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MANGANESE(III) MEDIATED RADICAL CYCLIZATION. I. FACTORS AFFECTING PHENOL AND CYCLOPENTANONE SYNTHESIS

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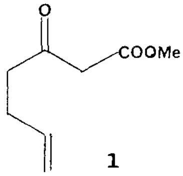
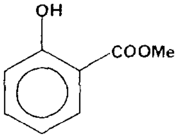
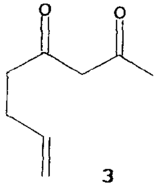
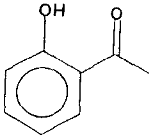
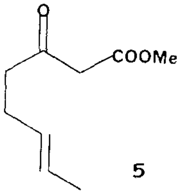
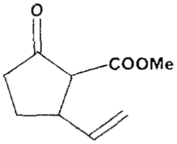
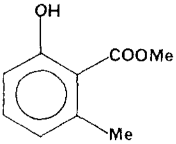
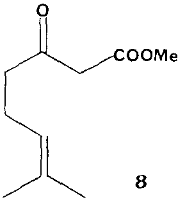
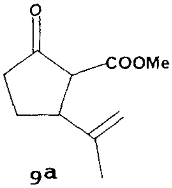
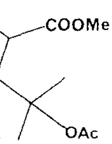
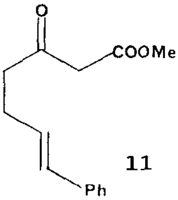
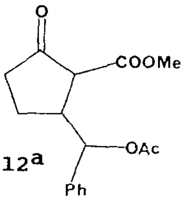
Summary: The oxidative radical cyclization of ω-unsaturated-ß-dicarbonyl compounds to 2-substituted phenols and cyclopentanones has been achieved with manganese(III) acetate.

Intramolecular radical cyclizations have become a powerful method for carbon-carbon bond construction, and have warranted considerable attention in cyclopentanoid natural product synthesis.[2] To date, radical cyclizations typically have been conducted under a reductive atmosphere, with hydrogen transfer terminating and limiting the synthetic utility of the ring closure sequence. Manganese(III) acetate, an efficacious oxidant of enolizable carbonyl compounds, has found widespread use for the annulation of a γ-lactone[3] or a dihydrofuran[4] ring onto an alkene. More recently, Snider has revealed carbocycle formation by employment of this reagent.[5] Their new intramolecular variant produced cyclopentanones and cyclohexanones by radical exo-ring closure while also incorporating serviceable functionality into the molecule. Carboxylic acid, ester, and nitrile substituents α to a carbonyl have been shown to promote the reduction of manganese(III).[3] Julia has demonstrated that these same substituents made the kinetically-favored exo-cyclization mode of the 5-hexenyl radical reversible, a circumstance that resulted in six-membered ring product formation.[6] For this reason, we anticipated that oxidative radical cyclizations of ω-unsaturated-ß-dicarbonyl compounds may be reversible. In this letter, we wish to report remarkable control of the mode of ring closure for manganese(III) mediated cyclizations by variation of the nature of the radical terminus.

Attention will be first directed to the oxidative cyclization of methyl 3-oxo-6-heptenoate[7], 1, Table.[8]. This substrate provided an excellent probe to the reversibility of these cyclizations as only recovered 1 and methyl salicylate, 2, were obtained when the reaction was performed according to the published procedure.[5] The exclusive formation of six-membered ring products

Table. Manganese(III) Mediated Radical Cyclization of ω-Unsaturated-β-dicarbonyl Compounds.

Entry	Substrate	Products	% Yield	Source
1	 **1**	 **2**	94[b]	c
2	 **3**	 **4**	96[b]	c
3	 **5**	 **6**[a]  **7**	**6** 21 **7** 5	d
4	 **8**	 **9**[a]  **10**[a]	**9** 8 **10** 10	d
5	 **11**	 **12**[a]	70[b]	c

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[a] The product exists as a mixture of cis and trans isomers. [b] Isolated % yield based on the equivalents of Mn(III) required to form the product following the procedure described in the text. [c] This work. [d] Reference 5.

was quite remarkable in view of the concentration (0.1M) of copper(II) ion.[9]

Further exploration of this reaction led to an optimal 94% yield of 2 by the following amelioration. A solution of manganese(III) acetate hydrate[10] (2 equiv) in acetic acid was added dropwise over a 30 min period to a preheated 50°C acetic acid solution of the ß-dicarbonyl compound (1 equiv, 0.1M), copper(II) acetate (1 equiv), and potassium acetate (5 equiv). The resulting mixture was stirred an additional 20 min at 50°C before dilution of the reaction with a three-fold volume of water and extractive workup.

δ-Vinylogous-ß-diketones also served as suitable substrates for 2-substituted phenol synthesis. The treatment of 3 in the manner described above delivered a high yield of 2′-hydroxyacetophenone, 4. Cycloreversion of the primary radical ring closure intermediate preempted both methylene-cyclopentanone and intramolecular dihydrofuran formation in this example.

An abrupt change in product distribution was observed as the terminal position of the alkene was structurally altered, however. Two examples reported earlier by Snider[5] have been included in the Table to exemplify this fact (entries 3 and 4). The secondary radical species formed during oxidative exo-ring closure of methyl 3-oxo-6-octenoate, 5, must have suffered two fates. In this example interception of the radical by oxidant to yield cyclopentanone 6 competed quite favorably with cycloreversion to a six-membered ring. In a similar manner, the oxidative cyclization of 8 to five-membered carbocycles 9 and 10 would have proceeded through a tertiary radical intermediate that apparently obviated ring opening.

Unfortunately, the moderate yields of cyclopentanones that Snider[5] had obtained by this methodology had precluded its application in five-membered ring natural product synthesis. We are pleased to now offer a potential solution to the problem. The oxidative ring closure of 11 (entry 5) proceeded through a secondary benzylic radical intermediate that not only rendered the cyclization irreversible, but provided sufficient impetus to the reaction to deliver cyclopentanone 12 in a much improved 70% yield.

In summary, the radical character of the exo-ring closure intermediate was found to regulate product formation in oxidative cyclizations of ω-unsaturated-ß-dicarbonyl compounds. Syntheses of aromatic and triquinane natural products that utilize the different ring closure modes of manganese(III) mediated radical cyclizations uncovered in this report are currently underway.

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Reference and Notes

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