Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: P. A. Zoretic, M. Ramchandani & M. L. Caspar (1991) Aspects of Manganese (III) - Promoted Oxidative Free Radical Cyclizations to Functionalized Bicyclic Systems, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:7, 915-922, DOI: 10.1080/00397919108019776

To link to this article: http://dx.doi.org/10.1080/00397919108019776

SYNTHETIC COMMUNICATIONS, 21(7), 915-922 (1991)

ASPECTS OF MANGANESE (III) - PROMOTED OXIDATIVE FREE RADICAL CYCLIZATIONS TO FUNCTIONALIZED BICYCLIC SYSTEMS

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SUMMARY: The stereospecific formation of *trans*-decalin **7** from oxidative radical cyclization of **6** and formation of functionalized bicyclic systems from radical cyclization of **3** are detailed.

Since the simultaneous pioneering work by Bush and Finkbeiner[1] and Heiba and co-workers[2] on manganese (III) oxidative free radical cyclizations of olefins to γ-lactones, the utilization of Mn (III) has recently been extended to intramolecular polycyclizations of β-keto esters by Snider.[3] The tandem use of Cu (II)[4] with Mn (III)[3] has extended the usefulness of radical cyclizations,[5] since the newly produced radical center is oxidatively converted to a double bond in a predetermined position for further chemical elaboration.

Herein we report that free-radical cyclization of keto ester **6** with Mn (III) in tandem with Cu (II) afforded stereospecifically the highly functionalized *trans*-decalin **7**,

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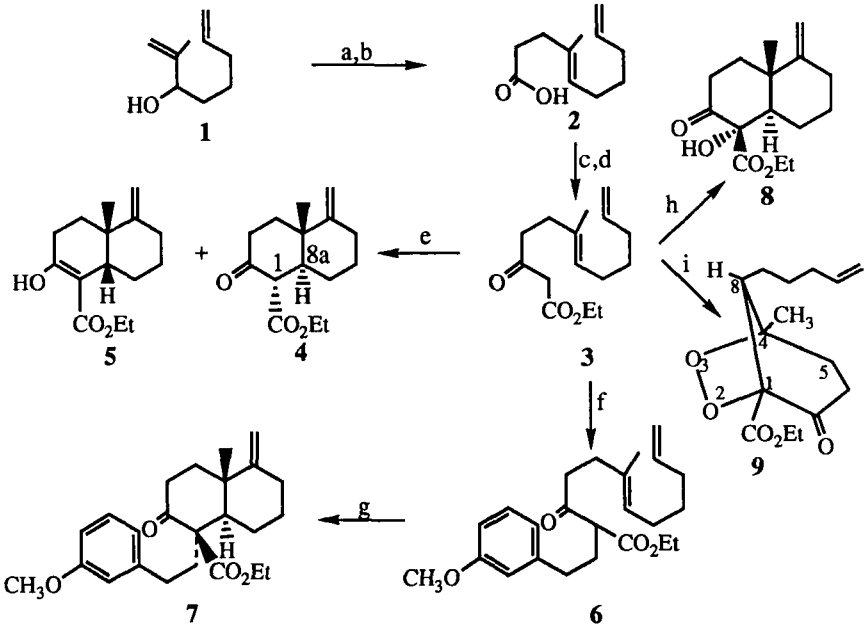
which is a potential intermediate to d,l-homoestrone and related steroid derivatives. The formation of different bicyclic systems resulting from variation of reagents and reaction conditions during the cyclization of **3** are also reported.

β-Keto ester **3** was prepared in 62% overall yield from allylic alcohol **1**[6]. Oxidative free-radical cyclization of **3** with a 2:1 molar ratio of $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ in

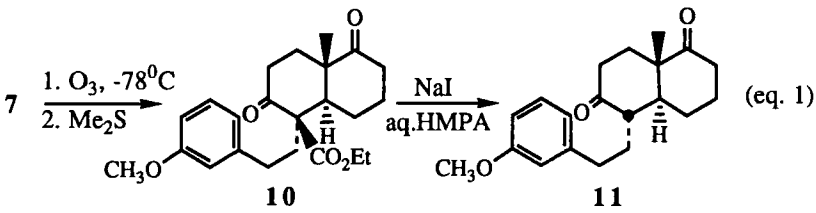


[a]$CH_3C(OEt)_3$, $EtCO_2H$, 139 °C, 1.5 h; [b]aq. NaOH-EtOH, Δ, 2.5 h; then aq. HCl; [c]ClCOCOCl, PhH, rt, 14 h; [d]2 eq. LICA, THF, 1 eq. EtOAc, -78 °C, 25 min; then aq. HCl; [e]$Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$ (2:1 molar equivalents), 0.1M deaerated HOAc, rt, 7 h, Ar; [f]EtONa-EtOH, *m*-$MeOPhCH_2CH_2Br$, Δ, 36 h; [g]e, 4 h; [h]e, 26 h; [i]2 eq. $Mn(OAc)_3 \cdot 2H_2O$, HOAc, 18 h.

deaerated acetic acid (0.1M) under Ar for 7 h at room temperature yielded the *trans*-decalin **4** (43%) and the *cis*-decalin **5** (12%), after chromatography. The ring juncture in **4**

was assigned as trans based on the 12.9 Hz coupling constant observed for the C-1 methine (d, δ3.25) and the fact that irradiation of the angular methyl in **4** caused an NOE enhancement of the C-1 methine. The ring juncture in **5** was assigned as cis, since the β-keto ester existed exclusively as the enol tautomer[7] (δ12.4). The upfield shift of the angular methyl (δ1.13) in **5** opposed to the deshielded resonance signal (δ1.23) in **4** is also consistent with that observed by Welch[8] in an analogous tricyclic system.

Excellent stereospecificity was obtained from an identical oxidative free-radical cyclization of the substituted keto ester **6** in which *trans*-decalin **7** was isolated in 57% yield, after chromatography. No comparable *cis*-decalin product was observed. The sharp ^{13}C NMR spectrum of **7** strongly suggests one stereoisomer. The assigned axial carboethoxy at C-1 is consistent with the observed deshielding of the C-3 axial proton (δ 3.07, 6 line ddd, J = 6.2, 14.8, and 14.8 Hz) as opposed to δ2.53 in **4**. The axial disposition of the carboethoxy group in **7** is also suggested from the fact that decarboethoxylation of

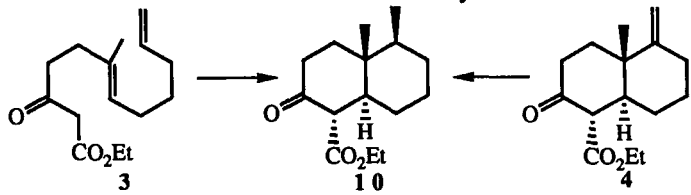


the sterically hindered ester[9] in **10** (eq. 1) with excess NaI in aqueous hexamethylphosphoramide (18 h, 160° C) afforded the known *trans*-decalin **11**[10,11] in only 15% yield[12] and unreacted **10** (25%), after chromatography.

It was also observed that stereospecific formation of higher functionalized bicyclic systems could be obtained from **3**, albeit in lower yields, by variation of reagents and experimental conditions. For example, oxidative cyclization of **3** *vide supra* for 26 h afforded stereospecifically hydroxy ketone **8**, in 23% yield, after chromatography, along with trace amounts of **4** (4%)

and **5** (3%). The ring juncture in **8** was assigned as trans, since it was shown that reaction of a 1:1.05 molar ratio of **4** and Mn (III)-acetate under identical reaction conditions as above yielded the same hydroxy ketone **8** (18%)[13] which was identical in all respects TLC, ^{1}H NMR and ^{13}C NMR to that obtained from the cyclization of **3** after 26 h. The stereochemistry at C-1 in **8** was tentatively assigned based on the deshielding resonance signal of the C-3 axial proton (δ3.16, 6 line ddd, J = 6.1, 14.6 and 14.7 Hz) which is consistent with an axially disposed carboethoxy group.

When the cyclization of **3** was conducted with Mn (III) and Cu (II) in a 1:2:1 molar ratio, *without deaerating the acetic acid* and in a non-inert atmosphere, the highly functionalized endoperoxide **9** was obtained as a single stereoisomer, along with **8** as an inseparable mixture (25%), after chromatography. Fortunately it was shown that reaction of a 1:2 molar ratio of **3** and Mn (III) in acetic acid (0.1M) in the absence of Cu (II) for 18 h at room temperature gave only **9**[14] (25%), after chromatography. It might be noted that passing oxygen through the reaction mixture or conducting the reaction in an atmosphere of O_2 did not increase the yield of **9**.[15] The sharp ^{13}C NMR spectrum of **9** was clearly consistent with a single isomer. The stereochemistry shown at C-8 in **9** was readily deduced from the ^{1}H COSY spectrum which showed 'W'-coupling between the C-5 endo and C-8 protons. The observed positive KI test and the mass spectrum m/e 282 are also consistent with the proposed structure. That endoperoxide **9** was indeed formed from triplet oxygen was proven, since reaction of **3** with Mn (III) in a 1:2 molar ratio using *degassed acetic acid* under identical reaction conditions afforded only the *trans*-decalin **10**



(17%), after chromatography. The *cis*-vicinal stereochemistry in **10** was substantiated, since catalytic reduction of **4** (less hindered face of the molecule) with hydrogen in the presence of Pd/C afforded the same keto ester.

Experimental Section

(d,l)-(1α,4aα,8aβ)-1-[2-(3-Methoxyphenyl)ethyl]-4a-methyl-5-methylene-2-oxo-1-naphthalenecarboxlic Acid, Ethyl Ester (7). A mixture of **6** (282 mg, 0.731 mmol) in HOAc (7.3 mL) was deaerated with Ar. $Mn(OAc)_3 \cdot 2H_2O$ (389 mg, 1.45 mmol) and $Cu(OAc)_2 \cdot H_2O$ (146 mg, 0.731 mmol) was added under Ar. The reaction mixture was stirred at room temperature for 4 h and then filtered through Celite and charcoal, (salts washed with CH_2Cl_2). The organic solution was extracted with water (15 mL), saturated $NaHCO_3$ (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an oil. Chromatography on silica gel (230-400 mesh), eluting with ethyl acetate-hexane solutions, gave 160 mg (57%) of **7**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, 1 H, J = 7.9 Hz), 6.71-6.82 (m, 3 H), 4.67 (m, 1 H), 4.61 (m, 1 H), 4.17 (dq, 2 H, J = 3.4, 7.1 Hz), 3.79 (s, 3 H), 3.07 (6 line ddd, 1 H, J = 6.2, 14.8, 14.8 Hz), 2.49-2.62 (m, 2H), 2.35 (6 line ddd, 1 H, J = 4.2, 12.6, 12.7 Hz), 1.82-2.29 (m, 10 H), 1.63 (dd, 1 H, J = 2.8, 12.5 Hz), 1.28 (t, 3 H, J = 7.1 Hz), 1.20 (s, 3 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 208.6, 173.3, 160.1, 157.3, 144.3, 129.7, 121.2, 114.3, 111.7, 106.9, 61.6, 61.3, 55.3, 52.2, 39.7, 37.8, 37.3, 35.8, 33.1, 31.1, 28.4, 24.2, 18.6, 14.1; IR (neat) 1718 (br) cm^{-1}; HRMS calculated for $C_{24}H_{32}O_4$ 384.2300, found 384.2289.

(E)-Ethyl 6-Methyl-3-oxo-6,11-dodecadienoate (3). Lithium isopropylcyclohexylamide was prepared by addition of n-butyllithium (2.5M in hexane, 23.9 mL, 59.9 mmol) to isopropylcyclohexylamine (8.45 g, 59.9 mmol) in dry THF (10 mL) under N_2 over 25 min at O °C. The reaction mixture was stirred for an additional 20 min and then cooled to -78 °C. Ethyl acetate (2.63 g, 29.9 mmol) was then added over 10 min and stirring was continued at -78 °C for 25 min. (E)-4-Methyl-4,9-

decadienoyl chloride (6.0 g, 29.9 mmol) in THF (50 mL) was added and after stirring for an additional 25 min at -78 °C the reaction mixture was quenched with dilute HCl, and then diluted with CH_2Cl_2 (100 mL). The organic solution was extracted with water (30 mL), saturated $NaHCO_3$ (15 mL), and brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. Chromatography on silica gel (230-400 mesh), eluting with ethyl acetate–hexane solutions, gave 6.19 g (82%) of **3** : ^1H NMR ($CDCl_3$) δ 5.72-5.92 (m, 1 H), 5.14 (m, 1 H), 4.92-5.08 (m, 2 H), 4.20 (q, 2 H, J = 7 Hz), 3.44 (s, 2 H), 2.65 (t, 2 H, J = 7.7 Hz), 2.28 (t, 2 H, J = ~7.7 Hz), 1.94-2.11 (m, 4 H), 1.60 (s, 3 H), 1.34-1.51 (m, 2 H), 1.28 (t, 3 H, J = 7 Hz); IR (neat) 1740 and 1622 cm^{-1}; HRMS calculated for $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1723. A small amount of the enol was also indicated by absorption at δ12.11.

Acknowledgment. We are indebted to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to Mr. Dean Marbury for the high-resolution mass spectra data and to Dr. Anthony A. Riebiro of Duke University for recording the 500 MHz ^1H NMR spectra.

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11 ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 1 H), 6.76 (m, 3 H), 3.81 (s, 3 H), 1.55-2.81 (m, 14 H), 1.34 (s, 3 H), 1.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 214.8, 211.3, 160.1, 144.5, 129.7, 121.2, 114.5, 111.5, 55.4, 49.2, 48.2, 37.8, 37.2, 33.0, 32.9, 29.8, 27.8, 25.8, 24.8, 16.3;
12. Decarboethoxylation in an analogously substituted *cis*-hydrindanone occurs in 75% yield: see accompanying communication.
13. ^{13}C NMR (200 MHz, CDCl3) δ 208.9, 170.4, 156.8, 106.0, 80.7, 62.0, 57.3, 39.8, 37.8, 36.1, 33.0, 28.0, 23.1, 19.4, 14.0; ^{1}H NMR (500 MHz, CDCl3) δ 4.65 [s (br), 1 H], 4.58 [s (br), 1 H], 4.58 [s (br), 1 H], 4.37 (s, 1 H, OH), 4.22 (overlapping dq, 2 H, J = 7 and 10 Hz), 3.16 (6 line ddd, 1 H, C_3-H_a, J = 6.1, 14.6 and 14.7 Hz), 2.70 (ddd, 1 H, C_3-H_e, J = 2.6, 4.4 and 14.4 Hz), 1.53 (dd, 1 H, C_{8a}- H, J = 3.2 and 12.3 Hz), 1.32 (t, 3 H, J = 7 Hz), 1.22 (s, 3 H); HRMS calculated for $C_{15}H_{22}O_4(M^+)$ 266.1517, found 266.1503.
14. ^{13}C NMR ($CDCl_3$) δ 204.7 (s, C-7), 165.5 (s, C-15), 138.3 (d, C-12), 115.8 (t, C-13), 91.6 (s, C-1), 86.3 (s, C-4), 62.5 (t, C-17), 61.7 (d, C-8), 34.6 (t), 33.9 (t), 32.9 (t), 27.3 (t), 21.1 (t), 19.7 (q, C-18), 14.1 (q, C-14); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71-5.96 (m, 1 H), 4.94-5.12 (m, 2 H), 4.28 (overlapping dq, 2 H, J = 7.1, 8.2 Hz), 3.17 (ddd, 1 H, C_6-H_a, J = 10.0, 10.9, 20.9 Hz), 2.92-3.02 (m, 1, C_6-H_e), 2.34 (dd, 1 H, C_8-H, J = 7.8, 15.8 Hz), 1.37 (s, 3 H), 1.30 (t, 3 H); HRMS calculated for $C_{15}H_{22}O_5$ (M^+) 282.1466, found 282.1475.
15 When a new bottle of acetic acid was used **9** could only be isolated in 10-20% yields.

(Received in USA 6 February, 1991)