

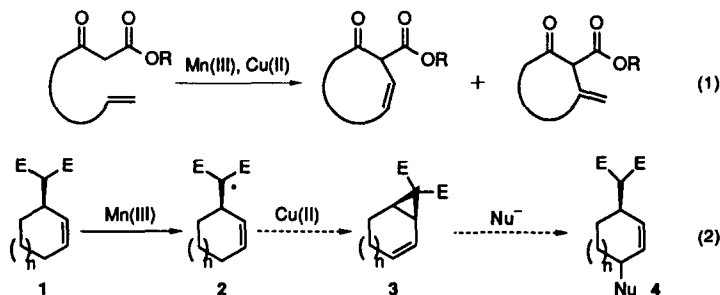
Manganese(III)-Based Oxidative Free-Radical Reaction of α -Allyl- β -Keto Ester with Molecular Oxygen

Takashi Ohshima, Mikiko Sodeoka, and Masakatsu Shibasaki*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

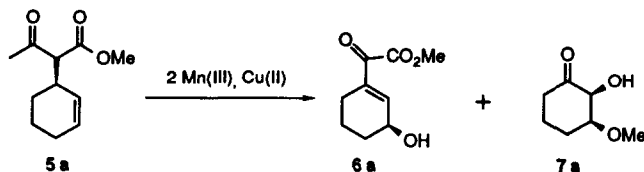
Abstract: Oxidative reactions of α -allyl- β -keto esters **5** with $Mn(OAc)_3 \cdot 2H_2O$ give the δ -hydroxy- β,γ -unsaturated- α -keto esters **6** in good yields. The mechanism of this reaction is discussed.

Manganese(III) acetate promoted oxidation of β -dicarbonyl compounds produces electrophilic radicals that have been used extensively for the intramolecular cyclization of unsaturated- β -dicarbonyl compounds. However, most of the reports in this field are concerned with the intramolecular cyclization of ω -unsaturated- β -dicarbonyl compounds (eq 1),¹ and examples of electrophilic radicals **2** which react directly with α -allylic olefins have not been reported. We planned to examine the cyclization of α -allyl- β -dicarbonyl compounds **1**, which can be easily prepared from the corresponding acetate by Pd catalyzed allylic substitution.² The oxidative free-radical cyclization of these compounds might be expected to give highly functionalized cyclopropanes **3** which could be converted into useful products **4** for the synthesis of natural products.³ In this paper we report the unexpected results of the oxidative free-radical reaction of various α -allyl- β -keto esters.



Scheme 1

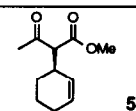
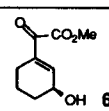
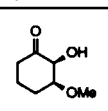
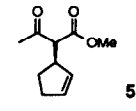
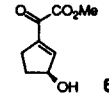
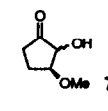
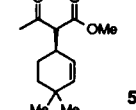
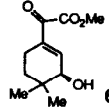
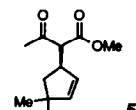
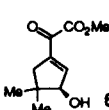
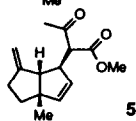
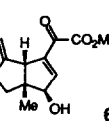
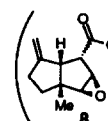
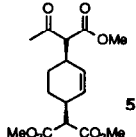
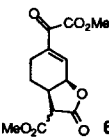
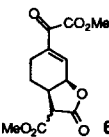
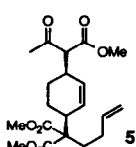
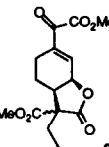
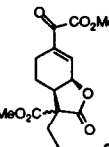
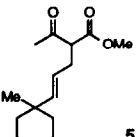
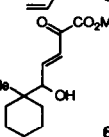
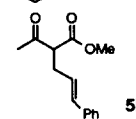
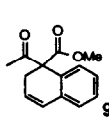
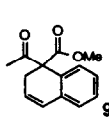
When compound **5a** was exposed to 2 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$ in acetic acid at 25°C, the cyclized product **3a** was not obtained and the δ -hydroxy- β,γ -unsaturated- α -keto ester **6a** was the only product which could be isolated from the reaction mixture. Since the conversion of **5a** into **6a** is very interesting both mechanistically and synthetically, we decided to investigate this novel oxidative cleavage reaction. Attempts to optimize⁴ this reaction led to the use of 2 equiv of $Mn(OAc)_3$ in methanol at 25°C and afforded **6a** in 78% yield. The β -methoxy- α -hydroxy ketone **7a** was also isolated in 19% yield.



Scheme 2

Several other α -allyl- β -keto ester derivatives were subjected to the reaction to determine its generality and stereochemistry. The results of these experiment are summarized in the table below.⁵

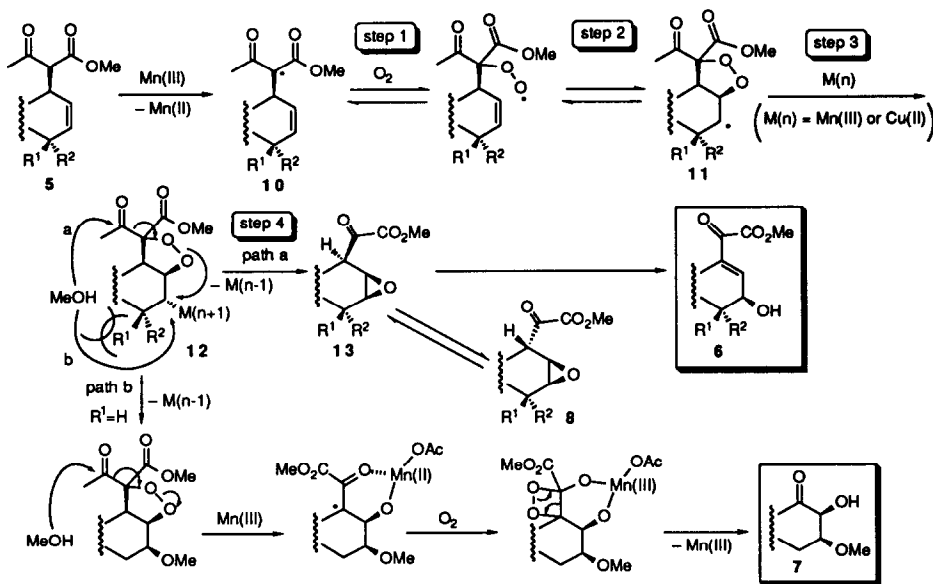
Table: Manganese(III)-Based Oxidative Free-Radical Reaction of 5^a

| Entry | Substrates 5 | Mn(OAc) ₃ | Cu(OAc) ₂ | time (d) | Products, ^b yield ^c |
|-------|---|----------------------|----------------------|----------|--|
| 1 |  5a | 2 eq | – | 1.5 |  6a 78%  7a 19% |
| 2 |  5b | 2 eq | – | 1.5 |  6b 67%  7b^d 15% |
| 3 |  5c | 2 eq | – | 2.5 |  6c¹⁰ 96% |
| 4 |  5d | 2 eq | – | 2 |  6d 80% |
| 5 |  5e | 2eq | 2eq | 1 |  6e 89%  8 |
| 6 |  5f | 2 eq | – | 1 |  6f 72% |
| | | 2 eq | 1 eq | 1 |  6f 83% |
| 7 |  5g | 2 eq | – | 4 |  6g 70% |
| | | 2 eq | 1 eq | 2 |  6g 85% |
| 8 |  5h | 2 eq | 1 eq | 0.5 |  6h 64% |
| 9 |  5i | 2 eq | – | 1 |  9 trace |
| | | 2 eq | 1 eq | 1 |  9 20% |

^a All reactions were carried out in methanol at 25°C using Mn(OAc)₃·2H₂O (2 equiv) in the presence or absence of Cu(OAc)₂·H₂O.

^b All compounds showed characteristic spectral data and exact mass spectroscopic data. ^c Isolated yields are given.

A number of points deserve comment. When the allylic position of **5** (ϵ to the ester) was blocked, the by-product **7** was not obtained, and the desired products **6** was obtained in excellent yield (entries 3-7). The relative stereochemistry of **6e** and **6f** was established on the basis of NOE experiments⁶ which indicate that the hydroxyl group was introduced to the same face as the β -keto ester group. In the reaction of **5e**, the unstable epoxide **8** could be isolated by rapid work up and converted to **6e** by silica gel or pyridine treatment. It is also noteworthy that no product was obtained when the reaction was carried out under vigorously deoxygenated conditions, and this suggests that molecular oxygen participates in the reaction.⁷ This result, the stereochemistry of the products observed and the isolation of **8** have led us to propose the mechanism shown in Scheme 3.



Scheme 3

First the electrophilic radical **10** generated with $\text{Mn}(\text{OAc})_3$ reacts with molecular oxygen to give the endoperoxide radical **11** (steps 1 and 2). Radical **11** is then converted to the metal complex **12** ($M = \text{Mn}$ or Cu) which undergoes nucleophilic attack by methanol at the carbonyl group causing cleavage of the methyl ketone group and affording keto-epoxide **13** (steps 3 and 4, path a).⁸ Finally, opening of the epoxide occurs to give **6**.

Substrate **5i**, which is expected to generate the stable benzylic radical **11i**, failed to give **6i**. Instead, cyclized product **9** was obtained in 20% yield, suggesting olefin isomerization had occurred. It is likely that steps 1 and 2 are reversible, and that **5i** is isomerized to its (*Z*)-isomer through these steps.

We attempted intramolecular trapping of the radical in **11** with an olefin (entry 7); however, none of the expected decalin derivative was observed with lactone **6g** being obtained in good yield. Apparently conversion of radical **11** to epoxide **13** is a very rapid process.

When the δ -carbon is sterically less hindered (**5a** and **5b**, $R_1 = R_2 = \text{H}$), methanol can displace the metal substituent of **12** (path b). Cleavage of the resulting methyl ketone and further oxidation gives the major by-product **7**.⁹

In summary, we have shown for the first time that the electrophilic radicals **10**, prepared by oxidation of β -dicarbonyl compounds with manganese(III) acetate, can be directly trapped by molecular oxygen and converted to δ -hydroxy- β,γ -unsaturated- α -keto esters in good yields. The overall transformation provides products of high functionality which should be useful for the synthesis of a variety of natural products.

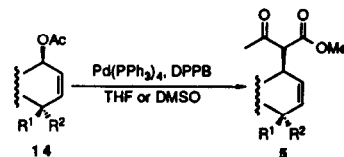
Representative Procedure:

Mn(OAc)₃·2H₂O (0.95 mmol) was added to a stirring solution of β-keto ester **5c** (0.47 mmol) in methanol (9.5 mL). The resulting brown mixture was stirred under air at 25°C for 2.5 days at which time it was filtered through a celite pad. The residue obtained after removal of the solvent was purified by flash chromatography, giving α-keto ester **6c**¹⁰ (96%).

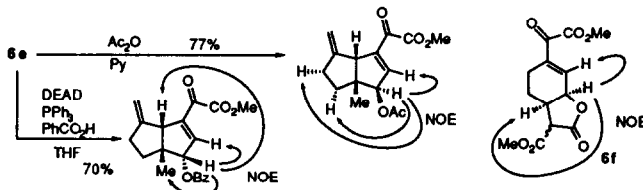
Acknowledgment: This study was financially supported by a Fellowships of Japan Society for the Promotion of Science for Japanese Junior Scientists.

References and Notes

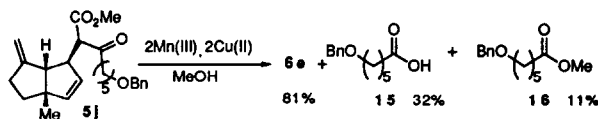
- For an authoritative background review and comprehensive list of references, see: (a) Snider, B. B.; Meritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* 1991, 56, 5544, and references cited therein. (b) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* 1991, 113, 6607.
- Substrates **5** were prepared from acetates **14** by Pd catalyzed allylic substitution:
5a^a (90%), **5b**^a (80%), **5c**^a (63%), **5d**^a (80%), **5e**^b (59%), **5f**^a (84%), **5g**^c (90%), **5h**^d (94%), **5i** (47%). (a) **14a-d** were prepared from commercially available enone.
 (b) Kagechika, K.; Shibasaki, M. *J. Org. Chem.* 1991, 56, 4093. (c) Bäckvall, J.-E.; Nyström, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* 1985, 107, 3676. (d) **14h** was prepared from 1-methyl-1-cyclohexanecarboxylic acid in five steps.



- For example, conversion of **3** into brefeldin has been reported ($n = 0$, $E = \text{CO}_2\text{Me}$, eq 2), see: Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* 1976, 4705.
- This reaction did not proceed with diester **1** ($E = \text{CO}_2\text{Me}$) and the starting material was recovered almost quantitatively.
- All new compounds gave satisfactory spectroscopic data.
- NOE experiments of **6e** and **6f** are shown.



- Recently it has been shown that alkyl radicals generated by the manganese(III)-induced reaction of β-dicarbonyls with olefins can be trapped with molecular oxygen. (a) Colombo, M. I.; Signorella, S.; Mischne, M. P.; Sierra, M. G.; Ruveda, E. A. *Tetrahedron* 1990, 46, 4149. (b) Tategami, S.; Yamada, T.; Nishino, H.; Korp, J. D.; Kurosawa, K. *Tetrahedron Lett.* 1990, 31, 6371. (c) Qian, C.-Y.; Nishino, H.; Kurosawa, K.; Korp, J. D. *J. Org. Chem.* 1993, 58, 4448, and references cited therein.
- When compound **5j** was exposed to 2 equiv of Mn(OAc)₃ and 1 equiv of Cu(OAc)₂ in methanol at 25°C, not only **6e** but also carboxylic acid **15** and ester **16** were obtained.



- Because of easy epimerization **7b** was obtained as an equilibrium mixture of the *syn* and *anti* isomer.
- Spectral data of **6c**: IR(neat) 3442, 2958, 1739, 1674, 1202, 1154, 1060 cm⁻¹; ¹H-NMR (CDCl₃) δ 6.79 (d, $J=2.6$ Hz, 1 H), 4.09 (d, $J=2.6$ Hz, 1 H), 3.89 (s, 3 H), 2.31-2.23 (m, 2 H), 1.80-1.64 (br-s, 1 H), 1.68-1.46 (m, 2 H), 1.04 (s, 3 H), 0.89 (s, 3 H); ¹³C-NMR (CDCl₃) δ 187.7, 164.3, 148.6, 135.8, 74.7, 52.6, 33.8, 33.0, 26.8, 20.1, 19.5; MS *m/z* 212 (M⁺, 4.3), 153 (74), 135 (22), 125 (20), 43 (100); HRMS calcd for C₁₁H₁₆O₄: 212.1049, found: 212.1039.

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