The synthesis and reactions of A-ring aromatic steroid complexes of manganese tricarbonyl

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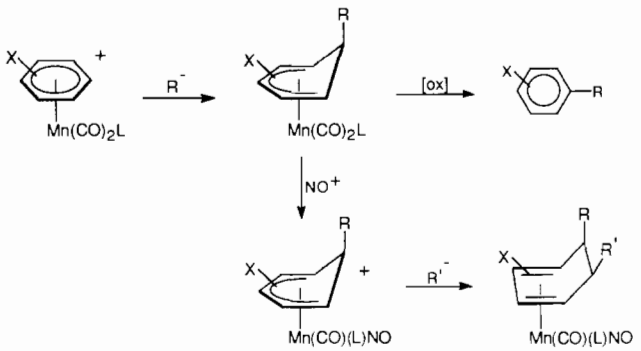
Abstract

Treatment of the A-ring aromatic steroids estrone 3-methyl ether and β-estradiol 3,17-dimethyl ether with $Mn(CO)_5^+BF_4^-$ in CH_2Cl_2 yields the corresponding $[(steroid)Mn(CO)_3]BF_4$ salts **1** and **2** as mixtures of α and β isomers. The X-ray structure of $[(estrone\ 3\text{-}methyl\ ether)Mn(CO)_3]BF_4 \cdot CH_2Cl_2$ (**1**) having the $Mn(CO)_3$ moiety on the α side of the steroid is reported: space group $P2_1$ with $a = 10.3958(9)$, $b = 10.9020(6)$, $c = 12.6848(9)$ Å, $\beta = 111.857(6)°$, $Z = 2$, $V = 1334.3(2)$ Å^3, $\rho_{calc} = 1.481$ cm^{-3}, $R = 0.0508$, and $wR = 0.0635$. The molecule has the traditional 'piano stool' structure with a planar arene ring and linear Mn–C–O linkages. The nucleophiles $NaBH_4$ and $LiCH_2C(O)CMe_3$ add to $[(\beta\text{-}estradiol\ 3,17\text{-}dimethyl\ ether)Mn(CO)_3]BF_4$ (**2**) in high yield to give the corresponding α- and β-cyclohexadienyl manganese tricarbonyl complexes (**3**). The nucleophiles add *meta* to the arene –OMe substituent and *exo* to the metal. The α and β isomers of **3** were separated by fractional crystallization and the X-ray structure of the β isomer with an *exo*-$CH_2C(O)CMe_3$ substituent is reported (complex **4**): space group $P2_12_12_1$ with $a = 7.5154(8)$, $b = 15.160(2)$, $c = 25.230(3)$ Å, $Z = 4$, $V = 2874.4(5)$ Å^3, $\rho_{calc} = 1.244$ g cm^{-3}, $R = 0.0529$ and $wR2 = 0.1176$. The molecule **4** has a planar set of dienyl carbon atoms with the saturated C(1) carbon being 0.592 Å out of the plane away from the metal. The results suggest that the manganese-mediated functionalization of aromatic steroids is a viable synthetic procedure with a range of nucleophiles of varying strengths.

Key words: Crystal structures; Steroid complexes; Manganese complexes; Estrone complexes; Estradiol complexes

Introduction

The activation of unsaturated organic molecules by coordination to transition metals is a well established phenomenon. In particular, arenes can be activated in this manner to nucleophilic attack, thereby providing synthetically useful routes to functionalized arenes and cyclohexadienes. The best known [1, 2] precursors to such chemistry are the complexes $(arene)Cr(CO)_3$ and $(arene)FeCp^+$. An alternative system is $(arene)Mn(CO)_3^+$, which is especially attractive because of the mild conditions required for attachment of the arene to the metal, the superior electrophilic activation that results [3], and the rapid and clean regio- and stereoselective reaction that occurs with a wide range of nucleophilic reagents [4–7]. Scheme 1 summarizes the relevant manganese-mediated chemistry. Most arenes can be coordinated to $Mn(CO)_3^+$ in moderate to high yield by simply adding the arene to $Mn(CO)_5^+BF_4^-$ in CH_2Cl_2 (made *in situ* from $Mn(CO)_5Br$ and $AgBF_4$) and gently warming the reaction mixture. Nucleophilic addition followed by oxidative cleavage of the metal affords the functionalized arene. This procedure is the basis for the recently reported synthesis of 2-arylpropionic acids, antibiotic stilbenes and arylglycine methyl esters [8, 9]. It also appears [7] that the carbocyclic ring in indoles can be functionalized in this manner.



Scheme 1.

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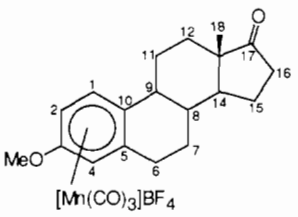
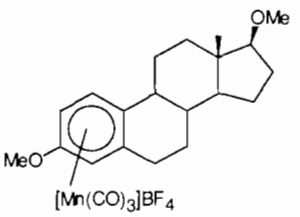
Instead of oxidative cleavage of the neutral cyclohexadienyl complex in Scheme 1, it is possible to replace a CO with NO^+ to give a 'reactivated' species that adds a second nucleophile (R'^-) to afford *cis*-disubstituted cyclohexadiene complexes [6, 10]. This chemistry has been utilized in the synthesis of the sesquiterpene (+)-juvabione [11].

In this paper we are concerned with the coordination of $Mn(CO)_3^+$ to A-ring aromatic steroids. It is shown that steroids based on estrone and β-estradiol readily coordinate to $Mn(CO)_3^+$ to give complexes that undergo high yield regio- and stereoselective attack on the arene ring by nucleophiles. It is anticipated from these results that the chemistry in Scheme 1 can be employed in the synthesis of a wide range of steroid derivatives, including ones arising from diterpene precursors [12].



1



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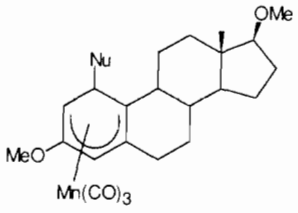

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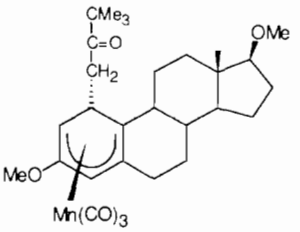

4

Compounds **1–4** are typical of those discussed herein. X-ray structures are reported for [(estrone 3-methyl ether)$Mn(CO)_3$]BF_4 (**1**) and for the dienyl complex **4** obtained from nucleophilic addition of $LiCH_2C(O)CMe_3$ to [(β-estradiol 3,17-dimethyl ether)$Mn(CO)_3$]BF_4 (**2**).

The steroids estrone and β-estradiol have previously been complexed to $M(CO)_3$ (M = Cr, Mo, W), $RuCp^+$ and $Co_2(CO)_6$ [13–17]. In these studies it was shown that coordination activates the benzylic sites to deprotonation [14] and activates the aromatic ring to nucleophilic displacement of a chloride substituent [15]. Interestingly, it has been suggested [17] that certain estradiol complexes of $Cr(CO)_3$ may be useful (via FT-IR) as indicators of steroid hormone receptor level variations, which are associated with some cancers. For the reasons mentioned above, we believe that the coordination of manganese to aromatic steroids may prove to be especially useful for regio- and stereoselective functionalization via nucleophilic addition and/or deprotonation/electrophile addition at benzylic sites [18].

Experimental

Synthesis of steroid complexes 1 and 2

$AgBF_4$ (0.514 g, 2.64 mmol) was added to $Mn(CO)_5Br$ (0.628 g, 2.29 mmol) in 60 ml of CH_2Cl_2 under argon and in the dark. The reaction mixture was refluxed for 30 min and cooled to room temperature. Estrone 3-methyl ether (0.453 g, 1.59 mmol) was then added and the mixture refluxed for 16 h. After filtration through Celite, the solvent was removed to leave a yellow oil that was dissolved in acetone. Precipitation with diethyl ether afforded a yellow solid that was dried in a vacuum dessicator. IR and ^1H NMR indicated a pure product (51% yield) consisting of a mixture of α and β isomers of **1** in the ratio of 1.0:1.5, respectively. (Note: 'α' refers to the structure having the $Mn(CO)_3$ on the side of the steroid opposite to that of the 18-methyl while the 'β' structure has the $Mn(CO)_3$ on the same side as the 18-methyl). The α and β isomers were separated by fractional crystallization from $CH_2Cl_2/Et_2O/C_6H_6$, which initially produced a pale yellow solid that ^1H NMR showed to be a pure single isomer; single crystals were grown from this solid, which was shown by X-ray analysis to have the α structure (*vide infra*). Spectroscopic data are given in Table 1.

To synthesize complex **2**, β-estradiol was first methylated to β-estradiol 3,17-dimethyl ether as follows [19]. A solution of β-estradiol (0.50 g, 1.8 mmol) in 10 ml of dry THF was added dropwise and with stirring to an ice cold suspension of NaH (0.130 g, 5.4 mmol) in 40 ml of THF under N_2. The mixture was heated for 19 h at just below the reflux temperature and then cooled in an ice bath. Excess CH_3I (1.5 ml) was added dropwise and the mixture refluxed for 24 h, cooled in an ice bath and quenched with water (4 ml). After extraction with diethyl ether, the aqueous layer was discarded and the organic layer dried over $MgSO_4$. Filtration and evaporation to dryness afforded a solid residue that was chromatographed on silica gel using hexanes/ethyl acetate (5:1) as the eluant. The product was recrystallized from hexanes/ethyl acetate (5:1) and dried *in vacuo* to give β-estradiol 3,17-dimethyl ether in 94% yield. ^1H NMR indicated that the product was pure. Metallation was achieved by adding the steroid (0.303 g, 1.0 mmol) in 7 ml of CH_2Cl_2 to a solution of $Mn(CO)_5^+BF_4^-$ (made as described above from 0.292 g $AgBF_4$ and 0.357 g $Mn(CO)_5Br$ in 40 ml of CH_2Cl_2) and refluxing for 16 h under N_2. Filtration through Celite and evaporation yielded a yellow oil. Precipitation from acetone with diethyl ether afforded a yellow powder that IR and ^1H NMR showed to be

TABLE 1. Characterization of complexes **1–4**

Compound[a]	Nucleophile (Nu)	
1(α)	none	IR (CH_2Cl_2): 2072, 2006; 1738 cm^{-1}; ^1H NMR (d^6-acetone): δ 7.34 (d, J=9, H^1), 6.38 (m, H^2, H^4), 4.15 (s, OMe), 0.92 (s, Me^{18})
1(β)	none	IR (CH_2Cl_2): 2072, 2006, 1738 cm^{-1}; ^1H NMR (d^6-acetone): δ 7.20 (d, J=8, H^1), 6.23 (dd, J=2.5, 8, H^2), 6.43 (d, J=2.5, H^4), 4.20 (s, OMe), 0.97 (s, Me^{18})
2(α)[b]	none	IR (CH_2Cl_2): 2070, 2006 cm^{-1}; ^1H NMR (d^6-acetone): δ 7.30 (d, J=7, H^1), 6.35 (m, H^2, H^4), 4.13 (s, OMe^{20}), 3.29 (s, OMe^{19}), 0.79 (s, Me); ^1H NMR (CD_2Cl_2): 6.87 (d, J=7, H^1), 6.10 (d, J=7, H^2), 5.93 ((H^4), 4.03 (s, OMe^{20}), 3.31 (s, OMe^{19}), 0.76 (s, Me^{18})
2(β)[b]	none	IR (CH_2Cl_2): 2070, 2006 cm^{-1}; ^1H NMR (d^6-acetone): δ 7.17 (d, J=7, H^1), 6.19 (d, J=7, H^2), 6.38 (H^4), 4.18 (s, OMe^{20}), 3.31 (s, OMe^{19}), 0.84 (s, Me); ^1H NMR (CD_2Cl_2): 6.77 (d, J=7, H^1), 5.96 (H^2), 5.93 (H^4), 4.06 (s, OMe^{20}), 3.32 (s, OMe^{19}), 0.81 (s, Me^{18})
3(α)	$CH_2C(O)CMe_3$[c]	IR (CH_2Cl_2): 2008, 1925, 1701 cm^{-1}; IR (hexanes): 2012, 1939, 1927, 1709 cm^{-1}; ^1H NMR (CD_2Cl_2): δ 5.50 (d, J=2.5, H^4), 3.5 (H^1), 3.39 (s, OMe^{20}), 3.28 (s, OMe^{19}), 3.21 (m, J=8, H^{17}), 3.17 (H^2), 1.00 (s, CMe_3), 0.67 (s, Me^{18})
4 (**3**β)	$CH_2C(O)CMe_3$[c]	IR (CH_2Cl_2): 2008, 1925, 1701 cm^{-1}; IR (hexanes): 2014, 1939, 1927, 1709 cm^{-1}; ^1H NMR (CD_2Cl_2): δ 5.52 (d, J=2.5, H^4), 3.47 (m, H^1), 3.39 (s, OMe^{20}), 3.31 (s, OMe^{19}), 3.21 (t, J=8, H^{17}), 3.11 (dd, J=2.5, 6, H^2), 1.00 (s, CMe_3), 0.81 (s, OMe^{18})
3(α)[b]	H[d]	IR (CH_2Cl_2): 2006, 1921 cm^{-1}; IR (hexanes): 2012, 1935, 1925 cm^{-1}; ^1H NMR (CD_2Cl_2): δ 5.58 (d, H^4), 3.48 (s, OMe^{20}), 3.28 (s, OMe^{19}), 2.3 (d, J=12, H^{1-exo}), 0.66 (s, Me^{18})
3(β)	H[d]	IR (CH_2Cl_2): 2006, 1921 cm^{-1}; IR (hexanes): 2012, 1937, 1925 cm^{-1}; ^1H NMR (CD_2Cl_2): δ 5.57 (d, J=2.5, H^4), 3.46 (s, OMe^{20}), 3.31 (s, OMe^{19}), 3.22 (t, J=8, H^{17}), 2.97 (q, J=6, 12, H^{1-endo}), 2.88 (dd, J=2.5, 6, H^2), 2.11 (d, J=13, H^{1-exo}), 0.81 (s, Me^{18})

[a]The disposition of the $Mn(CO)_3$ moiety is indicated by α or β. [b]The sample consisted of a mixture of α and β isomers. [c]Added as the lithium salt. [d]Added as $NaBH_4$.

pure **2** with an α:β isomeric ratio of 1:1. Table 1 provides relevant spectroscopic data. The yield of **2** was 91% (satisfactory elemental analysis was obtained). Unlike the case with **1**, an appropriate solvent medium was not found that allowed separation of the α and β isomers of **2** by fractional crystallization.

Nucleophilic addition to [(β-estradiol 3,17-dimethyl ether)Mn(CO)$_3$]BF$_4$ (2)

Nucleophilic reagents were found to react rapidly with **2**. In this paper, the reactions with the H-donor $NaBH_4$ and the ketone enolate $LiCH_2C(O)CMe_3$ are described; the chemistry that obtains with other nucleophiles is under study [20]. A typical procedure is as follows. Complex **2** (0.107 g, 0.203 mmol) in 30 ml of CH_2Cl_2 under argon was cooled to −78 °C and treated with 4 ml of a *c.* 0.1 M solution of $LiCH_2C(O)CMe_3$ in THF (made by deprotonation of pinacolone with lithium diisopropylamide in THF at −78 °C). The reaction mixture was stirred for 30 min and warmed to room temperature. After filtration through a pad of alumina, the solvent was stripped and the residue chromatographed on deactivated neutral alumina with hexanes/diethyl ether (10:1). A broad yellow band was collected, the solvent evaporated, and the resulting yellow solid vacuum dried. IR and ^1H NMR indicated that the product (**3**) consisted of a clean mixture of two isomers, tentatively identified as the α and β isomers of **3**. The combined yield was 86%. The isomers were separated by fractional crystallization from CH_2Cl_2/hexanes and also by TLC on silica gel using petroleum ether/diethyl ether (7:1). An X-ray structure of one of the isomers (**4**) defined the stereochemistry (*vide infra*). See Table 1 for spectroscopic data (satisfactory elemental analysis was obtained).

Complex **3** (Nu = H) was synthesized by adding excess $NaBH_4$ to **2** (0.200 g, 0.38 mmol) in 30 ml of THF under argon at room temperature. The mixture was stirred for 30 min and the solvent evaporated. The product was extracted with diethyl ether and filtered through a pad of alumina. The solvent was then stripped and the residue chromatographed on deactivated neutral alumina with petroleum ether/CH_2Cl_2 (3:1). Further purification by TLC with petroleum ether/diethyl ether (5:1) afforded a mixture of two isomers of **3** (α and β). Fractional crystallization from hexanes successfully separated the two isomers, which were individually assigned via ^1H NMR in analogy to the known stereochemistry of **3** (Nu = $CH_2C(O)CMe_3$). The combined

yield was 87%. Spectroscopic details are provided in Table 1.

X-ray structure of 1 and 4

Crystals of **1** were grown from the single isomer obtained from fractional crystallization of a mixture of α and β isomers (*vide supra*) by dissolving *c.* 25 mg in 2 ml of CH_2Cl_2, adding 5 drops of benzene and then adding diethyl ether until a slight trace of cloudiness (precipitation) appeared. This solution was then cooled to 5 °C for 10 days. The crystals that formed were observed to slowly fracture in the absence of solvent, so the crystal selected for X-ray analysis was sealed in a capillary along with some mother liquor. The X-ray data were collected at 298 K with a Siemens P4 diffractometer. Solution was via Patterson methods and least-squares refinements were carried out using SHELXTL PC version 4.2 software. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in theoretical positions with a C–H bond length of 0.96 Å and with a thermal parameter equal to 1.2 times the equivalent isotropic value at the attached carbon. Refinement quickly showed that each molecule of **1** crystallized with one molecule of solvent CH_2Cl_2. The final difference Fourier map contained no significant residual electron density peaks or holes. Tables 2–4 and Figs. 1 and 2 give structural information for $\mathbf{1}\cdot CH_2Cl_2$.

A crystal of **4** was grown by dissolving *c.* 30 mg in 0.5 ml of CH_2Cl_2, adding 5 ml of hexanes, and cooling to −15 °C for two days. A large single crystal formed, which was cut to an appropriate size and glued to the end of a glass fiber. X-ray data collection and subsequent data treatment were analogous to that described for **1**, except that the SHELXL-93 program [21] was utilized, which performs the refinements with F^2 rather than F. The refinement went smoothly, with no significant residual electron density peaks or holes present in the final difference Fourier map. Tables 2, 5 and 6 and Figs. 3 and 4 give structural information for **4**.

Results and discussion

Complexes **1** and **2** were easily synthesized by simply warming the steroid with a CH_2Cl_2 solution of $Mn(CO)_5{}^+BF_4{}^-$, which itself was readily prepared *in situ* by treating $Mn(CO)_5Br$ with $AgBF_4$. Complexation of the $Mn(CO)_3{}^+$ moiety to estrone 3-methyl ether was found to occur on both sides of the steroid, with a slight preference for the β face (α:β ratio 1:1.5), whereas there was no discrimination between α and β coordination with β-estradiol 3,17-dimethyl ether. By way of comparison, $RuCp^+$ was reported [15] to give an α:β ratio of 7:3 for coordination to estrone 3-methyl ether, while $RhCp^{*2+}$ prefers the α face in estradiol by a 7:1 ratio [22]. $Cr(CO)_3$ was found [23] to coordinate with equal facility (α:β ratio 1:1) to β-estradiol derivatives.

We were not able to separate the α and β isomers of **2** or grow crystals of either suitable for X-ray studies. However, the isomers of the estrone analogue (**1**) could

TABLE 2. Summary of crystal structure data for complexes **1** and **4**

Formula	$C_{23}H_{26}BCl_2F_4MnO_5$	$C_{29}H_{39}MnO_6$
Formula weight	595.1	538.6
Space group	$P2_1$, monoclinic	$P2_12_12_1$, orthorhombic
Crystal dimensions, mm	0.41 × 0.74 × 1.10	0.75 × 0.81 × 0.90
Scan type	ω	ω
a (Å)	10.3958(9)	7.5154(8)
b (Å)	10.9020(6)	15.160(2)
c (Å)	12.6848(9)	25.230(3)
β (°)	111.857(6)	90
V (Å^3)	1334.3(2)	2874.4(5)
Z	2	4
ρ_{calc} (g cm^{-3})	1.481	1.244
F(000)	608	1144
Radiation (Å)	Mo Kα, 0.71073	Mo Kα
μ (cm^{-1})	7.54	4.97
2θ Limits (°)	3.5–55.0	4.2–55.0
Reflections collected	3288	4750
Independent reflections	3121	4510
No. variables	326	326
R[a]	0.0508 ($F > 4\sigma(F)$)	0.0529 ($I > 2\sigma(I)$)
wR[b]	0.0635	
$wR2$[c]		0.1176
GOF	1.17[d]	1.04[e]

[a] $R = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma|F_o|$. [b] $wR = [\Sigma w(F_c - F_o)^2/\Sigma w(F_o)^2]^{1/2}$. [c] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4]^{1/2}$. [d] Based on F. [e] Based on F^2.

TABLE 3. Selected atomic coordinates ($\times 10^4$) and isotropic thermal parameters ($\times 10^3$) for 1

	x	y	z	U_{eq}
Mn	2546(1)	10000	9983(1)	38(l)
C(1)	3980(7)	11456(7)	10085(6)	50(3)
C(2)	3196(8)	11278(8)	8957(6)	57(3)
C(3)	1714(9)	11388(8)	8562(6)	54(3)
C(4)	1103(7)	11526(7)	9360(5)	47(2)
C(5)	1933(6)	11758(6)	10531(5)	42(2)
C(6)	1194(7)	12050(8)	11299(6)	52(3)
C(7)	2101(7)	11945(8)	12555(5)	54(3)
C(8)	3500(6)	12606(7)	12776(5)	45(2)
C(9)	4300(6)	11907(7)	12162(5)	42(2)
C(10)	3402(6)	11709(6)	10912(5)	41(2)
C(11)	5694(7)	12511(9)	12334(6)	56(3)
C(12)	6577(8)	12727(10)	13619(7)	70(3)
C(13)	5757(9)	13388(8)	14190(6)	62(3)
C(14)	4409(8)	12706(8)	14001(6)	55(3)
C(15)	3850(10)	13281(11)	14851(7)	83(4)
C(16)	5232(12)	13441(11)	15920(7)	96(5)
C(17)	6380(11)	13479(9)	15476(7)	77(4)
C(18)	5547(11)	14748(8)	13794(7)	78(4)
C(20)	−492(9)	11133(13)	7033(7)	94(4)
C(21)	1607(7)	9252(7)	10777(6)	50(3)
C(22)	1863(8)	8893(8)	8830(7)	49(3)
C(23)	4032(8)	9046(8)	10746(7)	61(3)
O(1)	1035(7)	8812(7)	11286(5)	78(3)
O(2)	1387(6)	8267(6)	8065(5)	69(2)
O(3)	5015(6)	8514(7)	11247(6)	95(3)
O(4)	7597(9)	13568(10)	16046(5)	115(4)
O(5)	1024(6)	11191(7)	7443(4)	74(2)

TABLE 4. Selected bond lengths (Å) and bond angles (°) for 1

Bond lengths			
Mn–C(1)	2.149(8)	Mn-C(2)	2.179(9)
Mn–C(3)	2.265(8)	Mn-C(4)	2.181(7)
Mn-C(5)	2.212(7)	Mn-C(10)	2.207(6)
Mn-C(21)	1.834(8)	Mn-C(22)	1.825(8)
Mn-C(23)	1.815(8)	C(1)–C(2)	1.372(9)
C(1)–C(10)	1.416(11)	C(2)–C(3)	1.437(11)
C(3)–C(4)	1.389(13)	C(3)–O(5)	1.347(8)
C(4)–C(5)	1.436(8)	C(5)–C(6)	1.482(11)
C(5)–C(10)	1.421(8)	C(6)-C(7)	1.524(9)
C(7)–C(8)	1.552(10)	C(8)–C(9)	1.536(11)
C(8)–C(14)	1.492(8)	C(9)–C(10)	1.527(8)
C(9)–C(11)	1.531(10)	C(11)–C(12)	1.562(10)
C(12)–C(13)	1.493(14)	C(13)–C(14)	1.524(12)
C(13)–C(17)	1.518(10)	C(13)–C(18)	1.555(12)
C(14)–C(15)	1.536(14)	C(15)–C(16)	1.576(12)
C(16)–C(17)	1.498(18)	C(17)–O(4)	1.205(12)
C(20)–O(5)	1.466(11)	C(21)–O(1)	1.134(11)
C(22)–O(2)	1.137(10)	C(23)–O(3)	1.140(10)
Bond angles			
C(2)–C(1)–C(10)	123.3(6)	C(1)–C(2)–C(3)	119.7(8)
C(2)–C(3)–C(4)	118.4(6)	C(2)–C(3)–O(5)	115.8(8)
C(4)<(3)-O(5)	125.2(7)	C(3)–C(4)–C(5)	120.8(6)
C(4)–C(5)–C(6)	117.3(5)	C(4)-C(5)-C(10)	120.0(7)
C(6)–C(5)–C(10)	122.7(5)	C(5)–C(6)–C(7)	113.6(5)
C(6)–C(7)–C(8)	109.1(6)	C(7)–C(8)–C(9)	109.0(6)
C(8)–C(9)–C(10)	111.1(5)	C(1)–C(10)–C(5)	117.1(5)
C(1)–C(10)–C(9)	122.2(5)	C(5)-C(lO)-C(9)	120.7(6)
Mn–C(21)–O(1)	178.4(7)	Mn–C(22)–O(2)	175.2(7)
Mn–C(23)–O(3)	175.6(8)	C(3)-O(5)-C(20)	117.5(7)

be separated and crystals of what turned out to be the α form were readily grown. The X-ray structure is shown in Figs. 1 and 2. The molecule has the classic 'piano stool' structure with a planar arene ring and linear Mn-C-O linkages. The average Mn-arene bond length is 2.20(1) A, with Mn-C(4) being the longest at 2.265(8) A. It was found that nucleophiles readily add to the arene ring in 1, as shown by the characteristic change in IR ν(CO) bands. For example, with the hydride donor $NaBH_4$, the ν(CO) bands in CH_2Cl_2 changed from 2072, 2006 cm-' to 2004, 1914 cm^{-1}. However, an IR band at 1738 cm-' in 1, due to the C(17) carbonyl group, disappeared after addition of $NaBH_4$. This indicates that hydride, and probably most other nucleophiles, attack 1 at both the arene and C(17) carbonyl carbon. While this may be useful in some instances, in the initial studies of manganese steroid chemistry it unnecessarily complicates product characterization. For this reason, most of our work dealing with nucleophilic additions has centered on complex 2 rather than 1.

The primary reason for coordinating $Mn(CO)_3^+$ to A-ring aromatic steroids is to impart electrophilic activation so that the arene ring (and/or benzylic sites) can be functionalized. Initial testing with a variety of

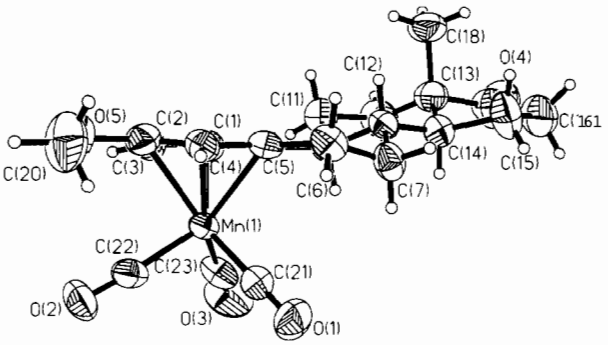

Fig. 1. An ORTEP drawing of the cation in [(estrone 3-methyl ether)$Mn(CO)_3$]$BF_4 \cdot CH_2Cl_2$ (1) with the thermal ellipsoids at the 50% level. Note that the metal is located on the α side of the steroid.

nucleophiles indicated that Grignard reagents, stabilized cnolatcs and hydridc donors add to thc ring in 2 to give 3 in high yield [24]. In this paper, the reactions with $NaBH_4$ and $LiCH_2C(O)CMe_3$ are discussed. These nucleophiles were added to a 1:1 mixture of the α and β forms of 2. An analysis of the IR and ^1H NMR spectra of the products showed that the respective nucleophile (H^- or $CH_2C(O)CMe_3^-$) had added to C(l), the carbon *meta* to the –OMe substituent, to give

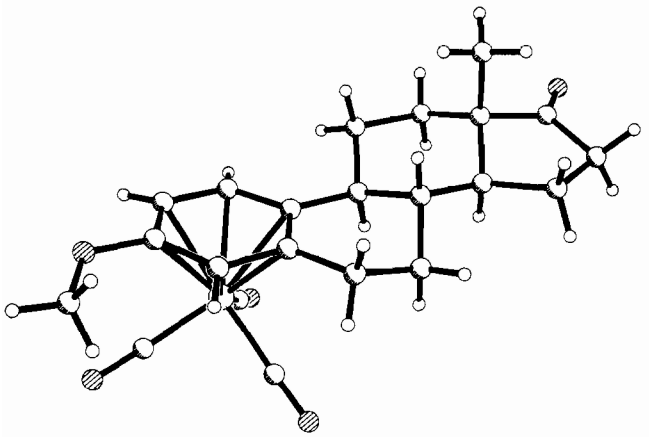

Fig. 2. A view of **1** showing the disposition of the steroid backbone.

TABLE 5. Selected atomic coordinates ($\times 10^4$) and isotropic thermal parameters ($\times 10^3$) for **4**

	x	*y*	*z*	U_{eq}
Mn	2728(1)	4976(1)	1990(1)	57(1)
O(1)	−425(6)	4429(4)	1386(2)	128(2)
O(2)	1818(7)	3599(3)	2766(2)	134(2)
O(3)	648(5)	6408(3)	2478(2)	100(1)
O(4)	3523(5)	4923(2)	751(1)	84(1)
O(5)	5427(5)	7835(2)	1234(2)	92(1)
O(6)	5504(5)	6743(2)	4870(1)	76(1)
C(1)	5134(6)	6316(3)	1848(2)	49(1)
C(2)	3860(6)	5932(3)	1449(2)	55(1)
C(3)	4193(6)	5094(3)	1246(2)	59(1)
C(4)	4992(6)	4474(3)	1581(2)	58(1)
C(5)	5581(6)	4727(3)	2098(2)	50(1)
C(6)	6424(7)	4032(3)	2447(2)	58(1)
C(7)	7291(6)	4394(3)	2947(2)	58(1)
C(8)	6102(5)	5085(2)	3200(1)	47(1)
C(9)	5930(6)	5875(2)	2822(2)	49(1)
C(10)	5336(6)	5603(3)	2270(2)	47(1)
C(11)	4791(8)	6617(3)	3060(2)	72(2)
C(12)	5433(9)	6904(3)	3614(2)	67(1)
C(13)	5564(7)	6114(3)	3985(2)	53(1)
C(14)	6792(6)	5422(3)	3729(2)	54(1)
C(15)	7147(9)	4765(3)	4178(2)	81(2)
C(16)	7138(10)	5351(3)	4686(2)	94(2)
C(17)	6566(8)	6278(3)	4500(2)	65(1)
C(18)	3714(7)	5752(3)	4110(2)	74(1)
C(19)	6451(9)	7021(4)	5323(2)	88(2)
C(20)	3408(10)	4058(4)	584(2)	103(2)
C(21)	6927(6)	6623(3)	1619(2)	53(1)
C(22)	6723(6)	7368(3)	1223(2)	54(1)
C(23)	8174(7)	7487(3)	812(2)	59(1)
C(24)	9988(7)	7419(4)	1052(2)	82(2)
C(25)	7893(12)	6763(4)	400(2)	117(3)
C(26)	7965(9)	8392(4)	546(2)	104(2)
C(27)	826(8)	4644(4)	1619(2)	86(2)
C(28)	2186(8)	4139(4)	2472(2)	82(2)
C(29)	1466(7)	5840(4)	2299(2)	65(1)

TABLE 6. Selected bond lengths (Å) and bond angles (°) for **4**

Bond lengths			
Mn–C(2)	2.167(4)	Mn–C(3)	2.185(4)
Mn–C(4)	2.131(4)	Mn–C(5)	2.194(4)
Mn–C(10)	2.290(4)	Mn–C(27)	1.782(4)
Mn–C(28)	1.803(6)	Mn–C(29)	1.794(6)
O(1)–C(27)	1.155(6)	O(2)–C(28)	1.138(6)
O(3)–C(29)	1.151(6)	O(4)–C(3)	1.371(5)
O(4)–C(20)	1.380(7)	O(5)–C(22)	1.204(5)
O(6)–C(19)	1.410(6)	O(6)–C(17)	1.415(6)
C(1)–C(2)	1.506(6)	C(1)–C(10)	1.526(5)
C(1)–C(21)	1.537(6)	C(2)–C(3)	1.393(7)
C(3)–C(4)	1.400(6)	C(4)–C(5)	1.430(6)
C(5)–C(10)	1.409(6)	C(5)–C(6)	1.511(6)
C(6)–C(7)	1.522(6)	C(7)–C(8)	1.518(5)
C(8)–C(9)	1.536(5)	C(9)–C(10)	1.519(6)
C(21)–C(22)	1.516(5)	C(22)–C(23)	1.515(6)
C(23)–C(24)	1.495(7)	C(23)–C(25)	1.527(7)
C(23)–C(26)	1.535(6)	C(13)–C(18)	1.527(7)
Bond angles			
C(3)–O(4)–C(20)	118.7(4)	C(19)–O(6)–C(17)	113.5(4)
C(2)–C(1)–C(10)	104.9(3)	C(2)–C(1)–C(21)	115.1(3)
C(10)–C(1)–C(21)	112.9(3)	C(3)–C(2)–C(1)	118.9(4)
O(4)–C(3)–C(2)	116.2(4)	O(4)–C(3)–C(4)	125.5(4)
C(2)–C(3)–C(4)	117.9(4)	C(3)–C(4)–C(5)	120.3(4)
C(10)–C(5)–C(4)	119.5(4)	C(10)–C(5)–C(6)	122.1(4)
C(5)–C(6)–C(7)	114.3(3)	C(8)–C(7)–C(6)	110.2(3)
C(7)–C(8)–C(9)	109.1(3)	C(10)–C(9)–C(8)	112.5(3)
C(5)–C(10)–C(9)	120.0(4)	C(5)–C(10)–C(1)	117.7(3)
C(9)–C(10)–C(1)	118.5(3)	C(22)–C(21)–C(1)	112.6(4)
O(5)–C(22)–C(23)	121.8(4)	O(5)–C(22)–C(21)	120.4(4)
C(23)–C(22)–C(21)	117.9(4)	Mn–C(27)–O(1)	178.8(5)
Mn–C(28)–O(2)	178.2(6)	Mn–C(29)–O(3)	177.4(5)

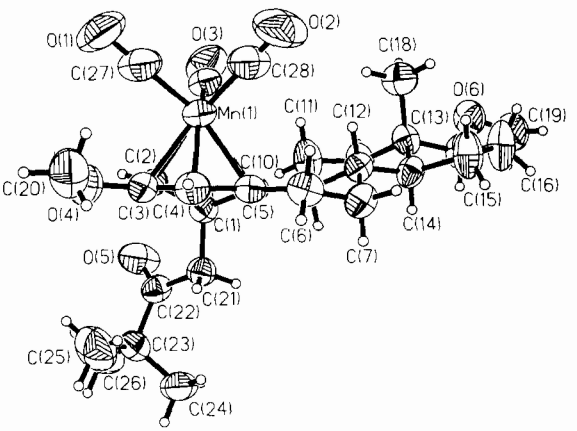

Fig. 3. An ORTEP drawing of complex **4**, obtained from the addition of $LiCH_2C(O)CMe_3$ to [(β-estradiol 3,17-dimethyl ether)$Mn(CO)_3$]BF_4 (**2**). Note that the metal in **4** is located on the β side of the steroid.

3. That –OMe directs nucleophiles regioselectively to *meta* positions in (arene)$Mn(CO)_3^+$ complexes had been established previously [5], and was therefore anticipated in the present reactions. However, it may be noted that along with predominant *meta* addition, the nu-

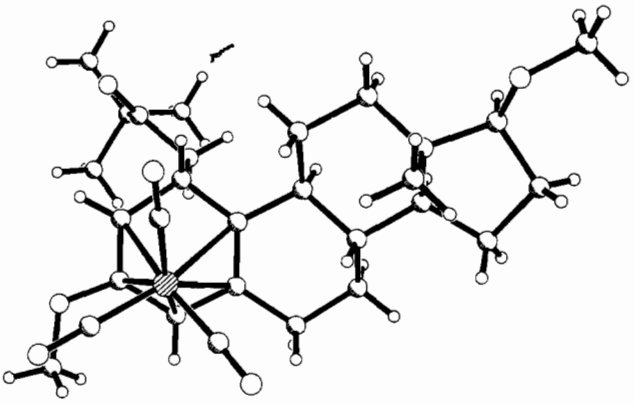

Fig. 4. A view of **4** showing the disposition of the steroid backbone.

cleophiles PhMgBr and MeMgCl also give non-trivial amounts of the products of *ortho* addition to C(2) and C(4) [24]*.

With the nucleophile $LiCH_2C(O)CMe_3$, the correlation of the α and β structures with their respective set of NMR resonances was established by the X-ray structure determination of one of the two isomers, which were separated by fractional crystallization of the original isomeric mixture. A crystal of a pure isomer was slowly grown and cut into sections so that the ^1H NMR spectrum of a portion of the same crystal as that used in the X-ray data collection could be recorded. This eliminated any chance that the crystal selected for X-ray analysis was not representative of the bulk material. The structure obtained is shown in Figs. 3 and 4. The $Mn(CO)_3$ moiety is situated β and the nucleophile is attached *meta* to the –OMe substituent on the face opposite the metal (i.e. α). Addition *exo* to the metal in this manner is the normal stereochemical route found in nucleophilic additions to coordinated π-hydrocarbons [3]. The five dienyl carbons in **4** are planar (mean deviation 0.024 Å), with the saturated carbon C(1) located 0.592 Å out of this plane away from the metal. C(1) is folded about the dienyl plane by 40.2°, which is a value typical of cyclohexadienyl manganese complexes [25]. The average Mn–dienyl bond length is 2.193(4) Å with the longest being Mn–C(10) at 2.290(4) Å. The Mn–C–O linkages are highly linear.

The hydride donor $NaBH_4$ also added to **2** to give a high yield of α- and β-**3** (Nu = H). Fractional crystallization was used to separate the isomers, the structures of which were assigned (Table 1) by a comparison of the ^1H NMR spectra with those of the structurally defined isomers of **3** ($Nu = CH_2C(O)CMe_3$). In particular, the chemical shift of the Me^{18} seems to be diagnostic, with that of the α form being *c.* 0.14 ppm lower than the β form.

*This is also true for $Mn(CO)_3^+$ complexes of podocarpic acid [12].

In conclusion, we have shown that the A-ring aromatic steroids estrone 3-methyl ether and β-estradiol 3,17-dimethyl ether readily coordinate to $Mn(CO)_3^+$ and that the aromatic ring is thereby electrophilically activated to high yield attack by nucleophiles at the position *meta* to the –OMe substituent. It is anticipated that a wide range of synthetically useful nucleophiles will react in this manner and that the resultant dienyl complexes can be demetallated and rearomatized or reactivated to a second nucleophilic attack. Thus, the manganese-mediated functionalization of aromatic steroids promises to be of significant synthetic value.

Supplementary material

Full listings of atomic coordinates, anisotropic thermal parameters, hydrogen coordinates and isotropic thermal parameters, bond lengths, bond angles, and observed and calculated structure factors for **1** and **4** are available from the authors on request.

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