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MANGANESE (III) ACETATE AND LEWIS ACID MEDIATED CYCLIZATION OF OLEFINIC β-KETO ESTERS: A COMPARATIVE STUDY

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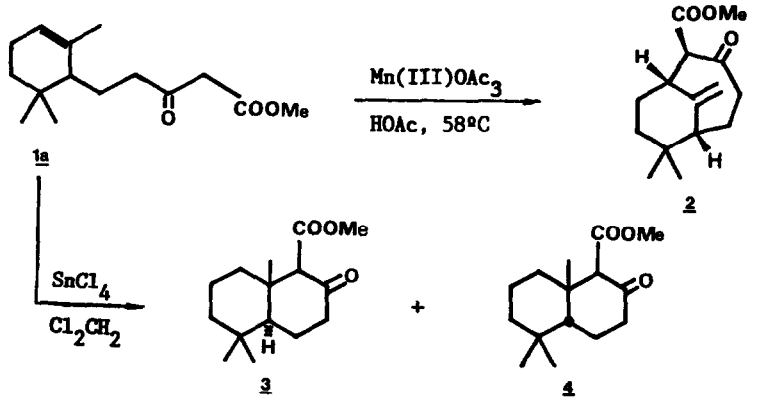
Abstract: Methyl-3-oxo-5'-(2',6',6'-trimethylcyclohex-2'-enyl and 1'-enyl) pentanoates 1a and 1b were submitted to both: Lewis acid (tin (IV) tetrachloride) and free radical (manganese (III) acetate) cyclization conditions. The structures of the different products are discussed in terms of the reaction mechanisms.

Lewis acid and photochemically mediated cyclizations have been commonly used for the construction of a great number of substituted decalin intermediates[1] for the synthesis of important natural products. More recently, free radical cyclizations of halo alkanes have also developed into a powerful method for the synthesis of polycyclic compounds. However, their reductive last step render somewhat less versatile products. The alternative Mn(III) oxidative cyclizations of β-keto esters seems to offer an interesting alternative to overcome these limitations.[2]

We were particularly interested in the outcome of such Mn(III) mediated cyclization reactions of unsaturated β-keto esters like 1, from the point of view of both, the regiochemistry and stereochemistry of the reaction, in comparison with the behavior of the same compound under Lewis acid catalysis.

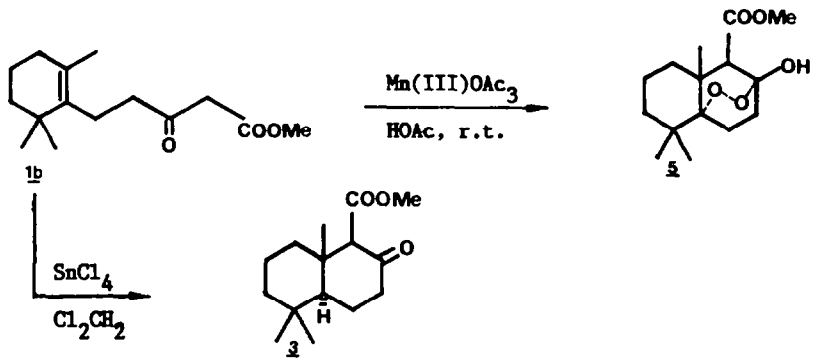
Scheme 1



Compounds 1a and 1b were easily prepared from alpha and beta ionone respectively,

by selective reduction of the conjugated double bonds[3,4] followed by carbomethoxylation with methyl carbonate/sodium hydride.[5]

Scheme 2



On treatment with two equivalents of Mn(III) acetate in acetic acid at 58°C, β-keto ester 1a produced compound 2 as the major product in ca. 60% isolated yield (Scheme 1). The structure of compound 2 was determined through a complete NMR analysis,[6] including one and 2-D experiments, and the relative stereochemistry was established by NOE difference experiments as shown in Figure 1. The complete carbon and proton chemical shift assignments are listed in Table 1.

Table 1. ^{1}H (400 MHz) and ^{13}C NMR spectral data of compounds 2 and 5.

	2			5	
	^{13}C(ppm)	^{1}H δ(J,Hz)		^{13}C(ppm)	^{1}H δ(J,Hz)
1	58.82	4.03(d,8.65)	1	61.46	2.85(d,2.7)
2	206.41	——	2	99.09	——
3	39.92	2.2(ddd,19.0,13.4,4.3) 2.37(dt,19.0,3.5)	3	27.21	1.8(ddt,11.3,2.5,12.7) 2.7(ddd,12.7,11.5,6.9)
4	22.02	1.70-1.90(overlp. m) 2H	4	23.03	2.01(ddd,14.6,13.7,2.4) 2.26(ddd,14.6,13.8,6.9)
5	51.00	2.05(t,9.0,6.1)	4a	83.57	——
6	34.58	——	5	37.26	——
7	28.72	1.13(brd,11.0) 1.79-1.90(ovrlp. m)	6	36.94	1.13(dm,11.87) 1.55(td,11.9,4.0)
8	27.10	1.38(brd,9.3) 1.78-1.9(overlp. m)	7	18.20	1.39-1.59(overlp. m)
9	40.10	3.10(brd,8.65)	8	39.31	1.77(brdm,16.9) 1.96(brtd,16.9,4.37)
10	147.1	——	8a	41.56	——
11	114.2	4.7(d,1.97) 4.87(d,1.97)	11	170.95	——
12	26.90	0.88(s)	12	27.29	0.96(s)
13	27.46	0.899(s)	13	26.38	1.00(s)
14	170.2	——	14	20.74	1.09(s)
OCH_3	52.19	3.68(s)	OCH_3	51.37	3.66(s)

On the other hand, treatment of compound 1b with two equivalents of Mn(III) acetate in acetic acid, at room temperature afforded compound 5 as the main product, in ca. 30% isolated yield (Scheme 2). The elucidation of structure 5 was also accomplished by 2D NMR, and a series of NOE difference experiments provided the basis for the stereochemistry assignment shown in Figure 2. In addition, the existence of a 1-H/3-H^U coupling, reflects their w disposition and therefore places the carbomethoxy group in a β-position.

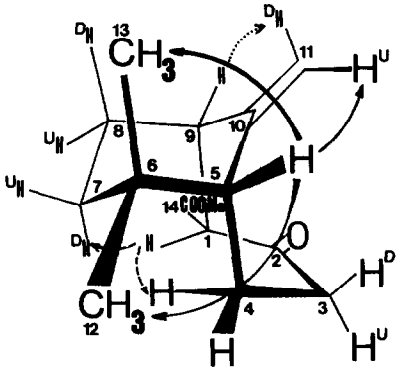


Figure 1. Relative stereochemistry of compound 2 and proton-proton through-space connectivities, obtained by NOE difference experiments. ^{U}Upfield signal; ^{D}Downfield signal

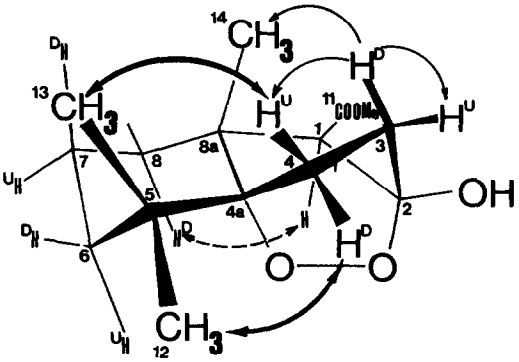
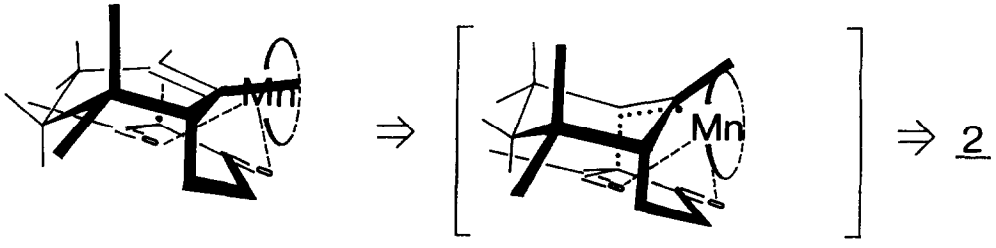


Figure 2. Relative stereochemistry of compound 5 and proton-proton through-space connectivities, obtained by NOE difference experiments. ^{U}Upfield signal; ^{D}Downfield signal

The formation of the endoperoxide 5 suggests that the radical attack of the β-keto ester is followed by the trapping of molecular oxygen which then, produces the cyclic peroxide, in a similar way as that described by J. Yoshida et al.[7]

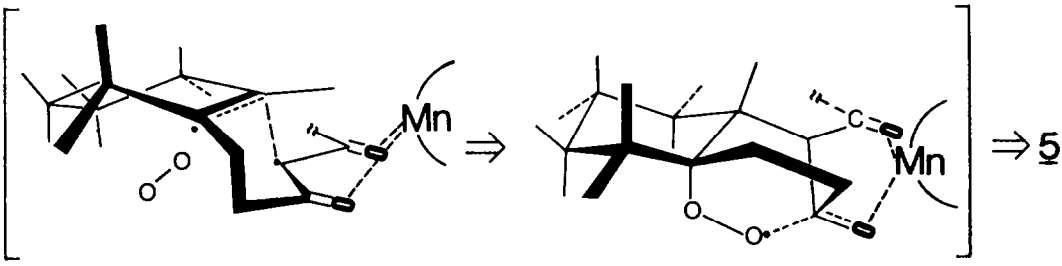
The different outcome of both radical mediated cyclizations of compounds 1a and 1b, may be rationalized as follows: The carbon centered radical,[8] in compound 1a adds to the less substituted carbon of the double bond, in accordance with the results obtained previously[2h,9] for the formation of seven membered rings by Mn(III) induced 7-endo cyclization of electrophilic radicals. The tertiary radical so formed, will be available to the Mn(III) for being oxidized to the end alkene, via the intermediary carbocation, as shown in Scheme 3.

Scheme 3



On the other hand, the β-keto ester radical in compound 1b undergoes addition only at the methyl bearing carbon, due to the steric hindrance imposed by the neighboring neopentylic position and, for the same reason, the tertiary radical formed can not be oxidized to the corresponding carbocation and is available only to the smaller oxygen molecules, trapping them without suffering β-hydrogen elimination (Scheme 4).

Scheme 4



It is interesting to compare the results just discussed, with the outcome of the 1a and 1b Lewis acid mediated cyclizations[1,10] as presented in Schemes 1 and 2 respectively.

In both reactions the tin(IV) enol complex may be the effective nucleophile, acting upon the double bond through a chair-like conformation transition state[1] to yield the cyclic products.

Concluding remarks: The Mn(III) promoted cyclizations of isomeric substrates 1a and 1b produced two different new compounds 2 and 5 in moderate yields, and they represent new examples of Mn(III) induced cyclizations. The formation of compound 2 seems particularly interesting as an easy entry into a functionalized [4.3.1] bicyclo system. In addition, the formation of 5 represents an example of an intramolecular radical-initiated formal [2+2+2] cycloaddition of molecular oxygen.

Experimental

Melting points were determined on an Ernst Leitz hot stage apparatus and are uncorrected. IR spectra were recorded on a Beckman Acculab 8 spectrometer as solids in KBr disks. Most NMR spectra were recorded on a Bruker WP-80-SY spectrometer for deuteriochloroform solutions with tetramethylsilane as internal standard at 80.13 MHz for protons and 20.25 MHz for carbons. High-field measurements and 2D experiments were recorded on a Bruker AM 400 also in deuteriochloroform solutions. For the 2D COSY and NOE experiments Bruker standard software was employed. Column chromatography was performed on silicagel 60H, slurry packed, run under low pressure of nitrogen. The homogeneity of all intermediates prior to the high-resolution mass spectral determinations was carefully verified by TLC, using the following solvent systems: hexane-ethyl acetate (7:3), chloroform-methanol (9:1), and cyclohexane-ether (6:4) on Merck aluminium plates precoated with silica gel 60 F-254 (0.2 mm).

Methyl-3-oxo-5'-(2',6',6'-trimethylcyclohex-2'-enyl and 1'-enyl) pentenoates, 1a and 1b: Both compounds were prepared following known literature procedures[1a,10] and their spectroscopic characteristics were in agreement with those previously reported.

Methyl-6,6-dimethyl-10-mthylene-2-oxo-5β,9β-[4,3,1] bicyclodecane-1β-carboxylate 2: To a stirred solution of Mn(III) acetate (213 mg, 0.795 mmol) in glacial acetic acid (5 mL) heated at 58°C in an oil bath, a solution of the β-keto ester 1a (100 mg, 0.4 mmol) in acetic acid (1 mL) was added. After the solution turns colorless (ca. 15 min) it was poured into water (25 mL) and the mixture extracted with ether (3x25 mL). The combined ether extract was washed successively with water, saturated aqueous sodium hydrogen carbonate and brine, dried over anh. sodium sulfate, decanted and evaporated in vacuo. After column chromatography (1% gradient ethyl acetate in hexane), afforded 61.3 mg (0.25 mmol, 62%) of pure 2 as a colorless solid; mp: 91-92°C (hexane). IR (neat) ν_{max}: 3060, 2928, 2866, 1707, 1645.5, 1465, 1163 and 895 cm^{-1}; ^{1}H y ^{13}C NMR see Table 1; m/z 250(M^+,40), 219(23), 218(43), 203(14), 190(10), 179(12), 177(17), 175(27), 162(64), 161(29), 157(17), 150(25), 149(39), 148(27), 147(42), 138(17), 137(64), 135(60), 134(61), 133(51), 129(13), 123(27), 122(29), 121(72), 120(44), 119(77), 117(24), 109(30), 108(28), 101(40), 97(16), 96(16), 95(58), 94(43), 93(92), 92(55), 90(100), 89(10), 83(21), 82(19), 81(76), 80(40), 79(100), 78(61), 77(100), 74(13), 71(14), 69(100), 67(87), 63(23), 59(84), 57(24), 55(100), 53(99), 52(51), 51(75);(Found: M^+, 250.1589 Calc. for $C_{15}H_{22}O_3$: 250.1569); Anal. Calc. for $C_{15}H_{22}O_3$: C 71.98, H 8.89, found: C 71.87, H 9.07.

Methyl Perhydro-5,5,8aβ-trimethyl-2β-hydroxy-2α,4aα-peroxy-naphthalene-1β-carboxylate 5: To a stirred suspension of Mn(III) acetate (213 mg, 0.795 mmol) in glacial acetic acid (6 mL) was added compound 1b (100 mg, 0.4 mmol) and the mixture was stirred 24 h at room temperature. The reaction mixture was then diluted with water (50 mL) and extracted with ether (5x30 mL). The combined ether extract was then successivelly washed with water, saturated aqueous sodium hydrogen carbonate and brine, dried over anh. sodium sulfate, decanted and evaporated in vacuo. After column chromatography (1% gradient of ethyl acetate in hexane) afforded 5 (35 mg, 0.12 mmol, 31%) as a colorless solid, and starting keto ester 1b (25 mg, 0.1 mmol). Compound 5 mp.: 134-135°C (hexane). IR (neat) ν_{max}: 3500, 3000-2880, 1750, 1470, 1460, 1455, 1445, 1400, 1370, 1340, 1200, 1180, 1150, 1120 and 970 cm^{-1}; ^{1}H and ^{13}C NMR see Table 1; m/z 284(M^+, 3), 251(5), 235(25), 234(12), 219(15), 191(36), 149(15), 147(10), 145(8), 137(16), 136(7), 133(7), 127(5), 126(4), 125(11), 124(6), 123(34), 122(4), 121(17), 119(8), 109(25), 108(8), 107(17), 105(10), 101(17), 97(12), 96(6), 95(45), 93(15), 91(13), 85(10), 83(18), 82(16), 81(44), 79(19), 77(12), 73(20), 69(89), 68(20), 67(43), 65(10), 55(100), 53(30); (Found for M^+: 284.1635, $C_{15}H_{24}O_5$ requires M, 284.1617). Anal. Calc. for $C_{15}H_{24}O_5$: C 63.36, H 8.51, found: C 63.37, H 8,74

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