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AN OXIDATIVE FREE-RADICAL CYCLIZATION APPROACH TO d,l-Δ^8-14-EPIESTRONE-3-METHYL ETHER

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SUMMARY: A Stereospecific free-radical cyclization of β-keto esters **4** and **5** to *cis*-hydrindanones **9** and **6**, respectively, and conversion of **6** to d,l-14-epiestrone intermediate **8** are reported.

Since the initially reported radical cyclizations by Julia[1] and the insight of radical chemistry provided by Beckwith[2] the use of radicals in constructing carbon-carbon bonds has become increasingly evident. The application of copper (II) as an oxidative radical termination process by Breslow[3], Kochi[4], Heiba[5] and Nikishin and Vinogradov[6] and the current reports by Corey[7], Fristad[8] and Snider[9] on the manganese (III) acetate promoted oxidative free-radical cyclizations[10] of β-keto acids and esters to alkenes has extended the usefulness of radical chemistry in carbon-carbon bond construction. The recent publication by Snider[9h] on the Mn(III) promoted oxidations of unsaturated β-ketoesters to *cis*-hydrindanones prompted us to communicate our complementary results herein.

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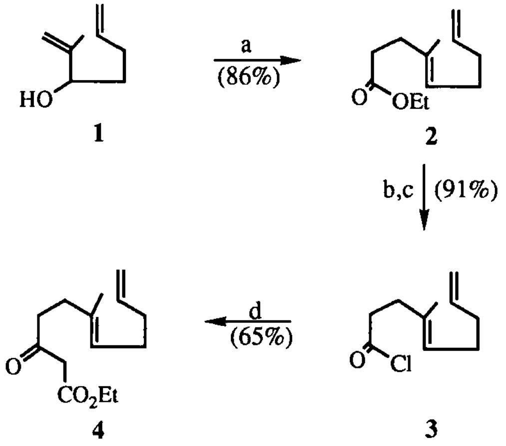
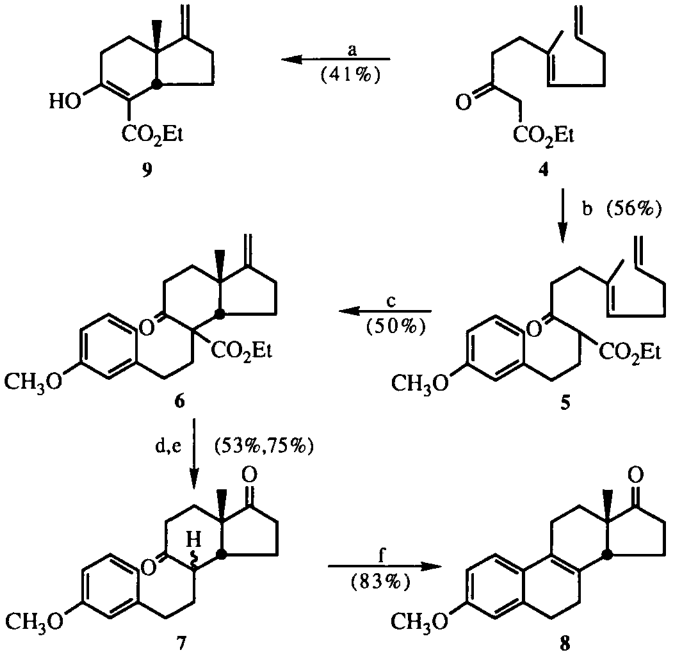


^{a} CH$_3$C(OEt)$_3$, EtCO$_2$H, 139 °C, 1.5 h; ^{b} aq. NaOH-EtOH, Δ, 2.5 h; then aq. HCl; ^{c} ClCOCOCl, PhH, rt, 14 h; ^{d} 2eq. LICA, THF, 1 eq. EtOAc, -78 °C, 25 min; then aq. HCl.

Scheme I

Of particular interest to us was the utilization of Mn (III) in tandem with Cu (II) as an entry to steroid intermediate **8** which has previously been converted to 19-nortestosterone and the corresponding retrosteroid by Crabbé and co-workers.[11] Ortho Claisen rearrangement of **1**[12] (Scheme I) with ethyl orthoacetate in the presence of an acid gave ester **2**[12] (86%). Subsequent saponification of **2** and treatment of the corresponding acid with oxalyl chloride afforded **3** (91%). Reaction of **3** with the lithium enolate of ethyl acetate in the presence of one equivalent of lithium isopropylcyclohexylamide (LICA) followed by acidification gave keto ester **4** (65%), after chromatography. Alkylation of the sodium enolate of **4** (Scheme II) with 2-(*m*-methoxyphenyl)ethyl bromide afforded the desired monoalkylated β-keto ester **5** (56%). Oxidative



[a] $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$ (2:1 molar ratio), deaerated HOAc, Ar, rt, 4 h; [b] EtONa-EtOH, Δ, m-$MeOPhCH_2CH_2Br$, 20 h; [c] a, 7 h; [d] O_3, CH_2Cl_2, -78 °C; then Me_2S; [e] 18 eq. NaI, aq. HMPA, 160 °C, 22 h; [f] 10N HCl-MeOH, rt, 5 h; then 0 °C, 1.5 h.

Scheme II

free-radical cyclization of **5** with a 2:1 molar ratio of $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ in deaerated acetic acid gave a single stereoisomer **6** in 50% yield, after chromatography. The ^1H NMR and the sharp ^{13}C NMR spectra is totally consistent with a single stereoisomer, however the stereochemistry at C-4 cannot be unambiguously determined. The cis ring juncture stereochemistry in **6** was established by conversion to the known tetracyclic intermediate **8**. Thus ozonolysis of **6** and subsequent reduction of the corresponding ozonide with Me_2S afforded an intermediate diketo ester in 53% yield. Decarboethoxylation of the diketo ester with excess NaI in aqueous HMPA at 160 °C gave diketones **7** (75%). Acid catalyzed cyclization of **7** with a 10N HCl-MeOH solution afforded an 83% yield of **8**.[11,13]

It was also found that oxidative free-radical cyclization of **4** with Mn (III) in the presence of Cu (II) in deaerated acetic acid under Ar afforded **9**[14] in 41% yield, after chromatography. The keto ester **9** existed exclusively as the enol tautomer.[15] The use of a chiral ester as an auxiliary in **4** and the resulting diastereofacial selectivity resulting from radical cyclization will be reported in due course.

Experimental Section

(E)-Ethyl 2-[2-(3-Methoxyphenyl)ethyl]-6-methyl-2-oxo-6,10-undecadienoate (5). *Two seperate reactions were performed as detailed below.* To a solution of sodium ethoxide [prepared by the addition of Na (58 mg, 2.52 mmol) to absolute ethanol (2 mL)] was added **4** (600 mg, 2.52 mmol) in ethanol (2 mL) at room temperature. The reaction mixture was brought to reflux and *m*-methoxyphenylethyl bromide (704 mg, 3.27 mmol) in ethanol (2 mL) was added dropwise and refluxing was continued for 20 h. Ethanol was evaporated *in vacuo* and the mixture was diluted with CH_2Cl_2. The organic solution was extracted with water (20 mL), and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. *The combined oils* were chromatographed on silica gel (230-400 mesh), eluting with ethyl acetate-hexane solutions, to give 1.05 g (56%) of **5**: ^1H NMR ($CDCl_3$) δ 7.16-7.28 (m, 1 H), 6.70-6.81 (m, 3 H), 5.70-5.91 (m, 1 H), 5.08-5.19 (m, 1 H), 4.90-5.07 (m, 2 H), 4.20 (q, 2 H, J = 7.2 Hz), 3.80 (s, 3 H), 3.45 (t, 1 H, J = 7.3 Hz), 2.42-2.75 (m, 4 H), 2.12-2.32 (m, 4 H), 2.02-2.11 (m, 4 H), 1.58

(s, 3 H), 1.28 (t, 3 H, *J* = 7.2 Hz); IR (neat) 1720 and 1750 cm^{-1}; HRMS calculated for $C_{23}H_{32}O_4$ (M^+ + 1) 373.2378, found 373.2383.

(d,l)-4-[2-(3-Methoxyphenyl)ethyl]-7a-methyl-1-methylene-5-oxo-1[H]-indene-4-carboxylic Acid, Ethyl Ester (6). A mixture of **5** (238 mg, 0.640 mmol) in HOAc (8.4 mL) was deaerated with Ar. $Mn(OAc)_3 \cdot 2H_2O$ (343 mg, 1.28 mmol) and $Cu(OAc)_2 \cdot H_2O$ (128 mg, 0.640 mmol) was added under Ar. The reaction mixture was stirred at room temperature for 3.5 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), and 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 119 mg (50%) of **6**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (m, 1 H), 6.75-6.83 (m, 3 H), 4.89 (m, 1 H), 4.77 (m, 1 H), 4.14 (overlapping dq, 2 H), 3.81 (s, 3 H), 2.63 (6 line ddd, 1 H, *J* = 4.8, 12.8, 12.8 Hz), 2.57 (dt, 1 H, *J* = 5.3, 17.7 Hz), 2.37-2.50 (m, 3 H), 2.27 (ddd, 1 H, *J* = 4.4, 12.7, 13.6 Hz), 1.85-2.13 (m, 6 H), 1.80 (dt, 1 H, *J* = 5.4, 14.3 Hz), 1.26 (t, 3 H, *J* = 7.2 Hz), 1.20 (s, 3 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 210.0, 172.1, 161.6, 160.3, 144.2, 129.9, 121.3, 114.6, 111.8, 104.2, 61.4, 61.0, 55.5, 53.7, 44.2, 37.4, 36.9, 32.1, 32.0, 31.6, 30.4, 26.7, 14.1; IR (neat) 1711 (br) cm^{-1}; HRMS calculated for $C_{23}H_{30}O_4$ (M^+ + 1) 371.2221, found 371.2230.

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13. ^{1}H NMR (CDCl$_3$) δ 7.06-7.18 (m, 1 H), 6.67-6.78 (m, 2 H), 3.80 (s, 3 H), 2.76 (m, 2 H), 2.02-2.51 (m, 8 H), 1.66-1.90 (m, 2 H), 1.39-1.57 (m, 1 H), 1.08 (s, 3 H); ^{13}C NMR (CDCl$_3$) δ 224.1, 158.7, 137.6, 132.4, 129.5, 126.9, 123.6, 113.9, 111.4, 55.6, 48.9, 47.5, 37.0, 29.1, 27.7, 27.1, 25.6, 22.2, 20.8.

14. After completion of this work, Snider reported the same oxidative free-radical cyclization of **4** to **9**; see reference 9h.

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