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MANGANESE (III) BASED OXIDATIVE FREE-RADICAL CYCLIZATIONS. 2. POLYCYCLIZATION REACTIONS PROCEEDING THROUGH TERTIARY CATIONS.

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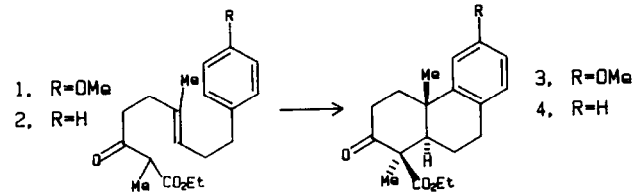
Summary: Oxidative cyclization of 5 with $Mn(OAc)_3 \cdot 2H_2O$ gives mainly the bicyclic products 7 and 8. On the other hand, oxidative cyclization of 16 and 17 gives mainly the lactones 18 and 20. These data suggest that oxidation of a monocyclic radical to a cation precedes cyclization to form 3, 4, 7, and 8.

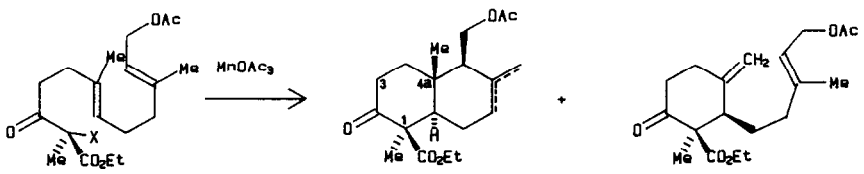
Oxidative free-radical cyclizations should vastly extend the synthetic utility of radical cyclizations[1] since the terminal radical will be trapped oxidatively rather than by reductive delivery of a hydrogen atom giving rise to a more highly functionalized and therefore synthetically useful adduct.[2] We[3] and others[4,5] have recently shown that the well-known oxidative addition of acetic acid to alkenes, using two equiv. of $Mn(OAc)_3 \cdot 2H_2O$, to give γ-lactones,[6,7] can be extended to oxidative free radical cyclization of unsaturated β-ketoacids, β-ketoesters and malonic acids. We found that oxidative cyclization of 1 (0.2 M) with $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid for 1 h at 15-20 °C gave 3 in 50% yield as a single stereoisomer.[3] We report here further studies which indicate the scope and limitations of this reaction and help to define its mechanism.



1. R=OMe
2. R=H

3. R=OMe
4. R=H

Termination of a radical cyclization by addition to a benzene ring and oxidation to regenerate the aromatic system does not constitute a true test of an oxidative radical cyclization since Julia has shown that oxidative rearomatization occurs even under non-oxidative conditions.[8] We therefore prepared the acetoacetate derivative 5[9] and subjected it to oxidative cyclization with $Mn(OAc)_3 \cdot 2H_2O$. Reaction of 5 as a 0.2 M solution in acetic acid with three equiv. of $Mn(OAc)_3 \cdot 2H_2O$ for 30 min at 25 °C followed by chromatographic purification gave 6 (6%), and a 10:3:1 mixture of 7, 8, and 9 (68%) which were separated by reverse phase HPLC. The stereochemistry of the major products 7 and 8 was established to be the same as that of 3 by NOE experiments.[10] Irradiation of the axial 4aβ-methyl group of 7 led to 5.3% NOE enhancement of one of the protons on the CH_2OAc group indicating that the acetoxymethyl group is equatorial, 9.5% enhancement of the axial 3β hydrogen and 2% enhancement of the methyl protons of the carboethoxy group indicating that the ester is axial and the methyl group is



5. X=H
6. X=OAc (6%)

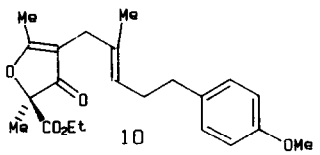
7. exocyclic (48%)
8. endocyclic (15%)

9 (5%)

equatorial. Irradiation of the 1α-methyl group did not lead to any NOE enhancement of the axial 3β proton indicating that the 1α-methyl group is equatorial. Similar results were obtained in NOE studies of **8**.

The formation of the acetoxy ketone **6** is not surprising in view of the report that $Mn(OAc)_3 \cdot 2H_2O$ converts enones into α'-acetoxy enones.[11] We had observed similar results in the oxidative cyclization of **1**. If the reaction was carried out at 50 °C for 24 hours we obtained only a 5-10% yield of **3**. The major product under these conditions was the furanone **10** which was obtained in 20-25% yield. This product was presumably formed by acetoxylation to give an acetate analogous to **6** which undergoes an aldol reaction to give **10**. The formation of **10** was suppressed by carrying out the reaction at 15-20 °C.

We briefly explored the possibility of development of this reaction into a general synthesis of furanones. Oxidation of ethyl methylacetoacetate with $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid-potassium acetate at reflux gave the furanone **11** in 28% yield. β-ketoesters that do not have an α-substituent such as methyl acetoacetate do not give rise to any furanone.



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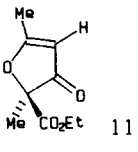
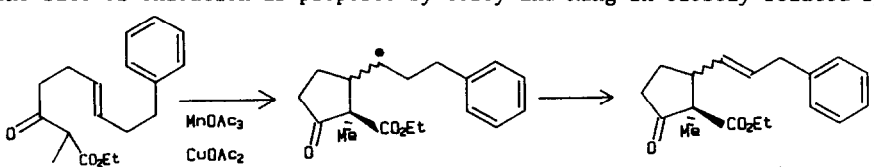


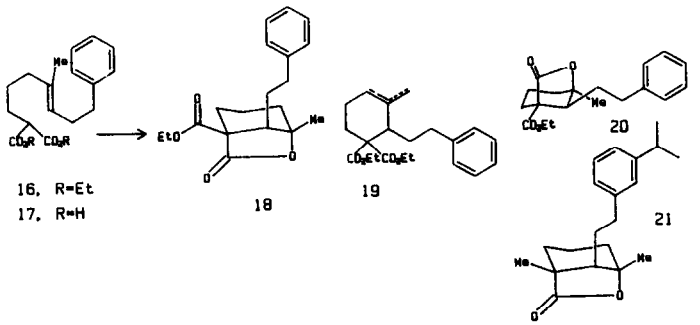
11

We have also explored the effect of substituents on the double bond of **1**. Oxidative cyclization of **12** with $Mn(OAc)_3 \cdot 2H_2O$ at 25 °C was slower than the cyclization of **1** and gave a complex mixture of polar products. Oxidative cyclization of **12** with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2$ at 50 °C gave a 64% yield of a 3:1 mixture of **14** and **15** as the only isolable products. This indicates that the presence of the phenyl group does not perturb the preference for five- rather than six-membered ring formation from 1,2-disubstituted alkenes.[3] As we have previously reported[3] the use of $Cu(OAc)_2$ is necessary to convert secondary radicals to alkenes. In the absence of $Cu(OAc)_2$, **13** abstracts a hydrogen atom from **12** to give dihydro **14** and a second molecule of **13**. Apparently, addition of the radical of **13** to the benzene ring to give an indane is slow relative to intermolecular hydrogen abstraction.[6d] The oxidative cyclization of **12** is much slower than that of **2** (*vide infra*) indicating that the reactivity of the alkene influences the rate of oxidation as proposed by Corey and Kang in closely related systems.[4]



12 13 14. β-chain 15. α-chain

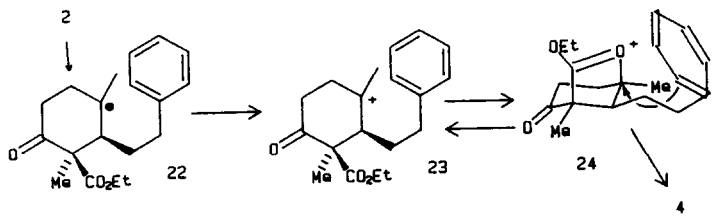
In order to extend the scope of this reaction we explored the use of malonate diesters rather than β-ketoesters as the oxidizable substrate. Reaction of diester **16** with $Mn(OAc)_3 \cdot 2H_2O$ gave a 40% yield of **18** and a 55% yield of **19** as a 4:1 mixture of endocyclic and exocyclic isomers. A similar reaction carried out in the presence of one equiv. of $Cu(OAc)_2$ gave a 61% yield of **18** and a 33% yield of **19**. Oxidation of the malonic acid **17** with $Mn(OAc)_3 \cdot 2H_2O$ followed by treatment with diazoethane gave a 1:2 mixture of **18** and **20** in 61% yield. A similar reaction carried out in the presence of one equiv. of $Cu(OAc)_2$ gave a 2:3 mixture of **18** and **20** in 62% yield. No tricyclic adducts were obtained from the cyclization of either **16** and **17**. The stereochemistry of **18** and **20** was established by examination of the ^{13}C NMR spectrum which showed the expected shielding for the axial phenethyl side chain of **18**.[12a] Lactone **18**, which is the only lactone obtained from oxidation of **16** with $Mn(OAc)_3 \cdot 2H_2O$ possesses the same relative stereochemistry as the unusual natural product secodehydro-abietanolide (**21**).[13] This oxidative cyclization should provide an attractive route to **21**.

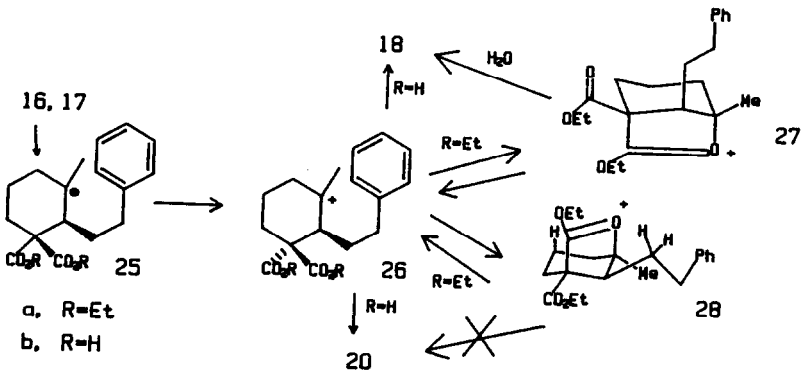


The remarkable change in the nature of the product on changing the oxidizable group from a β-keto ester to a malonic acid derivative was puzzling. The absence of tricyclic products from **16** and **17** and the formation of **18** as the only lactone from **16** are particularly noteworthy. Initially, we felt that the methoxy group of **1** might be responsible for the difference in the reaction pathway. We therefore prepared **2** and on treating it with $Mn(OAc)_3 \cdot 2H_2O$ as described above for the cyclization of **1**, obtained **4**[14] in 90% yield. The methoxy group is obviously not necessary for the formation of the tricyclic product and, surprisingly, its presence lowers the yield, perhaps due to overoxidation of the electron rich aromatic system. Therefore the difference in reactivity is due solely to the difference in the oxidizable group.

These results seem to be best accommodated by the proposed reaction schemes shown below. Oxidative cyclization of **2** will give **22**. The rate difference in the cyclizations of **2** and **12** implies double bond participation in the initial oxidation step[4] suggesting that **22** is the initial intermediate. Oxidation of **22** affords the cationic intermediate **23** which reacts reversibly with the carbonyl group to give oxonium ion **24** which can then cyclize with inversion to give **4**. Intermediates analogous to **24** have been previously proposed[12] to account for the stereospecificity of cation-olefin cyclizations leading to tricyclic diterpenes. In a similar manner **16** will undergo oxidative cyclization to give **25a** which will be oxidized to **26a**. Reversible cyclization will give both **27** and **28**. Addition of water to the unhindered exo face of the complexed carbonyl group of **27** will occur readily to give **18**. Both faces of the complexed carbonyl groups of **24** and **28** are too hindered to react with water. Intermediate **28** is trapped by loss of a proton to give **19** or reversion to **26a** which is converted to **18** via **27**. On the other hand, intermediate **26b** formed from the free diacid collapses directly to a mixture of **18** and **20**. Intermediate **24** can only undergo cyclization to give **4**. *The observation of monocyclic products* **9** *and* **19** *and lactones* **18** *and* **20** *proves that oxidation of the tertiary radical to the cation precedes the second cyclization*. This reaction can be viewed as a cation-olefin cyclization reaction with a novel oxidative initiation. However, in related cyclizations in which the intermediate radical is secondary rather than tertiary we have demonstrated that the second cyclization precedes oxidation.[15]

The reasons for the stereospecific formation of intermediates such as **22** are currently being examined. These results provide further evidence of the synthetic utility of $Mn(OAc)_3 \cdot 2H_2O$ oxidative free-radical cyclizations and begin to provide a mechanistic framework which will allow them to be used predictably in synthesis.





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References and Notes

1. For recent reviews see: (a) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883 (b) Surzur, J.-M. In "Reactive Intermediates"; Abramovitch, R. A. Ed.; Plenum Press: New York, 1982; Vol. 2, pp 121-295. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (d) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.
2. (a) Breslow, R.; Olin, S. S.; Groves, J. T. *Tetrahedron Lett* **1968**, 1837. (b) Bhandal, H.; Pattenden, G.; Russell, J. J. *ibid.* **1986**, *27*, 2299 and references cited therein. (c) Patel, V. F.; Pattenden, G.; Russell, J. J. *ibid.* **1986**, *27*, 2303. (d) Kraus, G.; Landgrebe, K. *ibid.* **1984**, *25*, 3939.
3. Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.
4. Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc.* **1984**, *106*, 5384.
5. Ernst, A. B.; Fristad, W. E. *Tetrahedron Lett.* **1985**, *26*, 3761.
6. (a) Bush, J. B., Jr.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968**, *90*, 5903. (b) Heiba, E. I.; Dessau, R. M.; Koehl, W. J., Jr. *ibid.* **1968**, *90*, 5905. (c) Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *ibid.* **1974**, *96*, 7977. (d) Heiba, E. I.; Dessau, R. M. *ibid.* **1972**, *94*, 2888. (e) Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1974**, *39*, 3456. (f) Vinogradov, M. G.; Petrenko, O. N.; Verenchikov, S. P.; Nikishin, G. I. *Izv. Akad. Nauk SSSR, Ser. Khim* **1979**, 1916. (g) Heiba, E. I.; Dessau, R. M.; Williams, A. L.; Rodewald, P. G. *Org. Syn.* **1983**, *61* 22. (h) Nikishin, G. I.; Vinogradov, M. G.; Fedorova, T. M. *J. Chem. Soc., Chem. Commun.* **1973**, 693.
7. For recent detailed studies of this reaction see: (a) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10. (b) Fristad, W. E.; Hershberger, S. S; *ibid.* **1985**, *50*, 1026. (c) Fristad, W. E.; Peterson, J. R.; Ernst, A. B. *ibid.* **1985**, *50*, 3143. (d) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1985**, *26*, 4291. Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, *42*, 3429.
8. Chottard, J. C.; Julia, M. *Bull. Soc. Chim. Fr.* **1968**, 3700.
9. Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.*, 1977, *99*, 3864.
10. For similar results obtained in the oxidative cyclization of farnesyl acetate see ref 2a.
11. Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839 and references cited therein.
12. (a) Ghatak, U. R.; Chatterjee, N. R.; Sanyal, B. *J. Org. Chem.* **1979**, *44*, 1992. (b) Ghatak, U. R.; Chakravarty, J.; Dasgupta, R.; Chakraborti, P. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2438. (c) Ghatak, U. R.; Chakravarty, J.; Banerjee, A. K. *Tetrahedron*, **1968**, 1577. (d) Kanjilal, P. K.; Alam, S. K.; Ghatak, U. R. *Synth. Commun.* **1981**, *11*, 795.
13. Herz, W.; Mohanraj, S. *J. Org. Chem.* **1980**, *45*, 5417.
14. Wenkert, E.; Afonso, A.; Bredenberg, J. B.; Kaneko, C.; Tahara, A. *J. Am. Chem. Soc.* **1964**, *86*, 2038. Wenkert, E.; Afonso, A.; Beak, P., Carney, R. W. J. Jeffs, P. W.; McChesney, J. D. *ibid.* **1965**, *30*, 713.
15. Mohan, R.; Kates, S. A.; Dombroski, M.; Snider, B. B. *Tetrahedron Lett.* accompanying paper

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