Nucleophilic Addition Reactions and Functionalization of (3-Methoxyestrone)- and (3,17-Dimethoxyestradiol)manganese Tricarbonyl Complexes

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Nucleophilic addition of MeMgCl and PhMgBr to the A-ring aromatic steroid complex [(η^6-3,17-dimethoxyestradiol)$Mn(CO)_3$]$^+$ gives stable η^5-cyclohexadienyl complexes and occurs at the C-1 site *meta* to the -OMe group when the metal is on the "β" side of the steroid; addition to the "α" analogue is less regioselective due to steric interactions and occurs at C-1, C-2, and C-4. A manganese-mediated procedure is reported for the functionalization of estrone at the C-1 position to give 1-methylestrone in 42% yield.

Introduction

The transition-metal fragments $M(CO)_3$ (M = Cr, Mo, W), $CpRu^+$, Cp^*Rh^{2+}, and $Os(NH_3)_5^{2+}$ have been coordinated to the steroids estrone (**1**) and estradiol (**2**), or their methylated derivatives, *via* the aromatic A-ring.[1−3] The effect of this coordination is to activate the benzylic sites to deprotonation and the aromatic ring to nucleophilic displacement of a chloride substituent. An interesting application of estradiol complexes having $Cr(CO)_3$ coordinated to the aromatic ring,[3] or other metal fragments attached to C-17,[4] is their potential use (*via* FT-IR) as indicators of steroid hormone receptor level variations, which are associated with some cancers. We recently reported[5] that the $Mn(CO)_3^+$ moiety is readily attached to the methylated analogues of **1** and **2** to afford cationic η^6 complexes in which the metal is bonded β ("up") or α ("down"), as illustrated in structures **3** and **4**, respectively. The product was found to contain a nearly equal distribution of α- and β-isomers.

In comparison to $Cr(CO)_3$ and $CpRu^+$, the $Mn(CO)_3^+$ fragment exerts much more electrophilic activation when coordinated to an arene.[6] As a result, most [(arene)$Mn(CO)_3$]$^+$ complexes undergo high-yield nucleophilic addition reactions with a wide range of C- and H-donors to afford stable cyclohexadienyl complexes.[7] With (**3** and **4**) it was shown previously[5] that $NaBH_4$ and $LiCH_2C(O)CMe_3$ add regioselectively to the C-1 position *meta* to the -OMe substituent to give **5**. No products resulting from nucleophilic attack at the *ortho* positions (C-2, C-4) were detected. However, we show herein that with the nucleophiles MeMgCl and PhMgBr the *ortho* sites are accessible to give **6** and **7**, but only when the metal is in the α-orientation. It is also demonstrated that the neutral **5**(β) can be "reactivated" by conversion to the cationic **8**, which undergoes further nucleophilic attack by $NaBH_4$ to generate a 1:1 mixture of cyclohexadiene complexes **9** and **10**.

It has been demonstrated[7−9] that the manganese-mediated functionalization of arenes is a viable synthetic procedure. Generally this involves coordination of $Mn(CO)_3^+$, regioselective nucleophilic addition, and oxidative removal of the metal with concomitant rearomatization. In the present study, this methodology is applied to the functionalization of estrone (**1**) at the C-1 position to give 1-methylestrone and 1-phenylestrone.

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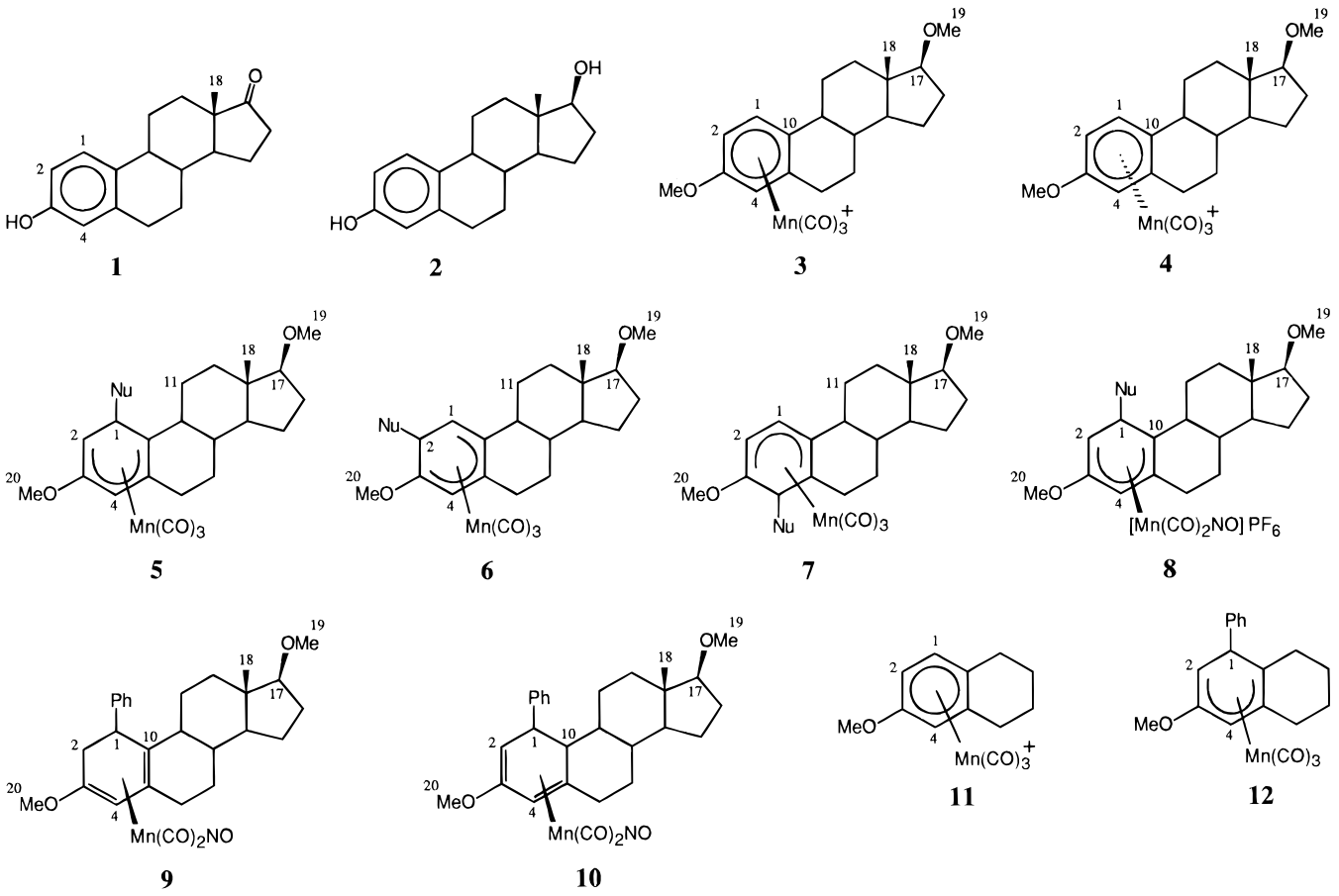
Chart 1



Results and Discussion

It was anticipated that the addition of MeMgCl (or LiMe) and PhMgBr (or LiPh) to a 1:1 mixture of **3** and **4** would result in highly regioselective nucleophilic attack at the C-1 position. This expectation was based on the strongly *meta*-directing effect of an -OMe substituent[8] and on the behavior found with the nucleophiles $LiCH_2C(O)CMe_3$ and $NaBH_4$.[5] IR and NMR spectra of product mixtures obtained after MeMgCl or PhMgBr addition indicated the presence of isomers other than **5**(α) and **5**(*β*). Fortunately, in most cases the isomers could be separated by chromatography or fractional crystallization. Although ^{1}H NMR could be used to assign structure **5**, **6**, or **7** with a fair level of confidence, assigning the orientation of the metal (α or *β*) was more problematic. In order to definitively resolve these difficulties, the X-ray structures of a series of six complexes were determined. Crystals were grown from samples of pure isomers (not mixtures), and after X-ray data collection was complete, the ^{1}H NMR spectrum of each isomer was recorded using the *actual* crystal utilized in the X-ray work. This eliminated any possibility that a crystal not representative of the bulk material had been selected. The structures are shown in Figure 1, and relevant crystal data are listed in Table 1. IR and ^{1}H NMR data for the individual isomers are collected in Table 2.

All of the η^5-cyclohexadienyl complexes have the Mn(CO)$_3$ tripod oriented in the usual manner with a Mn−C−O link eclipsing the saturated carbon. Complex **8** also shows the "normal" tripodal rotational conformation, with the Mn−N−O link situated under the dienyl π system. Complex **5**(*β*, Nu = Ph) crystallizes with two independent molecules in the unit cell, both of which are shown in Figure 1. The primary difference between the two structures is the orientation of the phenyl group attached to C-1. With the individual isomers identified, the distribution of products as a function of nucleophile could be ascertained. The results are given in Table 3. The conclusion is that the *β*-isomer **3** is attacked only at the C-1 *meta* position, which is known to be favored for electronic reasons.[8] With the α-analogue **4**, both electronic and steric factors play a role, with the result that attack can occur at C-1, C-2, and/or C-4. The distribution among these sites is highly nucleophile-dependent. Thus, $NaBH_4$ and $LiCH_2C(O)CMe_3$ give only C-1 addition, MeMgCl (or LiMe) adds to all three positions with nearly equal facility, and PhMgBr (or LiPh) attacks **4** at C-2 and C-4 but not C-1.

An examination of the structural details in Figure 1 helps to provide an explanation for these results. Especially informative is a comparison of **5**(α, Nu = Me) and **5**(*β*, Nu = Me). The relevant interaction appears to be between the methyl group at C-1 and the CH_2 group at C-11. With **5**(*β*, Nu = Me) the methyl is 3.5 Å from the nearest hydrogen on C-11 (equatorial H-11), whereas in **5**(α, Nu = Me) the methyl is just 2.9 Å from the axial H-11. Similarly, the methyl to C-11 distances are 3.96 and 3.50 Å, respectively. It is suggested that a steric interaction between the CH_2 group at C-11 and a nucleophile situated *β* at C-1, as in **5**(α), constitutes a kinetic barrier to addition at C-1 in **4**. If the barrier is sufficient, competitive addition occurs at C-2 and C-4. With **3**, however, the steric barrier to addition at C-1 is

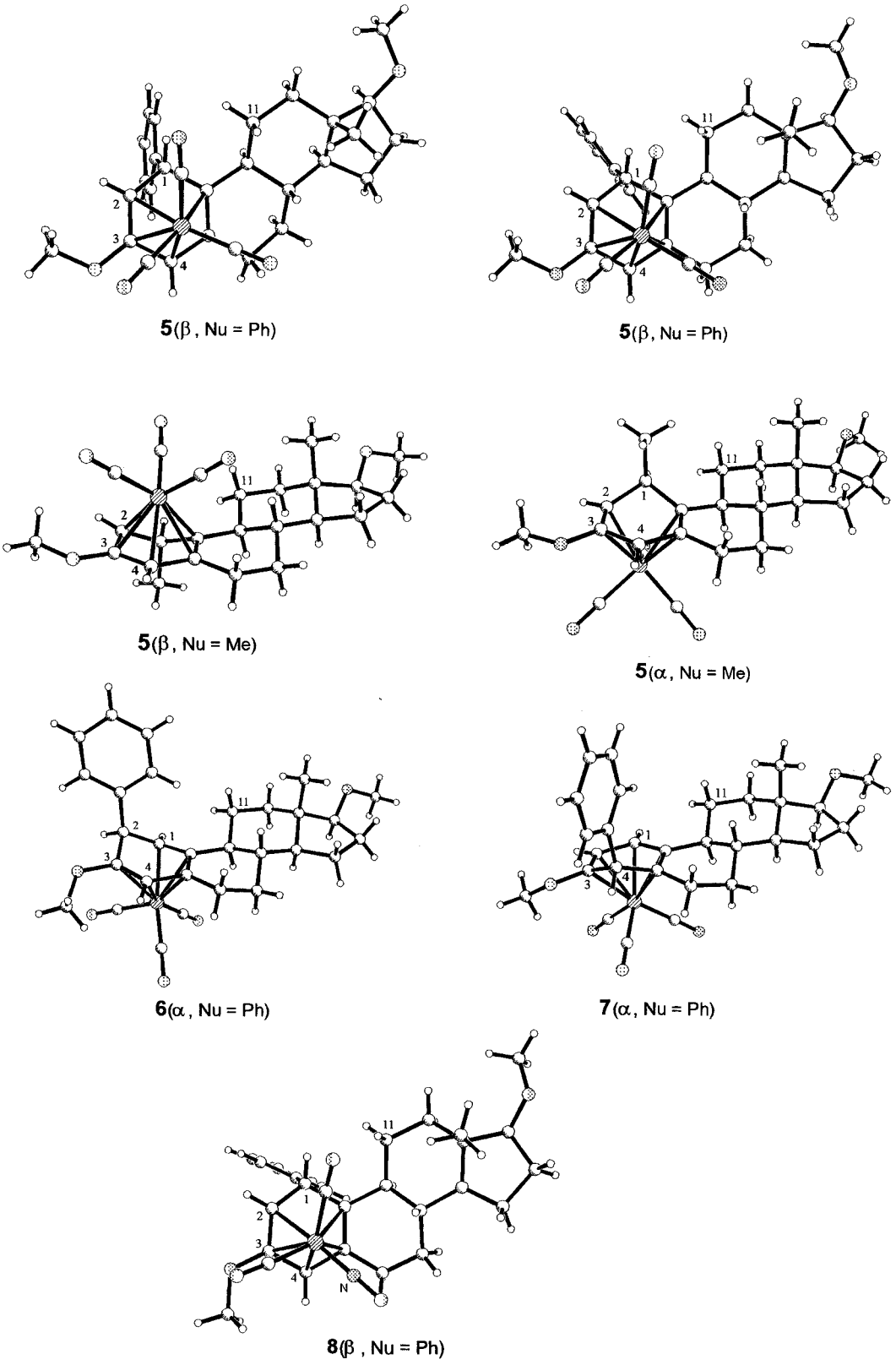


Figure 1. X-ray structures of η^5-cyclohexadienyl complexes derived from nucleophilic addition to (3,17-dimethoxyestradiol)-manganese tricarbonyl cations. The disposition of the metal is indicated by α and *β*.

smaller than in **4**, so that other sites do not compete. Somewhat analogous (and much more obvious) steric arguments obtain for reactions of the manganese tricarbonyl complex of podocarpic acid.[10] Strong evidence in support of the assertion that the methylene group at C-11 provides a steric barrier to nucleophile addition at C-1 when the metal is on the α-side of the steroid is provided by the observation[11] that PhMgBr addition to the 3-methoxytetrahydronaphthalene complex **11** gave

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Table 1. Summary of Crystal Structure Data for Estradiol Complexes 5−8[a]

	5(β, Nu = Ph)	**5**(β, Nu = Me)	**5**(α, Nu = Me)	**6**(α, Nu = Ph)	**7**(α, Nu = Ph)	**8**(β, Nu = Ph)
formula	$C_{29}H_{33}O_5Mn$	$C_{24}H_{31}O_5Mn$	$C_{24}H_{31}O_5Mn$	$C_{29}H_{33}O_5Mn$	$C_{29}H_{33}O_5Mn$	$C_{29}H_{35}Cl_2F_6NPO_5Mn$
fw	516.49	454.43	454.43	516.49	516.49	748.39
cryst size, mm	0.43 × 0.54 × 0.55	0.53 × 0.70 × 0.92	0.40 × 0.42 × 0.58	0.56 × 0.44 × 0.15	0.37 × 0.41 × 0.60	0.30 × 0.32 × 0.71
space group	$P2_12_12_1$, orthorhombic	$P2_12_12_1$, orthorhombic	$P2_12_12_1$, orthorhombic	$P2_12_12_1$, orthorhombic	$P2_12_12_1$, orthorhombic	$P2_1$, monoclinic
a, Å	7.8110(10)	7.7282(8)	10.4718(14)	7.663(3)	12.1248(10)	11.553(2)
b, Å	14.5220(10))	8.6301(12)	14.4003(14)	8.6007(11))	12.2379(14)	11.726(2)
c, Å	46.035(11)	34.397(4)	15.1733(11)	40.221(8)	17.680(2)	12.324(2)
β, deg						99.238(14)
V, Å^3	5222(2)	2294.1(5)	2288.1(4)	2651.0(12)	2623.4(4)	1647.8(5)
Z	8	4	4	4	4	2
ρ_{calcd}, g cm^{-3}	1.314	1.316	1.319	1.294	1.308	1.508
μ, mm^{-1}	0.542	0.606	0.608	0.534	0.539	0.684
θ range, deg	1.77−25.01	2.37−29.98	1.95−24.99	2.03−24.99	2.02−27.49	1.79−25.01
rflns collected	6640	4831	2962	3619	4239	3892
no. of indep rflns	6326	4568	2777	3362	4028	3364
no. of variables	631	275	271	319	317	406
*R*1 ($I > 2\sigma(I)$)	0.0535	0.0394	0.0440	0.0620	0.0382	0.0519
w*R*2 ($I > 2\sigma(I)$)	0.1330	0.0892	0.1011	0.1278	0.0820	0.1321
GOF on F^2	1.000	0.880	0.930	0.794	0.878	1.042

[a] The disposition of the manganese is indicated by α ("down") or β ("up").

Table 2. Spectroscopic Data for Steroid Complexes 5−10

compd[a]	"Nu"	ν_{CO} (cm^{-1})[b]	^{1}H NMR (δ (ppm), *J*(Hz))[c]
5(β)	Ph	2012, 1937, 1929	7.3−6.9 (m, Ph), 5.53 (d, *J* = 2.5, H^4), 4.24 (d, *J* = 6, H^1), 3.44 (OMe^{20}), 3.33 (dd, *J* = 6, 2.5, H^2), 3.28 (OMe^{19}), 3.15 (t, *J* = 8, H^{17}), 0.82 (Me^{18})
5(β)	Me	2010, 1935, 1925	5.51 (d, *J* = 2, H^4), 3.46 (OMe^{20}), 3.31 (OMe^{19}), 3.22 (t, *J* = 8, H^{17}), 3.06 (m, H^{1,2}), 0.81 (Me^{18}), 0.45 (d, *J* = 6, Me^1)
5(α)	Me	2010, 1935, 1925	5.48 (d, *J* = 2.5, H^4), 3.46 (OMe^{20}), 3.29 (OMe^{19}), 3.20 (t, *J* = 8, H^{17}), 3.10 (dd, *J* = 6, 2.5, H^2), 3.05 (m, *J* = 6, H^1), 0.69 (Me^{18}), 0.47 (d, *J* = 6, Me^1)
6(α)	Ph	2006, 1933, 1919	7.3−7.0 (m, Ph), 4.27 (dd, *J* = 6, 1.5, H^2), 4.11 (d, *J* = 1.5, H^4), 3.44 (d, *J* = 6, H^1), 3.28 (OMe^{19}), 3.22 (t, *J* = 8, H^{17}), 0.74 (Me^{18})
6(α)	Me	2004, 1928, 1915	3.92 (d, *J* = 1.2, H^4), 3.38 (OMe^{20}), 3.30 (OMe^{19}), 3.17 (t, *J* = 8, H^{17}), 0.80 (Me^{18}), 0.60 (d, *J* = 6, Me^2)
7(α)	Ph	2006, 1933, 1919	7.3−7.0 (m, Ph), 5.49 (d, *J* = 6, H^1), 4.21 (m, H^{2,4}), 3.36 (OMe^{20}), 3.30 (OMe^{19}), 3.24 (t, *J* = 8, H^{17}), 0.71 (Me^{18})
7(α)	Me	2004, 1927, 1917	5.44 (d, *J* = 6, H^1), 4.07 (dd, *J* = 6, 2, H^2), 3.36 (OMe^{20}), 3.30 (OMe^{19}), 3.24 (t, *J* = 8, H^{17}), 3.05 (dq, *J* = 6, 2, H^4), 0.77 (Me^{18}), 0.63 (d, *J* = 6, Me^2)
8(β)	Ph	2099, 2058, 1823[d]	7.4−6.9 (m, Ph), 6.53 (d, *J* = 2.5, H^4), 4.46 (d, *J* = 5, H^1), 4.20 (H^2), 3.90 (OMe^{20}), 3.28 (OMe^{19}), 3.18 (t, *J* = 8, H^{17}), 0.81 (Me^{18})
8(β)	Me	2097, 2058, 1819[d]	6.81 (d, *J* = 3, H^4), 4.32 (m, H^2, Me^{20}), 3.53 (q, *J* = 6, H^1), 3.28 (OMe^{19}), 3.28 (t, *J* = 8, H^{17}), 0.85 (d, *J* = 6, Me^1), 0.81 (Me^{18})[e]
9(β)		2027, 1968, 1724	7.3−7.1 (m, Ph), 5.71 (H^4), 3.66 (dd, *J* = 11, 3, H^1), 3.32 (OMe^{20}), 3.26 (OMe^{19}), 3.19 (t, *J* = 8, H^{17}), 2.66 (dd, *J* = 14, 11, H^{2-endo}), 0.69 (Me^{18})
10(β)		2027, 1975, 1742	7.3−7.1 (m, Ph), 5.40 (d, *J* = 2.5, H^4), 3.52 (OMe^{20}), 3.48 (dd, *J* = 10, 4, H^1), 3.38 (m, *J* = 4, 2.5, H^2), 3.16 (OMe^{19}), 3.01 (t, *J* = 8, H^{17}), 2.26 (t, *J* = 10, H^{10}), 0.63 (Me^{18})

[a] The disposition of the manganese is indicated by α ("down") or β ("up"). [b] IR in hexanes unless otherwise indicated. [c] In CD_2Cl_2 at 250 MHz unless otherwise indicated. [d] In CH_2Cl_2. [e] In CD_3COCD_3.

Table 3. Isomer Ratios Obtained from Nucleophilic Addition to a 1:1 Mixture of [3,4]BF$_4$[a]

nucleophile	**5**(α)	**5**(β)	**6**(α)	**6**(β)	**7**(α)	**7**(β)
$LiCH_2C(O)CMe_3$[b]	3	4				
$NaBH_4$[b]	3	4				
MeMgCl or MeLi	3	10	2		2	
PhMgBr or PhLi		10	4		3	

[a] The disposition of the metal is indicated by α ("down") or β ("up"). [b] From ref 5.

as the *sole* product the isomer arising from attack on C-1 (**12**). In this case, of course, there is no C-11 to provide a steric barrier.

The reaction of **5**(β, Nu = Me, Ph) with $NOPF_6$ resulted in essentially quantitative conversion to complex **8**. As is the case with simple cyclohexadienyl analogues,[7,12] **8** (Nu = Ph) was found to be quite electrophilic and to react rapidly with $NaBH_4$ to afford a 1:1 mixture of the diene complexes **9** and **10**.

In order to demonstrate the feasibility of manganese-mediated functionalization of aromatic steroids, the known[13] 1-methylestrone was synthesized from 3-methoxyestrone by the procedure outlined in Figure 2. This procedure is easily accomplished and, due to cost considerations, is an attractive alternative to purchasing the product (3-methoxyestrone, $20/g; 1-methylestrone, $45/5 mg[14]). The synthesis involves a series of simple and moderate- to high-yield steps: (1) protection of the C-17 ketone group (96%), (2) coordination of $Mn(CO)_3^+$ by an exchange reaction[15] with (acenaphthene)Mn(CO)$_3^+$ (85%), (3) nucleophilic addition of a methyl group to give a mixture of α-1-methyl- and β-1-methyl cyclohexadienyl products (72%), (4) removal of the ethylene ketal protecting group (93%), (5) removal of the metal and rearomatization (95%), and (6) demethylation of the

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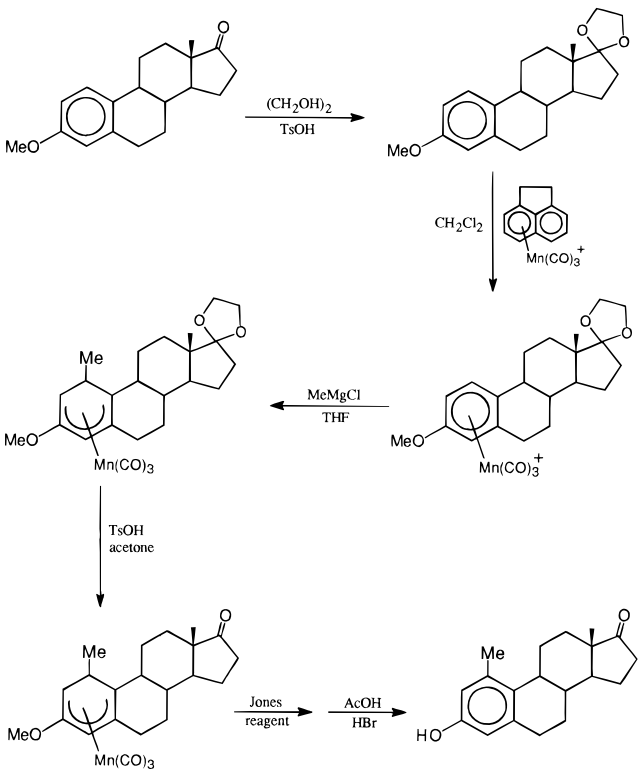

Figure 2. Steps in the manganese-mediated synthesis of 1-methylestrone.

3-methoxy group (80%). Overall, the conversion of 3-methoxyestrone to 1-methylestrone occurred in 42% yield. A similar procedure afforded 1-phenylestrone in 29% yield.

Experimental Section

General Comments. The manganese tricarbonyl complexes of 3-methoxyestrone and of 3,17-dimethoxyestradiol (**3** and **4**) were prepared as BF_4^- salts as previously described.[5] The α:β product ratio of the estradiol complex was found to be 1:1. Attempted separation of the diastereomeric BF_4^- salts by fractional crystallization was not successful, although the PF_6^- salts were readily separated by fractional crystallization from CH_2Cl_2/Et_2O.

X-ray structural studies of complexes **5**−**8** were carried out with a Siemens P4 single-crystal diffractometer controlled by XSCANS version 2.1 software. Data were collected at 25 °C with Mo Kα radiation. The structures were determined by direct methods and refined initially by use of programs in the SHELXTL PC version 5.1 package. Final refinements based on F^2 were carried out using SHELXL 93. In all of the structures half or more of the hydrogen atoms appeared in a difference map, and each was introduced in an ideal position, riding on the atom to which it is bonded and refined with an isotropic temperature factor 20% greater than that of the ridden atom. All other atoms were refined with anisotropic thermal parameters. Details of the structures are given in Table 1 and in the Supporting Information.

Nucleophilic Addition to Complex (3, 4). The addition of a phenyl group to a 1:1 isomeric mixture of **3** and **4** was achieved with both PhMgBr and PhLi as the nucleophilic reagent. A typical procedure is as follows: PhLi (0.65 mmol of a 1.8 M solution in 70:30 cyclohexane/Et_2O, from Aldrich Chemical Co.) was added to a solution of [**3,4**]BF_4 (0.105 g, 0.20 mmol) in CH_2Cl_2 (35 mL) at −78 °C under nitrogen. The mixture was stirred for 1 h and warmed to room temperature. After filtration through a pad of alumina, the solvent was stripped and the oily yellow residue chromatographed on deactivated neutral alumina with 10:1 hexanes/Et_2O. A broad yellow band was collected, the solvent evaporated, and the resulting yellow solid vacuum-dried. IR and ^{1}H NMR spectra indicated that the product consisted of four isomers, in a combined yield of 92%. Three of the isomers (constituting 84% yield) were separated from the fourth one by TLC on silica gel with 3:1 Et_2O/CH_2Cl_2. A subsequent TLC with 10:1 petroleum ether/Et_2O effected separation of the three isomers in the ratio 10:4:3, which were definitively assigned the structures **5**(β, Nu = Ph), **6**(α, Nu = Ph), and **7**(α, Nu = Ph), respectively, based on IR, ^{1}H NMR, and X-ray analyses. (Crystals were grown from hexane solutions.) See Table 2 for spectroscopic details. The fourth isomer was not characterized beyond its IR spectrum: ν_{CO} (hexanes) 2022, 1956, 1929 cm^{-1}.

The addition of a methyl group to **3,4** was successful using either MeMgCl or MeLi and following a procedure very similar to that described above for PhMgBr addition. With MeMgCl, the initial product mixture consisted of a 78% yield of ring addition products and 16% of the product of attack at CO (ν_{CO} (hexanes) 1960, 1906, 1614 cm^{-1}). The latter was separated from the former by chromatography on deactivated neutral alumina using 1:5 hexanes/Et_2O. TLC with 9:1 petroleum ether/Et_2O separated **7**(α, Nu = Me) from the other three isomers, which in turn were individually separated by fractional crystallization from hexanes. ^{1}H NMR and IR were used to assign structures to the four isomeric products, two of which were characterized by X-ray analysis of single crystals grown from hexane.

Synthesis and Reactions of Complex 8. To a solution of **5** (β, Nu = Ph) (0.32 g, 0.63 mmol) in CH_2Cl_2 (6 mL) was added $NOPF_6$ (0.115 g, 0.66 mmol) with stirring under argon. The reaction flask was capped, and after 30 min the mixture was filtered through celite and the solvent stripped. The residue was extracted with CH_2Cl_2, and the extract was filtered and treated with diethyl ether to precipitate the product [**8**(Nu = Ph)]PF_6 in quantitative yield. ^{1}H NMR and IR spectra (Table 2) indicated that the product was pure. The X-ray structure of a crystal grown from CH_2Cl_2 verifed the proposed structure. The reaction of **5**(β, Nu = Me) with $NOPF_6$ gave the corresponding salt [**8**(Nu = Me)]PF_6 in quantitative yield. Complexes **9** and **10** were synthesized by adding excess $NaBH_4$ (0.058 g, 1.5 mmol) to [**8**]PF_6 (β, Nu = Ph) (0.051 g, 0.076 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 20 min and filtered through a pad of neutral alumina and the solvent stripped. Chromatography through deactivated neutral alumina with 3:1 hexanes/Et_2O afforded a deep orange oil in 88% yield that was shown by IR and ^{1}H NMR spectroscopy to be a 1:1 mixture of isomers **9** and **10**. Separation of the two isomers was accomplished by TLC under nitrogen with 10:1 hexanes/Et_2O.

Synthesis of 1-Methylestrone and 1-Phenylestrone. The synthesis of 1-methylestrone[13] follows the procedure outlined in Figure 2. The ketone group in 3-methoxyestrone (Sigma Chemical Co.) was protected by conversion to the ethylene ketal (96% yield) as described in the literature.[16,17] Coordination of manganese tricarbonyl was accomplished by a recently reported exchange procedure.[15] Thus, the protected estrone (0.432 g, 1.32 mmol) and [(acenaphthene)$Mn(CO)_3$]BF_4 (0.500 g, 1.32 mmol) in CH_2Cl_2 (15 mL) were heated at 70 °C for 4 h in a sealed tube. The mixture was cooled to room temperature and filtered through Celite and the solution concentrated. Addition of diethyl ether precipitated the product as a yellow powder in 85% yield. A methyl group was added by treating the manganese estrone complex (0.500 g, 0.903 mmol) in THF (40 mL) at −78 °C with MeMgCl (0.50

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mL of 3.0 M solution in THF). After the mixture was warmed to room temperature and stirred for 30 min, any excess MeMgCl was quenched with a few drops of water, and the mixture was filtered through neutral alumina. After solvent removal, the residue was extracted with Et_2O and chromatographed on neutral alumina with 1:1 Et_2O/hexanes. Further separation by TLC using 7:1 hexanes/Et_2O afforded a 72% yield of a mixture of α-1-methyl- and *β*-1-methylcyclohexadienyl products. Next, the ethylene ketal protecting group was removed in 93% yield by the standard procedure[18] of stirring the complex for 24 h at room temperature in acetone (20 mL) containing *p*-toluenesulfonic acid (70 mg). Flash chromatography on neutral alumina with 1:3 diethyl ether/hexanes afforded the pure product. Removal of the metal and rearomatization to afford 1-methyl-3-methoxyestrone was readily accomplished (95% yield) with Jones reagent by a procedure we previously described.[8] Finally, demethylation of 1-methyl-3-methoxyestrone was achieved according to a published procedure[19] by treatment with glacial acetic acid and HBr. Chromatography on neutral alumina with 1:3 ethyl acetate/hexanes gave 1-methylestrone as the final product in 80% yield. Overall, the manganese-mediated conversion of 3-methoxyestrone to 1-methylestrone[13] took place with 42% conversion. ^{1}H NMR ($CDCl_3$): δ 6.50 (d, J = 2.6 Hz, H^2), 6.44 (d, J = 2.5 Hz, H^4), 2.30 (s, Me^1), 0.96 (s, Me^{18}). An essentially identical procedure was used to convert 3-methoxyestrone to 1-phenylestrone in an overall yield of 29%. ^{1}H NMR (CD_2Cl_2): δ 7.5−7.1 (m, Ph), 6.57 (d, J = 2.5 Hz, H^2), 6.51 (d, J = 2.5 Hz, H^4), 0.81 (s, Me^{18}).

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Supporting Information Available: Figures giving additional views and tables of positional and thermal parameters, bond distances and angles, and data collection parameters for **5**(*β*, Nu = Ph), **5**(*β*, Nu = Me), **5**(α, Nu = Me), **6**(α, Nu = Ph), **7**(α, Nu = Ph), and **8**(*β*, Nu = Ph) (68 pages). Ordering information is given on any current masthead page.

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