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INTRAMOLECULAR LACTONE ANNULATION OF ACTIVATED ACIDS WITH Mn(III)

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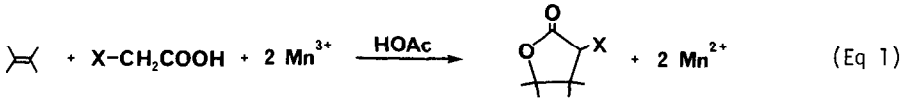
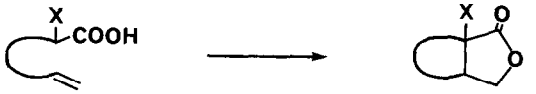
Abstract: Intramolecular lactone annulation of activated carboxylic acids onto olefins by manganese(III) acetate yields bicyclo[3.3.0] and [4.3.0]lactones.

Previous research on Mn(III) mediated γ-lactonization by us[1,2] and others[3] has demonstrated that carboxylic acids bearing an electron withdrawing substitutent, X, are particularly susceptible to oxidative lactonization (eq. 1). Intermolecular versions of this



(Eq 1)

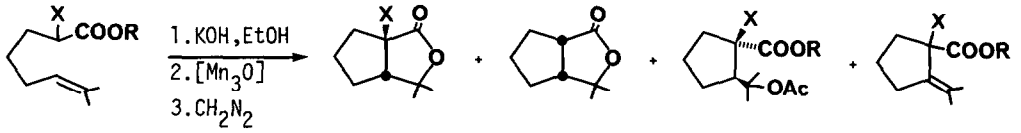


(Eq 2)

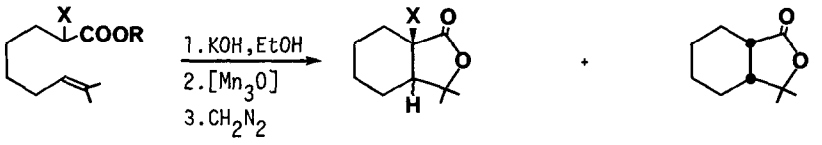
process worked well with X=CN, CO_2Me and yields generally were between 60-80%.[2] The intramolecular variation (eq. 2) introduces several new problems. An excess of the reactive acid can no longer be used, a much bulkier carboxylate must be incorporated into the oxo-centered manganese(III) acetate species in order to initiate one electron oxidation, and finally oxidation of the carboxylate must occur faster than decarboxylation. For synthetic purposes, acceptable carbocyclic ring sizes must be determined, and the activating X group should be easily removable at a later stage. During the course of these studies, a complimentary approach utilizing β-ketoacids to produce bicyclo[3.3.0] systems was published by Corey and Kang.[4]

A series of unsaturated ethyl cyanoacetates, **1-3**, and dimethyl malonates, **4-6**, were prepared by standard alkylation methods[5], with the appropriate unsaturated bromides.[6] These were converted to the potassium carboxylate salts, and treated with manganese(III) acetate, $[Mn_3O(OAc)_7(HOAc)]\cdot 5H_2O$ = $[Mn_3O]$[7] at either 70 or 25 °C.[8] The crude reaction mixture was esterified with diazomethane to facilitate chromatography of the products. The results are summarized in Scheme I.

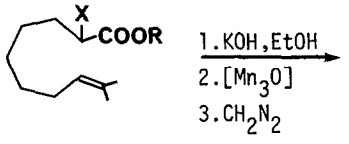
SCHEME I.



1, X=CN, R=Et **4**, X=CO_2Me, R=Me	70 °C	**7**, 17% 20%	**8**, 6%	17% 2%	9%
1 **4**	25 °C	14% 41%	3%	7%	



2, X=CN, R=Et **5**, X=CO_2Me, R=Me	70 °C	**9**, 50% (cis) **10**, 48% (1:4, trans:cis)	**11**, 8%
2 **5**	25 °C	**12**, 20% (cis) **10**, 40% (1:1, trans:cis)	**11**, 12%



no monomeric γ-lactones

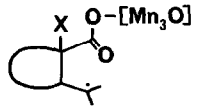
3, X=CN, R=Et
6, X=CO_2Me, R=Me

The intramolecular lactonization of **1** and **4** to the bicyclo[3.3.0] system proceeded in modest yields. The cyanoacid **1** produced, in addition to the lactone, two monocyclized oxidation products in comparable yield. These were due to oxidative trapping of the monocyclized stereoisomer which was incapable of lactone formation. Observation of external trapping of the intermediate radical was important, because it demonstrated that while the initial C-C bond is formed reversibly,[9] external trapping could compete with internal carboxylate trapping to give lactone. Half-acid ester **4** did not suffer the above complication, and only lactone products were obtained. It should be noted that lactonization in this case had occurred through both the carboxylate and ester moieties. G.C. analysis before and after diazomethane treatment showed that **7**, X=COOH and **7**, X=CO_2Me were both present in the primary reaction mixture in a 1:5 (25 °C) or 1:2 (70 °C) ratio.

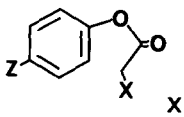
Intramolecular lactonization of **2** and **5** to the bicyclo[4.3.0] system proved substantially more efficient, and only lactone products were obtained from the reaction. Cyanoacid **2** produced the cis-fused cyanolactone stereospecifically, while half-acid ester **5** produced a cis:trans mixture which was temperature dependent. The structural assignment of cyanolactone **9** was made by conversion to cis-**10** (HCl/MeOH/ether),[10] while both cis and trans-**10** were decarbomethoxylated to **11**.[11]

The question of lactonization through the carboxylate or ester was again relevant. When the conversion of **5** to **10** was analyzed before diazomethane esterification, essentially all the material was in the form **10**, X=COOMe. Thus in this case where either mode was geometrically available, lactone formation occurred exclusively through the carboxylate and not the ester. Previous intermolecular oxidation of diethyl malonate[3b,c] and monomethyl malonate[2] had also given diester and ester lactone products respectively. An attractive explanation for these results is that oxidative lactonization preferrentially occurs through an intermediate of type **A**, where the carboxylate can still be complexed to the oxidant.

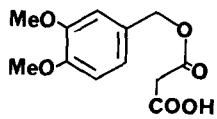
Attempted ring closure to form a bicyclo[5.3.0] system failed to produce any monomeric γ-lactone products. Thus this intramolecular lactonization procedure is apparently limited to entropically favorable 5- or 6-membered ring formation. Attempted intramolecular lactonization onto the aromatic rings of **13** or **14** also failed as well as the simple intermolecular addition of cyanoacetic acid to anisole.[12]



A



13 X = COOH, Z = H, OMe



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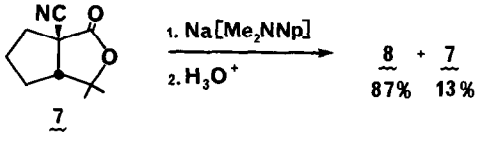
Removal of the activating groups X=CN, CO_2Me could be easily accomplished by several methods. The ester was decarbomethoxylated efficiently in refluxing 2% aq dioxane/basic Al_2O_3.[13] The nitrile was converted to the ester as discussed above, and it could also be reductively removed by 2 mol eq. sodium 1-dimethylaminonaphthalide/PhH/HMPA.[14] This reduction could be quenched by aq. HCl to generate **8** or **11** or by MeI to generate the alkylated product **15**. The reduction procedure is essentially a titration with the dark green dimethylaminonaphthalide solution, and the direct alkylation of the lactone enolate is a particularly attractive feature of this reaction sequence.



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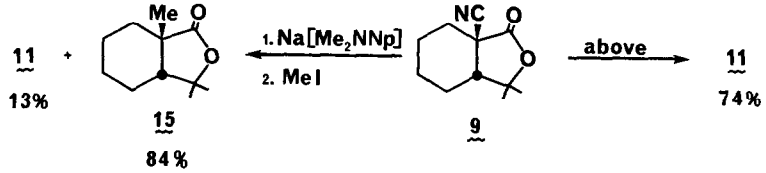

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8. The reaction conditions were briefly optimized for **4** at 70 °C. 2.5 eq Mn(III)/substrate, 0.10M substrate in HOAc, 70 °C; 2.5 eq Mn(III)/substrate, 0.10M substrate in $HOAc/Ac_2O$ (20:1), 25 °C. $[Mn_3O]$ is not soluble in glacial HOAc at 25 °C, and so the 25 °C solutions were prepared by heating the $HOAc/Ac_2O/[Mn_3O]$ mixture to 70 °C to effect dissolution, then cooled to 25 °C and used immediately. Intermolecular addition of diethyl malonate to olefins does not result in efficient lactone formation, but rather to alkylated malonate diesters.[3a] A carboxylic acid group is required for efficient cyclization to the lactone, and the monopotassium salt the most efficient way to prepare or store this species.

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