 in **19c** by the γ gauche effect from δ 39.9 in **7a** and δ 40.0 in **18c**.

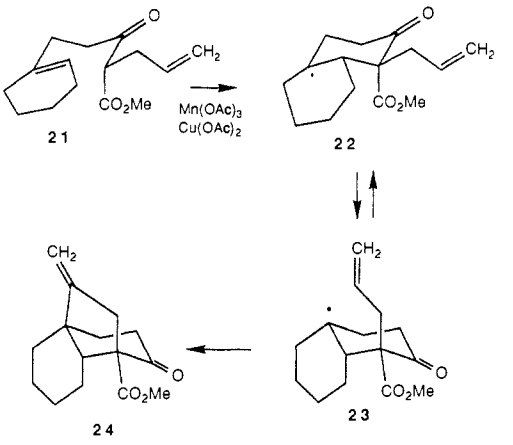
The preferential formation of **18a-c** suggests that cyclization proceeds as shown in Scheme II. Oxidation of **14** gives the (*E*)-enol radical **15**. Cyclization through a chair transition state gives **16** with an axial ester group and equatorial allyl and methyl groups. Chair inversion gives **17** with an axial allyl group which undergoes the second cyclization and oxidative elimination to give **18**. We have shown that enolization of α-substituted β-ketoesters is the rate-determining step in the oxidation.[13d] Therefore enolization gives the (*E*)-enolate, which is rapidly oxidized to **15**, rather than the (*Z*)-enolate which could chelate to manganese. Although a chelated enolate appears to be intuitively preferred, in fact, O-alkylation of β-ketoester enolates often leads to *E* products.[33]

The minor products **19a-c** could be formed through a boat transition state or from the (*Z*)-enolate. The α-methyl ketone **19a** could be formed by acid-catalyzed equilibration of **18a** during the reaction. Minor products **19a** and **19b** could also be formed through a chair transition state with an axial methyl group. Minor product **19c** could be formed from the *Z* isomer of **14c**; ^1H NMR analysis of **14c** suggests that less than 3% of the *Z* isomer is present indicating that this is not the only source of **19c**.

Alkylation of the dianion[16] of methyl allylacetoacetate[17] with 1-(bromomethyl)cyclohexene[34] gives **21** in 41% yield. Oxidative cyclization of **21** as described above affords **24** in 73% yield. The stereochemistry of **24** was assigned based on analysis of the ^1H and ^{13}C NMR spectra. The aliphatic carbon of the two-carbon bridge absorbs at the same frequency in **7a** (39.9 δ) and **24** (40.5 δ) which indicates that the cyclohexane of **24** is on the side of the three carbon bridge. The γ gauche effect should shield this carbon by several ppm in the stereoisomer with the cyclohexane on the side of the two-carbon bridge. This assignment was confirmed by NOE experiments. Irradiation of the allylic methylene group at δ 2.80-2.95 leads to an NOE enhancement of the methine proton on the one carbon bridge. The stereospecific formation of **24** is analogous to the formation of **18c** from **14c**. The initial cyclization gives the monocyclic radical **22**, with an axial ester group and an equatorial allyl group which then undergoes chair inversion to give **23** which cyclizes to **24**.

Examination of the Stereochemistry of the Second Cyclization and the Regiochemistry of the Oxidative Elimination. The second

Scheme IV



cyclization in the sequence converting radical **3** to **5** presumably gives a mixture of isomers which are both converted to **7** by oxidative elimination with cupric ion. The cyclization of **25** was examined to determine the stereochemistry of the second cyclization and to determine the nature of the oxidation products obtained from secondary and tertiary radicals **26** and **27**. Alkylation of methyl 6-methyl-3-oxo-6-heptenoate[35] with crotyl bromide and prenyl bromide gives **25b** and **25d** in 53% and 29% yield. Alkylation of methyl 3-oxo-6-heptenoate[16] with crotyl bromide and prenyl bromide gives **25a** and **25c** in 56% and 55% yield.

Oxidative cyclization of **25a** affords 39% of an inseparable 2:1 mixture of **28a** and **29a** and 22% of **34a**. Oxidative cyclization of **25b** affords 65% of an inseparable 2:1 mixture of **28b** and **29b** and 5% of **32b**. Oxidative cyclization of **25c** affords 27% of an inseparable 5:1 mixture of **28c** and **29c**, 10% of a 4:1 mixture of **30c** and **31c**, and 19% of **34c**. Oxidative cyclization of **25d** affords 45% of an inseparable 5:1 mixture of **28d** and **29d** and 24% of a 5:1 mixture of **30d** and **31d**. The formation of lactones **34a** and **34c** from cyclopentanemethyl radical **33** is strictly analogous to the formation of **10** from **7e**. Secondary radicals **26a,b** and **27a,b** undergo oxidative hydride elimination with high selectivity for the Hofmann product **28a,b** and **29a,b** as has been observed previously in lead tetraacetate-cupric acetate decarboxylations.[36,37] Only traces of the more substituted product **32a,b** are formed. Tertiary radicals **26c,d** and **27c,d** are oxidized by either manganic or cupric ion to the tertiary cations which lose a proton to give alkenes **28c,d** and **29c,d** and react with the solvent to give acetates **30c,d** and **31c,d**. The tetrasubstituted alkenes **32c,d** were not observed although this is not necessarily conclusive since the readily oxidizable tetrasubstituted double bonds might have been degraded if they were formed.

Since manganese(III) will oxidize tertiary radicals to cations, we examined the oxidative cyclization of **25c** without $Cu(OAc)_2 \cdot H_2O$. Two significant differences were noted in the cyclization in the absence of copper(II). The yield of acetates **30c** and **31c** (23% of a 3.5:1 mixture) increased at the expense of alkenes **28c** and **29c** (17% of a 5:1 mixture) suggesting that copper is, at least partially, oxidizing tertiary radicals **26c** and **27c** to alkenes by an oxidative elimination pathway. None of lactone **34c** is isolated. Instead, cyclopentane **37** (5%) and *trans*-bicyclo[3.3.0]octanes **36** (12% of a 5:1 mixture) are obtained. Oxidation of **33** to **34** requires copper(II). In the absence of copper(II) primary radical **33** abstracts a hydrogen atom to give **37** or undergoes a slow, but precedented,[18c,39b] cyclization to give the strained *trans*-bicyclo[3.3.0]octane radical **35**. Tertiary radical

(32) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.
(33) (a) Petrov, A. A.; Esakov, S. M.; Ershov, B. A. *J. Org. Chem. USSR* **1976**, *12*, 774; *Zh. Org. Khim.* **1976**, *12*, 775. (b) Raban, M.; Noe, E. A.; Yamamoto, G. *J. Am. Chem. Soc.* **1977**, *99*, 6527. (c) Raban, M.; Haritos, D. P. *J. Am. Chem. Soc.* **1979**, *101*, 5178. (d) Cambillau, C.; Guibe, F. *Can. J. Chem.* **1982**, *60*, 634. (e) Cambillau, C.; Bram, G.; Corset, J.; Riche, C. *Can. J. Chem.* **1982**, *60*, 2554.
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(35) Hirama, M.; Shimizu, M.; Iwashita, M. *J. Chem. Soc., Chem. Commun.* **1983**, 599.
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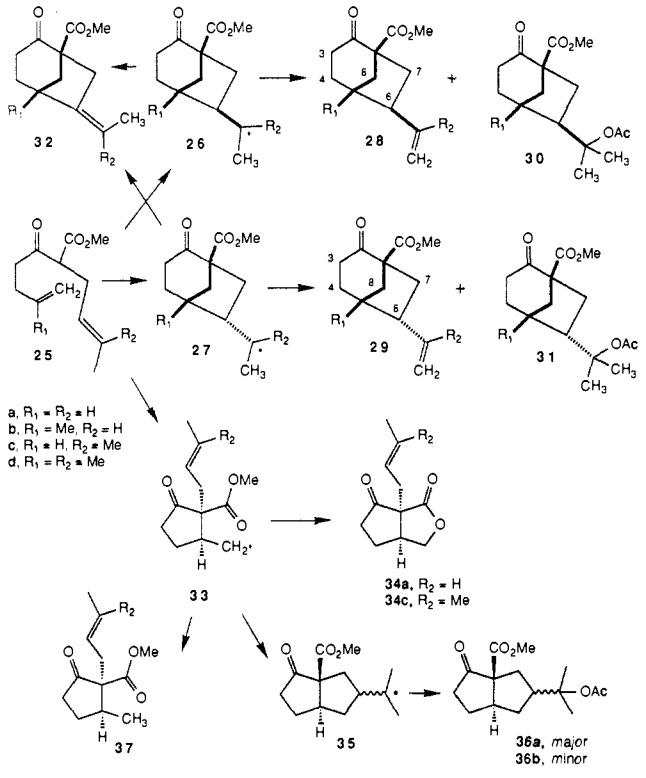
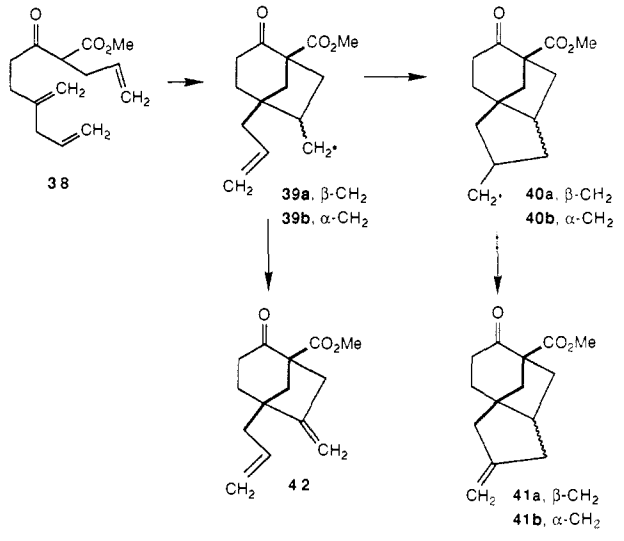
(38) Jaggi, F. J.; Buchs, P.; Ganter, C. *Helv. Chim. Acta* **1980**, *63*, 872.
(39) For other triple cyclizations, see: (a) Lallemand, J. J.; Julia, M.; Mansuy, D. *Tetrahedron Lett.* **1973**, 4461. (b) Beckwith, A. L. J.; Roberts, D. H.; Schiesser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349.

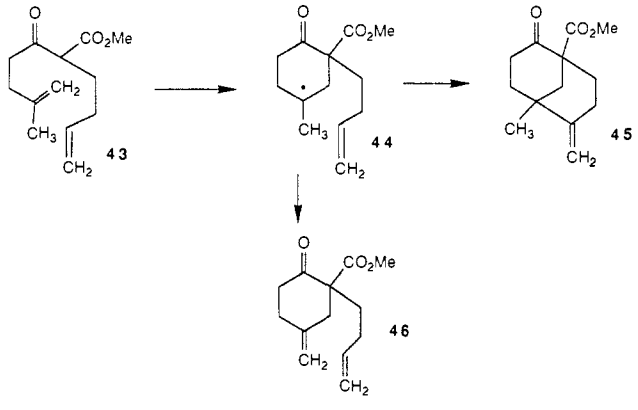
Scheme V



Scheme VI



Scheme VII



35 is oxidized by manganese(III) to a cation which reacts with acetic acid to give acetate **36**.

Assignment of the stereochemistry of **28–31** is not straightforward. The stereochemistry of the major isomers **28a** and **28c** follow from the coupling constant between H5 and H6 which is <1 Hz as expected (0.7 Hz) for a dihedral angle of 93°.[30] The stereochemistry of **29a** follows from the coupling constant between H5 and H6 of 6 Hz as expected (6.4 Hz) for a dihedral angle of 38°.[30] The ^1H NMR spectra of the other compounds do not aid in stereochemical assignment. Comparison of the ^{13}C NMR spectra to those of *endo*- and *exo*-6-methylbicyclo[3.2.1]octane[38] permits assignment of stereochemistry to **28** and **29**. In the major isomer **28** with an exo substituent on C6, the absorptions for C8 are shifted upfield 1.4–3.9 ppm from C8 in **29** due to the γ gauche effect. Upfield shifts are also observed for C7 in **28**. In the minor isomer **29** with an endo substituent on C6, the absorptions for C4 are shifted upfield 4.2–5.7 ppm from C4 in **28** due to the γ gauche effect. The stereochemistry of acetates **30** and **31** was assigned by analogy to **28** and **29**.

The major product **28** formed in all cyclizations is the less hindered exo product. With a *trans*-crotyl side chain a 2:1 mixture of stereoisomers **26** and **27** is formed. Primary radical **5a** should be formed as a similar mixture of stereoisomers since allyl and *trans*-crotyl side chains have similar steric requirements. Introduction of a second, *cis*-methyl group should and does increase the stereoselectivity of the second cyclization. A 5:1 mixture of **26** and **27** is formed with a prenyl side chain.

Triple Oxidation Free-Radical Cyclization. Triple oxidative free-radical cyclizations also proceed efficiently.[39] Alkylation of the dianion[16] of methyl allylacetoacetate[17] with 2-(bromomethyl)-1,4-pentadiene[40] gives **38** in 71% yield. Oxidative cyclization of **38** gives 39% of **41a** and 21% of **42**. Cyclization of **38** should give a 2:1 mixture of **39a** and **39b**. The major isomer **39a** should cyclize rapidly to **40a** which should react with cupric ion to give **41a** after oxidative elimination. The minor isomer **39b** must cyclize to **40b** which contains a highly strained *trans*-bicyclo[3.3.0]octane. This cyclization will be very slow. Radical **39b** therefore reacts with cupric ion to give **42** after oxidative elimination. The isolation of a 2:1 mixture of **41a** and **42** is consistent with the anticipated formation of a 2:1 mixture of **39a** and **39b**.

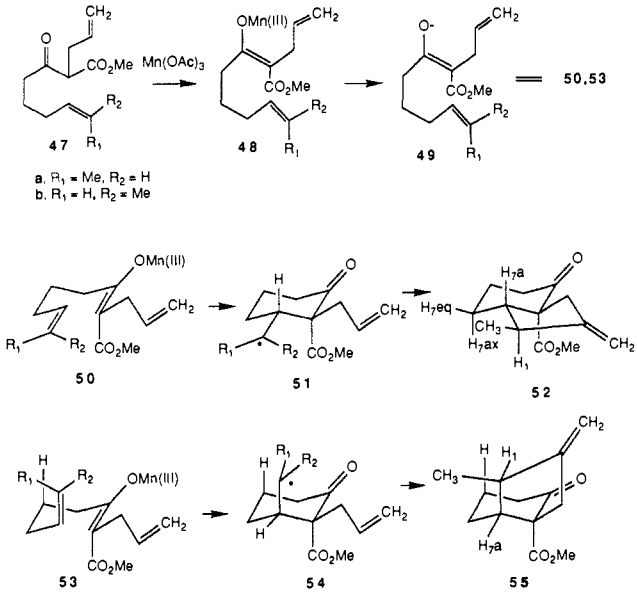
The oxidative cyclization of **43** was examined to determine whether the 6-exo cyclization of 6-heptenyl radical **44** in the second cyclization is faster than oxidation of **44** by cupric ion. Alkylation of methyl 6-methyl-3-oxo-6-heptenoate[35] with 4-bromo-1-butene gives 50% of **43**. Oxidative cyclization of **43** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv $Cu(OAc)_2 \cdot H_2O$ gives only 31% of **45**, along with 5% of **46** and 8% of recovered **43**. The initial cyclization of **43** should proceed normally to give **44**. Radical **44** is a 6-heptenyl radical which will cyclize much more slowly than 5-hexenyl radical **3** to give a primary radical that will react with cupric ion to give **45**. Reaction of cupric ion with **44** should give **46**, endocyclic isomers, and tertiary acetates. The low material balance suggests that these products are formed and react further. Oxidation of tertiary radical **44** by cupric ion is competitive with cyclization of a 6-heptenyl radical. We anticipated that a higher yield of **45** would be obtained with a lower concentration of cupric ion as observed in related systems.[13g] Surprisingly, less **45** was obtained when only 0.05 equiv of $Cu(OAc)_2 \cdot H_2O$ (0.005 M) was used.

Formation of *trans*-Hydrindanones. Cyclization of 6-heptenyl radicals in the first cyclization proceeds very efficiently providing an attractive procedure for the preparation of *trans*-hydrindanones. Alkylation of the dianion[16] of methyl allylacetoacetate with *cis*-5-bromo-2-pentene[41] and *trans*-5-bromo-2-pentene[41] gives **47a** and **47b** in 57% and 71% yield, respectively. Oxidative cyclization of **47a** gives 67% yield of a 25:1 mixture of **52** and **55**. Oxidative cyclization of **47b** gives a 46% yield of a 2:1 mixture of **52** and **55**. The stereochemistry of the major isomer **52** was established by analysis of the ^1H NMR spectrum. The ring fusion hydrogen, H-7a, absorbs at δ 1.35 (ddd, J = 11.8, 11.7, 4.2). The two large

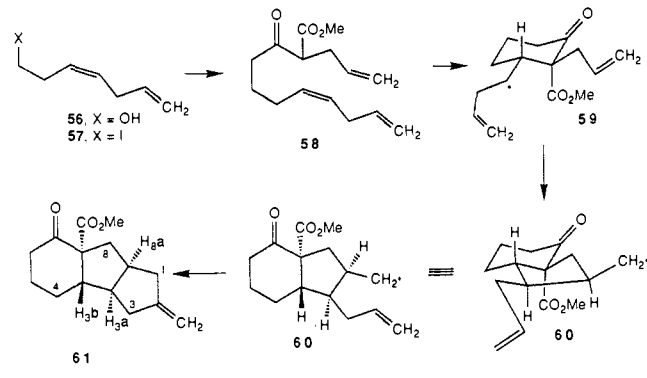
(40) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1.

(41) Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1475.

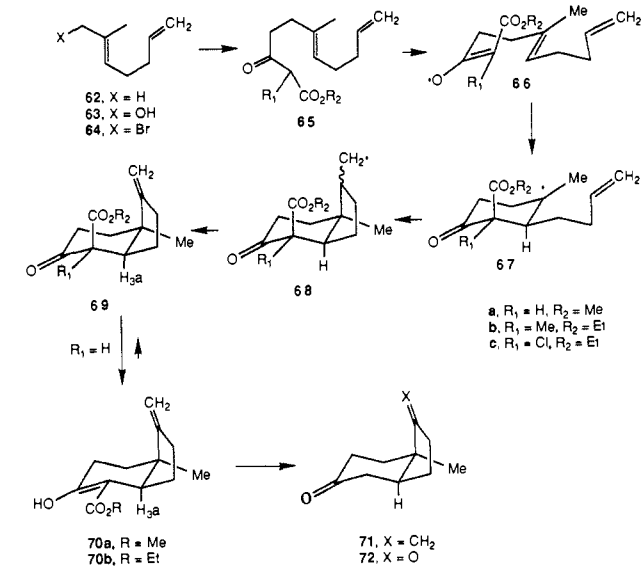
Scheme VIII



Scheme IX



Scheme X



vicinal coupling constants between H-7a and H-1, and H-7a and H-7ax require that the ring fusion hydrogen be axial on the cyclohexane and pseudo-axial on the cyclopentane. Furthermore, the methyl group must be α on the cyclopentane so that there can be a large dihedral angle between H-7a and H-1. Isomer **52** is the only one of the four possible diastereomers that can adopt a conformation which will give rise to two large vicinal coupling constants for H-7a. The stereochemistry of the minor isomer **55** was assigned based on the vicinal coupling constant of 12.8 Hz between H1 and H7a, which requires a dihedral angle of $\approx$180° between these protons.

The rate-determining step in the cyclization of **47** is formation of the manganese enolate **48** which reacts rapidly to give radical **49**.[13d] The *E* geometry of the enol radical has been established in the cyclizations of **14a–c** discussed above. A 6-exo cyclization of **49** can proceed through chair transition state **50** with an equatorial side chain to give **51** or through chair transition state **53** with an axial side chain to give **54**. Cyclization of 5-hexenyl radical **51** followed by oxidative elimination with cupric ion gives **52**. Isomer **52** with a pseudoequatorial methyl group is formed to avoid severe steric repulsion between the carbethoxy and methyl groups which would be in a 1,3-diaxial relationship in the stereoisomer. Cyclization of 5-hexenyl radical **54** followed by oxidative elimination with cupric ion gives **55**. Isomer **55** with an exo methyl group is formed to minimize steric repulsion. Cyclization to give **51** is the major process with **47b** and the virtually exclusive process with **47a** since there is a severe steric interaction between the methyl group (R_1) and axial hydrogen in **53a**. Similar effects of alkene geometry on ring stereochemistry have been observed in other 6-exo cyclizations.[42]

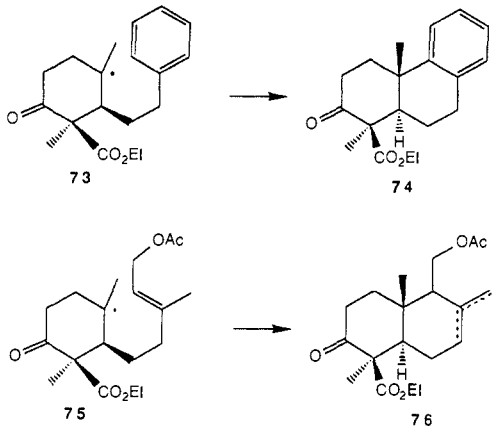
Triple Oxidative Free-Radical Cyclization. A highly selective oxidative triple cyclization[39] can be carried out with **58** in which the methyl group on the double bond of **47a** has been replaced by an allyl group. Alkylation of 3-butyn-1-ol with allyl bromide provides hept-6-en-3-yn-1-ol in 79% yield.[43] Partial hydrogenation of the triple bond over Lindlar catalysts, nickel boride,[44] or zinc[45] to give *cis*-3,6-heptadien-1-ol (**56**) proved to be remarkably difficult. Reduction of the terminal double bond or isomerization of the skipped diene invariably occurred. Selective reduction to give **56** in 74% yield was finally accomplished by reduction with iron fillings[46] in aqueous isopropyl alcohol at reflux for 7 days. Reduction was much faster with iron dust but was accompanied by partial isomerization to the trans double bond. Reaction of **56** with mesyl chloride and triethylamine followed by displacement with NaI in acetone gave iodide **57** in 87% yield. Alkylation of the dianion[16] of methyl allylacetoacetate with **57** gives **58** in 56% yield.

Oxidative cyclization of **58** gives monocyclic radical **59** which cyclizes to **60** with the allyl and methylene groups cis to each other and trans to the axial ester group to avoid severe steric interactions. Cyclization of 5-hexenyl radical **60** followed by oxidative elimination with cupric ion gives **61** in 60% yield. The stereochemistry of **61** is assigned based on analysis of the coupling constants in the ^{1}H NMR spectrum. H3a is coupled to the two H3's (7, <1 Hz), H8a (10 Hz), and H3b (11 Hz). H8a is coupled to the two H1's (8, 1 Hz), the two H8's (8, 9 Hz), and H3a (10 Hz). H3b, appearing upfield of all other absorptions as does H7a in **52**, is coupled to the two H4's (2, 13 Hz) and H3b (11 Hz). These coupling constants which fit closely with those calculated for an MM2 minimized geometry of **61** are consistent only with the indicated geometry.

Formation of *cis*-Hydrindanones. Tandem cyclization reactions in which both double bonds are on the same chain provide access to hydrindanones **69a–c**. Catalytic selenium dioxide oxidation[47] of diene **62** affords allylic alcohol **63** in 51% yield. Corey–Kim bromination[48] converts **63** into allylic bromide **64** in 66% yield.

(42) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859.
(43) Nicolaou, K. C.; Petasis, N. A.; Li, W. S.; Ladduwahetty, T.; Randall, J. L.; Webber, S. E.; Hernandez, P. E. *J. Org. Chem.* **1983**, *48*, 5400.
(44) Zábranský, J.; Černý, J. V.; Sedmera, P. *Coll. Czech. Chem. Commun.* **1976**, *41*, 3294.
(45) Crombie, L.; Jenkins, P. A.; Roblin, J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1099. Aerssens, M. H. P. J.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1984**, 735 and references cited therein. Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371.
(46) Morris, S. G.; Magidman, P.; Herb, S. F. *J. Am. Oil Chem. Soc.* **1972**, *49*, 505. Schrauzer, G. N.; Guth, T. D. *J. Am. Chem. Soc.* **1976**, *98*, 3508.
(47) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

Scheme XI



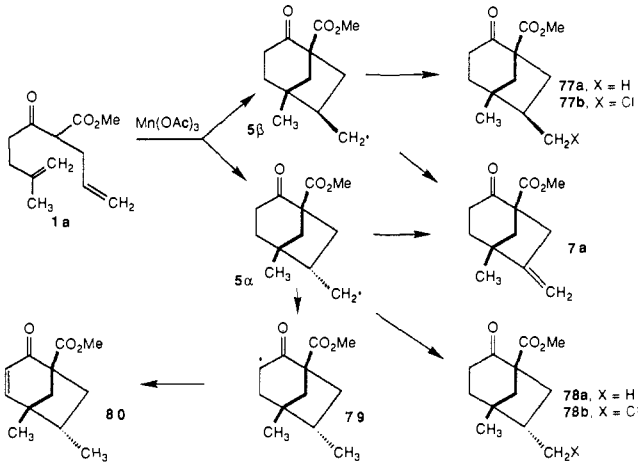
Alkylation of the dianion[16] of the appropriate acetoacetate ester with **64** affords substrates **65a–65c** in 50–55% yield. Oxidative cyclization of **65a** provides 44% of bicyclic β-ketoester **70a**. Similar treatment of **65b** and **65c** affords cycloadducts **69b** and **69c** in 33% and 48% yield, respectively. Oxidation of **65** gives (*E*)-enol radical **66** which cyclizes to give monocyclic tertiary radical **67**. 5-Exo cyclization of **67** gives cis-fused radical **68** which reacts with cupric ion to give **69**.

The stereochemistry of the ring fusion of **70a** was tentatively assigned as cis since the β-ketoester exists as the enol tautomer. Collins and Tomkins[49] reported that a closely related *cis*-hydrindane with a carbonyl rather than methylene group on the cyclopentane exists as the enol tautomer, while the *trans*-hydrindane exists as the keto tautomer with an equatorial ester group. The structure and stereochemistry of **70a** was established by conversion to dione **72**. Hydrolysis of **70a** with NaOH in MeOH–H_2O followed by careful workup at 0 °C with sodium dihydrogen phosphate to prevent double bond isomerization gives ketone **71** in 81% yield. Ozonolysis of **71** with reductive workup gives diketone **72** in 68% yield. The methyl singlet of **72** absorbs at δ 1.23 as reported for the cis fused isomer.[49] The methyl singlet of the trans fused isomer absorbs at δ 1.10.[49]

The ring fusion stereochemistry of **69c** was established by reductive removal of the chlorine with zinc dust in acetic acid to produce ethyl ester **70b** in 71% yield whose ^1H NMR spectrum corresponds closely to that of methyl ester **70a**. Ethyl ester **70b** can be prepared in 57% overall yield from **65c** by addition of zinc dust to the oxidative cyclization reaction prior to workup.[13f] Irradiation of the 7a-methyl group of **69c** led to a 13% NOE enhancement of the 3a-proton at δ 2.58 further indicating a cis ring fusion in **69c**. The cis ring fusion of **69b** was established by conversion of **70b** to **69b**. Methylation of **70b** with sodium hydride and methyl iodide afforded a 2:1 mixture of **69b** and its diastereomer in 41% yield and the methyl ether in 6% yield. The formation of **69b** indicates that the ring fusion is cis. The stereochemistry at C-4 cannot be unambiguously determined and is tentatively assigned based on analogy to the cyclization of **14c** and previous cyclizations.[13a,c]

Exclusive formation of *cis*-hydrindane **68** in the 5-exo cyclization of **67** is expected based on ample precedent.[1,18] This result appears to conflict with the formation of *trans*- rather than *cis*-decalins in oxidative cyclizations of radicals **73** and **75** which give **74** and **76**.[13a,b] Although 5-exo cyclizations always give *cis*-hydrindanes, many examples of 6-endo cyclizations giving *trans*-decalins are known.[1c,2] It is also possible that **74** and **76** are formed by a cationic rather than a radical cyclization. We have obtained evidence which suggests that **73** is oxidized to the cation which then undergoes a Friedel–Crafts alkylation to give **74**.[13b] We have not established that **75** is oxidized to the cation prior to cyclization, although this is entirely consistent with the observed product distribution. Clearly radical **67** cyclizes to **68** prior to oxidation, since a decalin would be obtained from cyclization of the tertiary cation.

Scheme XII



Oxidation of tertiary radicals **67**, **73**, and **75** should occur at the same rate. Cyclization of **67** must be much faster than cyclization of **73** and **75** if **67** cyclizes to radical **68**, while **73** and **75** are oxidized to cations. Cyclization of radicals to double bonds is much faster than to aromatic rings. Cyclization of the 5-hexenyl radical occurs with a rate constant of 10^5 s^{-1}, while cyclization of the 4-phenylbutyl radical occurs with a rate constant of $\approx 10^3$ s^{-1}.[1,50] Therefore the cyclization of **73** should be roughly 100 times slower than the cyclization of **67** so that oxidation of **73** can precede cyclization. 5-Exo cyclization of **75** should be 10^4 slower than 5-exo cyclization of **67** due to steric interactions between the tertiary radical and the highly substituted double bond.[1,18] 6-Endo cyclization of **75** should be roughly 50 times slower than 5-exo cyclization of **67**. Therefore, formation of **76** by either a slow 6-endo radical cyclization or by oxidation to a cation followed by electrophilic cyclization is consistent with the available data.

Oxidative Cyclization with $Mn(OAc)_3 \cdot 2H_2O$ and $Mn(OAc)_3 \cdot 2H_2O$–LiCl. Early studies demonstrated that use of both $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ is necessary if a high yield of oxidatively terminated product is to be obtained. We examined the oxidative cyclization of **1a** with $Mn(OAc)_3 \cdot 2H_2O$ to determine the nature of the termination process in the absence of an efficient method for the oxidation of primary radical **5**. We obtained only 14% of **7a**. The other products are **77a** (16%), **78a** (6%), and **80** (1%). Oxidative cyclization proceeds normally to give a 2:1 mixture of exo isomer **5β** and endo isomer **5α**. Oxidation to give **7a** is very inefficient. Hydrogen abstraction gives **77a** and **78a**, respectively. The endo isomer **5α** undergoes a 1,5-hydrogen atom shift to give α-keto radical **79** which undergoes oxidative β-hydrogen elimination to give enone **80**.

Vinogradov and Nikishin have demonstrated that use of $Mn(OAc)_3 \cdot 2H_2O$ and LiCl results in oxidative addition and delivery of a chloride to the radical center,[9l,m] and we have shown that LiCl can be used to terminate oxidative monocyclizations.[13d,f] Treatment of **1a** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 2 equiv of LiCl gives 50% of a 2:1 mixture of the expected chlorides **77b** and **78b**, 5% of recovered **1a**, 5% of the acyclic α-chlorination product **81**, and 8% of a mixture of monocyclic chlorides **82** which result from delivery of a chloride to the monocyclic tertiary radical **3a**.

The stereochemistry of **77** and **78** can be assigned unambiguously by analysis of their ^{13}C NMR spectra with 6-methyl- and 5,6-dimethylbicyclo[3.2.1]octanes as model compounds.[31,51] In

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(49) Collins, D. J.; Tomkins, C. W. *Aus. J. Chem.* **1977**, *30*, 443.

(50) Data in ref 24 establish that the first-order rate constant for the cyclization of the 4-phenylbutyl radical is 10^3 slower than the second-order rate constant for oxidation by cupric ion. A rate value of 10^3 s^{-1} follows from a value of 10^6 M^{-1} s^{-1} for oxidation by cupric ion.[21c,d,22-24]
(51) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London, 1987; p 128. Matveeva, I. A.; Sokolova, I. M.; Pekhk, T. I.; Petrov, A. A. *Neftekhimiya* **1975**, *15*, 646.

the major, exo isomer **77**, C8- and the C5-methyl are shielded and absorb upfield. In the minor, endo isomer **78**, C4- and the C6-methyl or methylene are shielded and absorb upfield.

Conclusion

Oxidative polycyclization with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ should be generally useful in organic synthesis. Polycyclization followed by oxidative termination proceeds in high yield with good control of both the stereochemistry and the oxidative termination process. Initiation by oxidation of a β-dicarbonyl compound leads to a more highly functionalized product than initiation by treatment of an alkyl halide with R_3SnH. Oxidative termination inserts a double bond regiospecifically into the product. The substrates are prepared remarkably easily, usually by alkylation of mono- or dianions of β-dicarbonyl compounds. We are continuing to explore the scope and limitations of this reaction and are applying it to total synthesis.

Experimental Section

General Procedure for Alkylation of Methyl 2-Allylacetoacetate. Methyl 2-(2-Propenyl)-3-oxo-6-methylhept-6-enoate (1a). To a stirred suspension of NaH (0.536 g of a 60% dispersion in mineral oil, 0.013 mol) in THF (6 mL) at 0 °C was added dropwise a solution of methyl 2-allylacetoacetate (2.045 g, 0.013 mol) in 3 mL of THF. The solution was stirred at 0 °C for 0.5 h at which time *n*-butyllithium (2.5 M in hexanes, 5.36 mL, 0.013 mol) was added dropwise. The solution was stirred for 0.5 h at 0 °C, and methallyl chloride (1.29 mL, 0.013 mol) was added dropwise. The mixture was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for an additional 2 h. The reaction was quenched by the dropwise addition of water (50 mL) and acidified with 1.5 M HCl. The aqueous phase was extracted with three portions of ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave 2.400 g of crude product. Purification of 1.235 g by flash chromatography (silica gel deactivated with 10% water, 23:1 hexane–ethyl acetate) gave 0.592 g (42%) of **1a** as a pale yellow oil: ^1H NMR 5.74 (ddt, 1, J = 7.0, 10.0, 17.5), 5.10 (br d, 1, J = 17.5), 5.07 (br d, 1, J = 10.0), 4.75 (br s, 1), 4.65 (br s, 1), 3.74 (s, 3), 3.58 (t, 1, J = 7.5), 2.72 (m, 2), 2.61 (t, 2, J = 7.6), 2.29 (t, 2, J = 7.6), 1.72 (s, 3); ^{13}C NMR 203.8, 169.6, 144.0, 134.2, 117.5, 110.3, 58.3, 52.4, 40.4, 32.2, 30.9, 22.6; IR (neat) 3075, 1742, 1713, 1642 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.67; H, 8.55.

General Procedure for Oxidative Cyclization. Methyl 5-Methyl-6-methylene-2-oxobicyclo[3.2.1]octane-1-carboxylate (7a). To a stirred solution of $Mn(OAc)_3 \cdot 2H_2O$ (0.804 g, 3.0 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.300 g, 1.5 mmol) in 13.5 mL of glacial acetic acid was added ketoester **1a** (0.307 g, 1.5 mmol) in 4 mL of glacial acetic acid. The reaction mixture was stirred at room temperature for 26 h at which time 100 mL of water was added. A solution of 10% $NaHSO_3$ was added dropwise to the mixture to decompose any residual $Mn(OAc)_3$. The resulting solution was extracted with three 30-mL portions of methylene chloride. The combined organic extracts were washed with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave 0.301 g (96%) of a yellow solid which was recrystallized from pentane to give pure **7a** (86%). A second recrystallization from pentane provided an analytical sample: mp 71.8–72.5 °C; ^1H NMR 5.08 (dd, 1, J = 2.3, 3.1, $=CH_2$), 5.01 (dd, 1, J = 2.3, 3.1, $=CH_2$), 3.76 (s, 3, $-OCH_3$), 2.94 (dddd, 1, J = 0.9, 1.9, 2.9, 18.4, H7 endo), 2.83 (br d, 1, J = 18.4, H7 exo), 2.52 (dddd, 1, J = 1.0, 8.9, 12.5, 17.0, H3 endo), 2.36 (ddd, 1, J = 2.0, 6.9, 17.0, H3 exo), 2.09 (br s, 2, 2 H8), 1.79 (ddd, 1, J = 6.9, 12.0, 12.5, H4 exo), 1.68 (ddddd, 1, J = 2.0, 2.0, 2.0, 8.9, 12.0, H4 endo), 1.25 (s, 3, C5-CH_3); ^{13}C NMR 207.5 (C2), 171.7 (OC=O), 153.5 (C6), 106.3 ($=CH_2$), 62.2 (C1), 52.1 (OCH_3), 47.0 (C8), 44.0 (C5), 40.3 (C4), 39.9 (C7), 35.5 (C3), 22.7 (C5-CH_3); IR ($CDCl_3$) 3082, 1743, 1717, 1660 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.89; H, 7.88.

Methyl (1α,4aβ,8aβ)-hexahydro-9-methylene-2-oxo-2*H*-1,4a-ethanonaphthalene-1-(5*H*)-carboxylate (24) was prepared as described previously for **7a** from $Mn(OAc)_3 \cdot 2H_2O$ (0.6325 g, 2.40 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.2355 g, 1.20 mmol), and **21** (0.2941 g, 1.20 mmol) in glacial acetic acid (11 mL). The reaction was stirred at room temperature for 25 h. Normal workup gave 0.2928 g of crude material. Purification of 0.274 g by flash chromatography (silica gel deactivated with methanol, 19:2 hexane–EtOAc) gave 0.199 g (73%) of **24** as a colorless solid. Recrystallization from pentane provided an analytical sample: mp 72.9–73.4 °C; ^1H NMR 5.02 (dd, 1, J = 1.9, 2.3, $=CH_2$), 4.96 (dd, 1, J = 2.3, 2.2, $=CH_2$), 3.74 (s, 3, $-OCH_3$), 2.93 (ddd, 1, J = 2.2, 2.3, 17.7, H10α), 2.83 (br ddd, 1, J = 1.9, 2.3, 17.7, H10β), 2.53 (dddd, 1, J = 1.0, 8.7, 12.0, 14.6, H3 endo), 2.42 (ddd, 1, J = 6.3, 12.0, 12.4, H4 exo), 2.26 (dd, 1, J = 6.3, 14.6, H3 exo), 2.16 (m, 1), 2.02 (br ddd, 1, J = 1.7, 3.3, 12.4, H8aα), 1.84 (m, 2), 1.63 (m, 1, H4 endo), 1.58–1.18 (m, 5); ^{13}C NMR 208.3 (C2), 171.9 (OC=O), 154.3 (C9), 105.1 ($=CH_2$), 64.5 (C1), 53.9 (C8a), 51.9 ($-OCH_3$), 45.4 (C4a), 40.5 (C10), 34.7 (C3), 33.4 (C4), 30.7 (C5-8), 25.8 (C5-8), 22.7 (C5-8), 21.3 (C5-8); IR (neat) 3075, 1733, 1706, 1655 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.94; H, 8.13.

Methyl 5-Hydroxy-7aα-methyl-1-methylene-2,3,3aα,6,7,7a-hexahydro-1*H*-indene-4-carboxylate (70a). A solution of β-keto ester **65a** (0.457 g, 2.04 mmol), $Mn(OAc)_3$ (1.095 g, 4.08 mmol), and $Cu(OAc)_2$ (0.409 g, 2.05 mmol) in 20 mL of glacial acetic acid was stirred for 5 days at 25 °C. Normal workup of the light blue solution afforded 0.464 g of crude product. Flash chromatography on silica gel (15:1 hexane–EtOAc) gave 0.200 g (44%) of **70a**: NMR (300 MHz, $CDCl_3$) 12.29 (enolic H), 4.87 (br t, 1, J = 2.2), 4.78 (br t, 1, J = 2.3), 3.77 (s, 3), 2.49–2.29 (m, 3), 2.26 (dd, 1, J = 6.1, 3.4, H3aα), 2.21–2.11 (m, 2), 1.70 (ddd, 1, J = 13.7, 11.0, 5.9), 1.38–1.34 (m, 2), 1.09 (s, 3); ^{13}C NMR ($CDCl_3$) 173.4, 171.7, 160.7, 104.0, 99.7, 51.3, 45.0, 42.7, 31.5, 31.1, 30.8, 26.7, 23.8; IR (neat) 3075, 2950, 2920, 2870, 1655, 1615, 1440, 1420, 1355, 1310, 1280, 1240, 1220, 1190, 1060, 1000 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_3$: 222.1256. Found: 222.1245.

Ethyl 4α,7aα-Dimethyl-1-methylene-5-oxo-2,3,3aα,4,5,6,7,7a-octahydro-1*H*-indene-4β-carboxylate (69b). A solution of β-ketoester **65b** (0.130 g, 0.52 mmol), $Mn(OAc)_3$ (0.277 g, 1.03 mmol), and $Cu(OAc)_2$ (0.105 g, 0.52 mmol) in 5 mL of glacial acetic acid was stirred for 4 days at 25 °C. Normal workup of the light blue solution afforded 0.124 g of crude product. Flash chromatography on silica gel (15:1 hexane–EtOAc) gave 0.025 g of a 2:1 mixture of recovered starting material and **69b** followed by 0.051 g (46%, 53% based on recovered starting material) of **69b**: NMR (300 MHz, $CDCl_3$) 4.87 (t, 1, J = 2.0), 4.76 (t, 1, J = 2.2), 4.10 (qd, 2, J = 7.2, 1.8), 2.59–2.34 (m, 4), 2.15 (ddd, 1, J = 10.3, 8.1, 3.8), 1.98–1.86 (m, 1), 1.79 (dt, 1, J = 10.2, 4.5), 1.40 (s, 3), 1.32–1.10 (m, 2), 1.23 (t, 3, J = 7.2), 1.19 (s, 3); ^{13}C NMR ($CDCl_3$) 210.4, 172.2, 160.9, 103.6, 61.0, 56.7, 55.4, 43.8, 35.9, 31.8, 31.6, 30.1, 26.4, 22.4, 13.8; IR (neat) 3075, 2980, 2960, 2875, 1715, 1650, 1455, 1370, 1220 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.82; H, 8.91.

Ethyl 4α-Chloro-7aα-methyl-1-methylene-5-oxo-2,3,3aα,4,5,6,7,7a-octahydro-1*H*-indene-4β-carboxylate (69c). A solution of β-ketoester **65c** (0.253 g, 0.93 mmol), $Mn(OAc)_3$ (0.498 g, 1.86 mmol), and $Cu(OAc)_2$ (0.186 g, 0.93 mmol) in 9 mL of glacial acetic acid was stirred for 2 days at 25 °C. Normal workup of the light blue solution afforded 0.242 g of crude product. Flash chromatography on silica gel (15:1 hexane–EtOAc) gave 0.011 g of recovered starting material followed by 0.121 g (48%, 50% based on recovered starting material) of **69c**: NMR (300 MHz, $CDCl_3$) 4.94 (t, 1, J = 2.0), 4.84 (t, 1, J = 2.0) 4.25 (q, 2, J = 7.0), 2.67 (ddd, 1, J = 12.8, 8.3, 4.8), 2.58 (dd, 1, J = 10.0, 7.8, H3aα), 2.49–2.37 (m, 2), 2.15–1.67 (m, 5), 1.37 (s, 3), 1.31 (t, 3, J = 7.0). Irradiation of the 7a-methyl group led to 13% enhancement of the 3a-proton at δ 2.58 ppm indicating that the ring was cis fused. ^{13}C NMR ($CDCl_3$) 200.0, 166.7, 159.2, 104.4, 70.9, 62.5, 55.9, 44.0, 34.9, 32.1, 31.5, 30.4, 28.7, 13.8; IR (neat) 3075, 2960, 2910, 2890, 2870, 1740, 1655, 1460, 1445, 1365, 1240, 1090, 1030, 885 cm^{-1}. Anal. Calcd for $C_{14}H_{19}ClO_3$: C, 62.11; H, 7.07; Cl, 13.09. Found: C, 61.96; H, 7.19; Cl, 13.14.

7aα-Methyl-1-methylene-2,3,3aα,4,5,6,7,7a-octahydro-1*H*-inden-5-one (71). A solution of β-ketoester **70a** (0.084 g, 0.38 mmol) and sodium hydroxide (≈0.19 g, 47.5 mmol) in 4 mL of methanol and 4 mL of water was refluxed for 24 h. The mixture was cooled to 0 °C. To the mixture was slowly added monobasic sodium phosphate until the pH was 5. The mixture was extracted with 5 × 10 mL of EtOAc and dried over $MgSO_4$. The solvent was removed in vacuo to afford 0.050 g (81%) of **71**: NMR (300 MHz, $CDCl_3$) 4.92 (t, 1, J = 1.9), 4.84 (t, 1, J = 2.3), 2.52–2.43 (m, 3), 2.32–2.09 (m, 3), 1.98 (ddd, 1, J = 14.3, 8.8, 5.4), 1.93–1.84 (m, 1), 1.70 (br dt, 1, J = 13.0, 6.3), 1.42–1.17 (m, 2), 1.22 (s, 3); ^{13}C NMR ($CDCl_3$) 213.0, 158.7, 104.4, 47.2, 43.5, 42.3, 37.4, 34.1, 30.2, 29.0, 26.0; IR (neat) 3075, 2950, 2875, 1720, 1650, 1450, 1415, 1370, 1145, 875 cm^{-1}.

7aα-Methyl-2,3,3aα,4,5,6,7,7a-octahydro-1*H*-inden-1,5-dione (72). Ozone was bubbled through a solution of alkene **71** (0.049 g, 0.30 mmol) in methanol (7 mL) for 1 min at −78 °C. To the mixture was added 7 mL of dimethyl sulfide at −78 °C, and the mixture was allowed to stir at −78 °C for 1 h and then overnight at 25 °C. The mixture was quenched with water (20 mL) and extracted with 5 × 10 mL of ether. The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo to afford 0.068 g of crude product. Flash chromatography on silica gel (5:1 hexane–EtOAc) gave 0.034 g (68%) of **72**:[49] NMR (300 MHz, $CDCl_3$) 2.60 (dd, 1, J = 14.8, 6.3) 2.51–1.97 (m, 8), 1.69–1.58 (m, 2), 1.25 (s, 3); ^{13}C NMR ($CDCl_3$) 210.7, 47.2, 44.5, 41.7, 37.0, 35.1, 29.8, 25.0, 20.5, carbonyl carbon was not observed; IR (neat) 2960, 2940, 2880, 1740, 1720, 1460, 1420, 1380, 1280, 1255, 1145, 1095, 1055, 915 cm^{-1}.

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Supplementary Material Available: Complete experimental details and spectral data (^{1}H NMR, ^{13}C NMR, and IR) for the preparation of β-keto esters and all cyclizations not given in the Experimental Section (27 pages). Ordering information is given on any current masthead page.

Bornanesultam-Directed Asymmetric Synthesis of Crystalline, Enantiomerically Pure Syn Aldols

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Abstract: *N*-acylsultams **2** furnish, via aldolization of their enolates **16** with aldehydes, diastereomerically pure, crystalline syn aldols. The absolute configuration of the product is controlled by the choice of the enolate counterion: **16**, M = B → **3**; **16**, M = Li or Sn(IV) → **5**. Hydroperoxide-assisted hydrolysis/esterification or reductive cleavage provided enantiomerically pure methoxycarbonyl aldols (**12** and **13**) or 1,3-diols (**11**) with recovery of auxiliary **1**. The chiral serricornin precursor **14** was thus prepared.

Asymmetric aldol reactions have attracted widespread interest over the past decade, promoting considerable gain in insight and methodology.[1] Nevertheless, applications in synthesis would greatly benefit from the prospect of purifying the initially formed aldol products by crystallization. As a complement to a previous communication,[2] this article reports the first example which meets this and other relevant criteria (accessibility, versatility of chiral auxiliary as well as yields, metal-directed diastereo- and π-face selectivities of reactions).

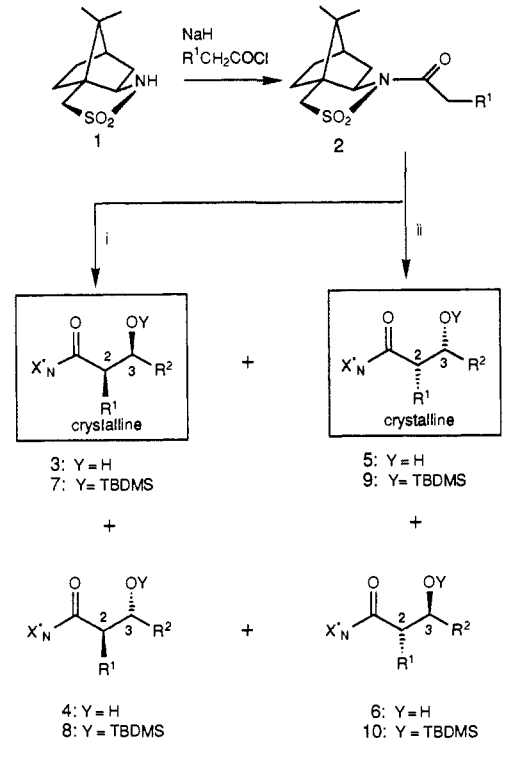
Results

Sultam **1** (as well as its antipode readily available on a kg-scale[3]) were smoothly acylated with acylchlorides/NaH to provide starting acylsultams **2**.

Boron-Mediated Aldolizations. We first addressed the firmly established dibutylboryl enolate methodology.[4] Treatment of acylsultams **2** with freshly prepared dibutylboryl triflate/EtN(*i*Pr)$_2$ (1.1 mol equiv) at −5 °C in CH_2Cl_2, followed by addition of an aldehyde R^2CHO at −78 °C provided, on workup, syn aldols **3** (Scheme I, Table I entries 1, 2, 4, 6-9, 11, 12). Although major isomers **3** were usually isolated in good yields, conversions **2** → **3** often remained incomplete. Employing an excess of Bu_2BOTf/EtN(*i*Pr)$_2$ resulted in lower stereoselectivities.

More conveniently and more efficiently, aldols **3** were obtained by using in situ prepared diethylboryl triflate/EtN(*i*Pr)$_2$ (2 mol equiv, entries 3, 5, 10) following a protocol described for *N*-acyloxazolidinone/azetidinone aldolizations.[5] HPLC analysis of the crude products **3** showed (independent of the boryl triflate) very high diastereomeric purity which was increased to virtually

Scheme I



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