Activation and Regioselective Ortho-Functionalization of the A-Ring of β-Estradiol Promoted by "Cp*Ir": An Efficient Organometallic Procedure for the Synthesis of 2-Methoxyestradiol

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5,6,7,8-Tetrahydro-2-naphthol (**3**) and β-estradiol (**1**) gave η^6-arene complexes using [Cp*Ir(solvent)$_3$][BF$_4$]$_2$ (**4**) prepared *in situ*; subsequent O-deprotonation with NEt$_3$ produced the corresponding complexes [Cp*Ir(oxo-η^5-dienyl)][BF$_4$] (**5** and **6a,b**). In the case of the complexed hormone, the Cp*Ir moiety coordinates the A-ring either α (metal down, **6a**) or β (metal up, **6b**) relative to the methyl group at C(13). The X-ray molecular structure of the α-isomer **6a** was determined. These (oxo-η^5-dienyl)iridium derivatives **5** and **6a** react with NaOMe in methanol at −40 °C to give respectively the novel iridium cyclohexadienone complexes [Cp*Ir(methoxy-η^4-dienone)] (**7a** and **8a**) in 95 and 91% yields, respectively, with nucleophilic attack occurring exclusively at the ortho-position relative to the C═O function. The novel iridium cyclohexadienone compound of the complexed steroid **8a** can be oxidized easily by iodine to produce 2-methoxyestradiol (**2**) in 60% overall yield from β-estradiol. This efficient organometallic procedure is preferable to the classical organic procedure, which requires five steps and affords **2** in less than 5% yield.

Introduction

The pioneering work of Nakamura and Tsutsui in 1963 on the coordination of estrone and 3-methylestrone by the organometallic fragment Cr(CO)$_3$ has paved the way to the use of transition metals in steroid chemistry.[1] Shortly afterwards Birch and co-workers[2] showed that group VIB metal carbonyls "M(CO)$_3$" (M = Cr, Mo, W) facilitate the aromatization of methoxylated diene steroids and provide organometallic steroid complexes in which M(CO)$_3$ is bonded to the A-ring. Most of these metal carbonyl steroid complexes are thermally unstable, especially those of β-estradiol (**1**). This inconvenience has hampered steroid functionalization by using such metallocarbonyl fragments, despite the fact that Cr(CO)$_3$ is a very useful and well-known synthon for organic synthesis.[3] Protection of hydroxyl groups seems to be required for producing M(CO)$_3$ complexes of the steroid. Thus, Sweigart and co-workers[4] have beautifully demonstrated that the organometallic fragments Mn(CO)$_3$ and/or Mn(CO)$_2$NO$^+$ can be used to activate the A-ring of 3,17-dimethoxyestradiol and methoxyestrone toward nucleophilic additions. In recent years a new type of transition-metal moiety has been used for synthetic organic purposes. For instance, Harman and co-workers[5] have elegantly shown that the electron-rich unit Os(NH$_3$)$_5^{2+}$ coordinates to one double bond of the A-ring of β-estradiol and provides a stable complex. The latter becomes activated toward attack by electrophiles via a Michael addition reaction. We and others[6] have shown that the transition-element fragments of group VIII such as Cp*Ru$^+$, CpRu$^+$, and Cp*Rh^{2+} can be introduced into the A-ring of β-estradiol and substituted derivatives and provide stable complexed hormones. In this paper we report a mature organometallic way to prepare 2-methoxyestradiol (**2**). The procedure consists of *selective ortho activation* of the A-ring of β-estradiol (**1**) toward nucleophilic attack with NaOMe by the Cp*Ir^{2+} moiety. Subsequent oxidative decomplexation provides the free steroid molecule **2**. 2-Methoxyestradiol (**2**) is a well-known anticancer agent, and its properties are well-established.[7]

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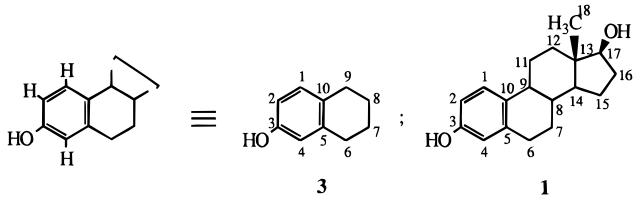
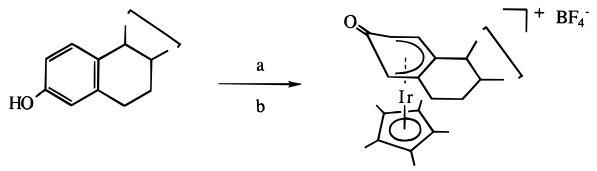


3 **1**

Figure 1. Atom-numbering system for **1** and **3**.

Scheme 1. Syntheses of the (Oxo-η^5-cyclohexadienyl)iridium Complexes 5 and 6a,b[a]



3 **5**
1 **6ab**

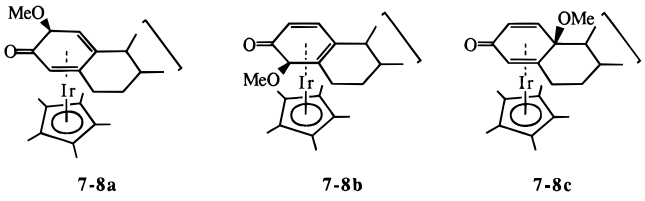
[a] Legend: (a) $[Cp^*Ir(acetone)_3][BF_4]_2$, 5,6,7,8-tetrahydro-2-naphthol/CH_2Cl_2 or β-estradiol/THF, room temperature; (b) NEt_3; acetonitrile, room temperature.

Results and Discussion

1. Complexation of 5,6,7,8-Tetrahydro-2-naphthol (3) with the "Cp*Ir" Moiety and Reactivity with NaOMe. We reported recently the first example of ortho-functionalization of a series of phenols (phenol, 3,5-dimethylphenol, and 3,4-dimethylphenol) by nucleophiles promoted by the "Cp*Ir" moiety.[8] Pursuing our research program in this area, we focused our attention on the functionalization of phenols possessing at least two fused arenes or other complex organic molecules: for instance, β-estradiol (**1**) (Figure 1). One important aspect of our research work was to ascertain whether or not a regioselective arene functionalization promoted by "Cp*Ir" could be achieved when the target molecule possesses several reactive organic functions which are not protected. In order to establish the regioselectivity of the nucleophilic attack by NaOMe at the A-ring of β-estradiol (**1**), we first studied the functionalization of 5,6,7,8-tetrahydro-2-naphthol (**3**) as the model system (Figure 1).

Placement of the Cp*Ir moiety on the aromatic ring of 5,6,7,8-tetrahydro-2-naphthol (**3**) was accomplished using $[Cp^*Ir(solvent)_3][BF_4]_2$ (**4**) in acetone/dichloromethane (Scheme 1). Subsequent treatment with NEt_3 afforded the iridium phenoxide complex $[Cp^*Ir(\eta^5\text{-}C_{10}H_{11}O)][BF_4]$ (**5**) as an off-white microcrystalline material in 86% yield. This compound was identified by elemental analysis and ^1H and ^{13}C NMR spectroscopy. The related ruthenium derivatives $[Cp^*Ru(\eta^5\text{-}C_6H_{5-n}R_nO)]$ (R = H, alkyl) have been extensively investigated by Koelle's group,[9] but their reactivity toward nucleophiles remains unknown.

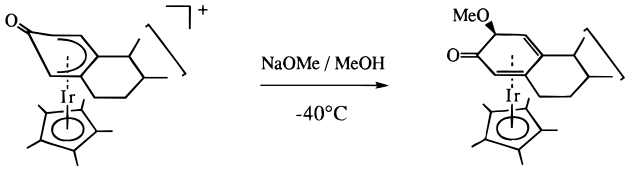
The (oxocyclohexadienyl)iridium complex **5** reacted with a 5-fold excess of NaOMe in methanol over 8 h at room temperature. Workup of the reaction mixture and extraction with ether afforded a mixture of three isomers (1:1:1), as determined by ^1H and ^{13}C NMR spectroscopy. The ^{13}C NMR shows the presence of three singlets between 184 and 190 ppm attributed to the ketonic functions C═O of neutral iridium η^4-dienone compounds.[8]



7-8a **7-8b** **7-8c**

Figure 2.

Scheme 2. Syntheses of the Neutral (η^4-Cyclohexadienone)iridium Complexes 7a and 8a



5 **7a**
6a **8a**

The ^{13}C NMR of the above mixture also shows the presence of three signals which appear in the area 55−60 ppm and are attributed to the MeO^- groups of the three products. The infrared spectrum shows the absence of the large band at 1050 cm^{-1} attributed to the free anion BF_4^-; evidently this large band is present in the starting material $[Cp^*Ir(\eta^5\text{-}C_{10}H_{11}O)][BF_4]$ (**5**). These data are in accord with the formation of three iridium dienone complexes $[Cp^*Ir\{\eta^4\text{-}(C_{10}H_{11}O)(OMe)\}]$ (**7a**−**c**) (Figure 2), which result from three different nucleophilic additions by MeO^- at the ortho and para positions of the coordinated arene in **5**. When the previous reaction was carried out at −40 °C, only one compound was obtained in 95% yield. Its ^{13}C NMR spectrum showed the presence of a singlet at 184.5 ppm attributed to the ketonic function and a peak at 57.7 ppm attributed to the MeO^- unit.

The 2D $^1H-^1H$ and $^1H-^{13}C$ experiments and infrared and elemental analysis suggest the formation of the iridium cyclohexadienone species **7a** (Scheme 2), where the MeO^- attack has occurred at the ortho position relative to the ketonic function. Therefore, the kinetic barrier favors an ortho nucleophilic addition at low temperature. Our results stimulated us to activate and functionalize the target compound β-estradiol (**1**).

2. Complexation of β-Estradiol to the Cp*Ir Moiety and X-ray Structure of α-$[Cp^*Ir(\eta^5\text{-}C_{18}H_{23}O_2)][BF_4]$ (6a). Treatment of β-estradiol (**1**) with one equivalent of $[Cp^*Ir(solvent)_3][BF_4]_2$ (**4**) followed by addition of NEt_3 gave two isomers (α/β 90/10) in 82% yield (Scheme 1). These complexes were identified by spectroscopic methods and elemental analysis as (α- and β-)$[Cp^*Ir(\eta^5\text{-}C_{18}H_{23}O_2)][BF_4]$ (**6a,b**). Further, the X-ray molecular structure of the α-isomer **6a** was determined. In these complexes **6a,b**, the Cp*Ir moiety is coordinated to the two distinct faces of β-estradiol (**1**), placing the metal down relative to the methyl group at C(13) in the α-isomer **6a** or the metal up in the β-isomer **6b**.

Crystals of **6a** were obtained by slow diffusion from acetone/Et_2O. The compound crystallizes in the ortho-

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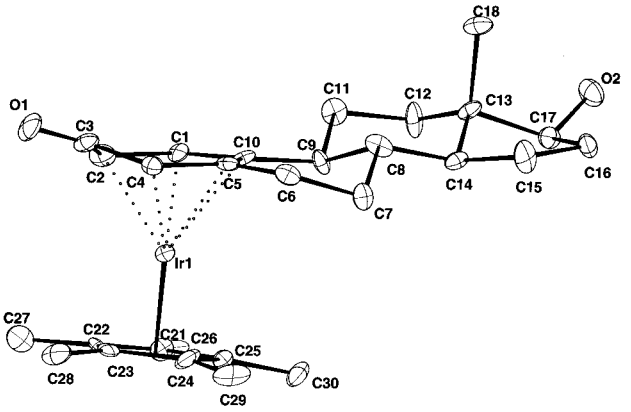


Figure 3. View of the cation $[Cp^*Ir(\eta^5\text{-}C_{18}H_{23}O_2)]^+$, showing the atom-numbering system and the absolute configuration of the molecule.

Table 1. Crystallographic Data for $[Cp^*Ir(\eta^5\text{-}C_{18}H_{23}O_2)][BF_4]$ (6a)

fw	685.6
a (Å)	8.357 (12)
b (Å)	12.385(6)
c (Å)	25.179(8)
α (deg)	90
β (deg)	90
γ (deg)	90
V (Å^3)	2606(4)
Z	4
cryst syst	orthorhombic
space group	$P2_12_12_1$
linear abs coeff μ (cm^{-1})	51.5
density ρ (g cm^{-3})	1.75
diffractometer	Enraf-Nonius CAD4
radiation	Mo Kα (λ = 0.710 69 Å)
scan type	$\omega/2\omega$
scan range (deg)	0.8 + 0.345 tan θ
θ limits (deg)	2−30
temp of measurement	room temp
octants collected	0−9; 0−14; 0−29
no. of data collected	2644
no. of unique data collected	2618
no. of unique data used for refinement	1779 ($(F_o)^2 > 3\sigma(F_o)^2$)
$R = \sum\|\|F_o\| - \|F_c\|\|/\sum\|F_o\|$	0.0417
$R_w = [\sum w(\|F_o\| - \|F_c\|)^2/\sum wF_o^2]^{1/2}$	0.0480, w = 1.0
second ext coeff (10^{-6})	no
abs cor	DIFABS (min 0.85, max 1.21)
no. of variables	326
$\Delta\rho_{min}$ (e Å^{-3})	−1.18
$\Delta\rho_{max}$ (e Å^{-3})	1.26

rhombic unit cell with space group $P2_12_12_1$. Figure 3 shows the absolute configuration of the complexed hormone α-$[Cp^*Ir(\eta^5\text{-}C_{18}H_{23}O_2)]^+$; crystallographic data collection parameters and selected bond lengths and angles are listed in Tables 1−3. The structure of **6a** shows that the Cp*Ir moiety is coordinated to only five carbons of the A-ring. Loss of aromaticity is manifested by the irregularity of the C−C bond distances of the A-ring; furthermore, the C−O bond distance is 1.14(3) Å, which is characteristic of a C═O bond of a ketonic function. We also note that the carbonyl function is bent upward relative to the organometallic unit Cp*Ir by the angle $\theta = 23°$, where θ is defined by the dihedral angle along C(2)-C(4). This angle is greater than that reported ($\theta = 16°$) for the analogous "Cp*Rh-steroid" derivative.[6b]

3. Reactivity of α-$[Cp^*Ir(\eta^5\text{-}C_{18}H_{23}O_2)][BF_4]$ (6a) with NaOMe and 2D-NMR Analysis. The π-complexed hormone **6a** reacted with NaOMe in a way similar to that for the naphthol system **5**. Thus, at room temperature we obtained the expected three isomers **8a**−**c**, while at −40 °C only **8a** was formed quantitatively (Scheme 2). The iridium dienone derivative of the π-complexed steroid α-$[Cp^*Ir\{\eta^4\text{-}C_{18}H_{23}O_2(OMe)\}]$ (**8a**) was obtained as an off-white microcrystalline material. The ^{1}H NMR spectrum of **8a** recorded in C_6D_6 shows the presence of three multiplets in the area of 3−4 ppm attributed to the protons of the A-ring; this upfield shift relative to the starting material ($\Delta\delta$ = 2.5 ppm) indicates significant changes in the nature of the A-ring in **8a**, whereby it loses the dienonylic form **6a** and acquires the novel dienone structure. We also note that the protons of the methoxy unit appear as a singlet at 3.58 ppm and those of the Cp*Ir moiety at 1.60 ppm. The ^{13}C NMR of **8a** is especially informative, showing a singlet at 186.4 ppm attributed to the C═O function, shifted downfield by $\Delta\delta$ = 20 ppm relative to the resonance in the spectrum of the starting material **6a**. These data suggest that the A-ring in **8a** adopts a η^4-cyclohexadienone form and is bound to the Cp*Ir moiety, while the methoxide unit is attached at C(2), ortho to the carbonyl function. Attempts to obtain crystals of **7a** or **8a** for an X-ray study have thus far been unsuccessful. In the absence of an X-ray structure and in order to confirm and to assign more thoroughly the ^{1}H NMR of **8a**, we analyzed the structure of **8a** by 2D ^{1}H−^{1}H homonuclear correlation spectroscopy and ^{1}H−^{13}C chemical shift correlation spectroscopy. Figure 4 shows the 2D ^{1}H−^{1}H spectrum of the complexed hormone **8a**. The 2D-NMR data confirm the attribution of H_1, H_2, and H_4 at 3.35, 3.82, and 3.68 ppm, respectively. These signals are correlated to the carbon peaks resonating at 38.7, 77.0, and 58.5 ppm, respectively. Further, H_{17} appears at 3.49 ppm and is correlated to the carbon peak at 81.6 ppm. It is noteworthy that the magnetic anisotropy of the Cp*Ir moiety shields the α-protons of the B-ring. In this respect $H_{6\alpha}$ appears at 1.67 ppm, while $H_{6\beta}$ appears at 2.68 ppm and the related carbon at 29.2 ppm; further, $H_{9\alpha}$ resonates at 1.62 ppm and the corresponding carbon at 43.7 ppm. We were able to identify all the protons of the steroid skeleton of **8a** and their related carbon resonances. However,

Table 2. Interatomic Distances for $[Cp^*Ir(\eta^5\text{-}C_{18}H_{23}O_2)][BF_4]$ (6a)

Ir(1)−C(1)	2.22(2)	Ir(1)−C(2)	2.25(2)
Ir(1)−C(4)	2.19(2)	Ir(1)−C(5)	2.25(2)
Ir(1)−C(10)	2.25(2)	Ir(1)−C(21)	2.20(2)
Ir(1)−C(22)	2.16(2)	Ir(1)−C(23)	2.16(2)
Ir(1)−C(24)	2.16(2)	Ir(1)−C(25)	2.23(2)
O(1)−C(3)	1.14(3)	O(2)−C(17)	1.41(3)
C(1)−C(2)	1.46(3)	C(1)−C(10)	1.47(3)
C(2)−C(3)	1.53(3)	C(3)−C(4)	1.48(3)
C(4)−C(5)	1.43(3)	C(5)−C(6)	1.47(3)
C(5)−C(10)	1.45(3)	C(6)−C(7)	1.54(3)
C(7)−C(8)	1.53(3)	C(8)−C(9)	1.59(3)
C(8)−C(14)	1.57(3)	C(9)−C(10)	1.52(3)
C(9)−C(11)	1.50(2)	C(11)−C(12)	1.56(3)
C(12)−C(13)	1.45(3)	C(13)−C(14)	1.52(3)
C(13)−C(17)	1.57(3)	C(13)−C(18)	1.58(3)
C(14)−C(15)	1.50(3)	C(15)−C(16)	1.54(3)
C(16)−C(17)	1.53(3)	C(21)−C(22)	1.39(3)
C(21)−C(25)	1.46(3)	C(21)−C(26)	1.47(3)
C(22)−C(23)	1.40(3)	C(22)−C(27)	1.52(3)
C(23)−C(24)	1.45(3)	C(23)−C(28)	1.46(3)
C(24)−C(25)	1.49(3)	C(24)−C(29)	1.50(3)
C(25)−C(30)	1.42(3)		
B(1)−F(1)	1.40(4)	B(1)−F(2)	1.36(3)
B(1)−F(3)	1.31(4)	B(1)−F(4)	1.38(4)

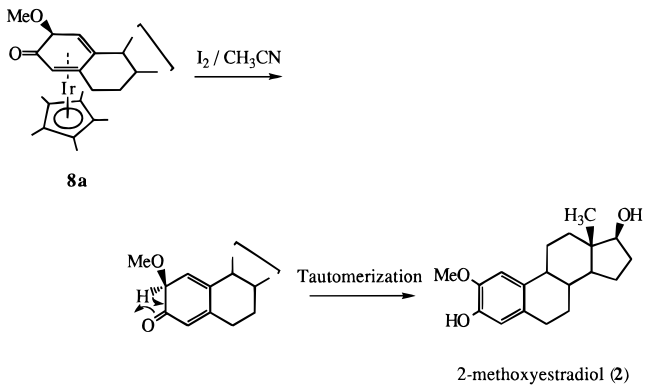
Table 3. Bond Angles (deg) for [Cp*Ir(η^5-$C_{18}H_{23}O_2$)][BF_4] (6a)

C(1)−Ir(1)−C(2)	38.2(8)	C(1)−Ir(1)−C(4)	78.1(8)
C(2)−Ir(1)−C(4)	66.2(8)	C(1)−Ir(1)−C(5)	67.5(7)
C(2)−Ir(1)−C(5)	80.9(8)	C(4)−Ir(1)−C(5)	37.7(7)
C(1)−Ir(1)−C(10)	38.4(7)	C(2)−Ir(1)−C(10)	70.0(7)
C(4)−Ir(1)−C(10)	67.5(7)	C(5)−Ir(1)−C(10)	37.5(7)
C(1)−Ir(1)−C(21)	108.0(7)	C(2)−Ir(1)−C(21)	114.1(8)
C(4)−Ir(1)−C(21)	170.8(8)	C(5)−Ir(1)−C(21)	150.8(8)
C(10)−Ir(1)−C(21)	121.5(8)	C(1)−Ir(1)−C(22)	121.9(8)
C(2)−Ir(1)−C(22)	102.6(8)	C(4)−Ir(1)−C(22)	133.7(8)
C(5)−Ir(1)−C(22)	168.4(8)	C(10)−Ir(1)−C(22)	154.0(7)
C(21)−Ir(1)−C(22)	37.2(8)	C(1)−Ir(1)−C(23)	155.6(9)
C(2)−Ir(1)−C(23)	121.2(10)	C(4)−Ir(1)−C(23)	107.5(8)
C(5)−Ir(1)−C(23)	131.2(8)	C(10)−Ir(1)−C(23)	165.8(9)
C(21)−Ir(1)−C(23)	64.1(8)	C(1)−Ir(1)−C(24)	161.1(8)
C(2)−Ir(1)−C(24)	160.1(9)	C(4)−Ir(1)−C(24)	111.8(9)
C(5)−Ir(1)−C(24)	109.8(9)	C(10)−Ir(1)−C(24)	128.7(8)
C(21)−Ir(1)−C(24)	64.6(9)	C(1)−Ir(1)−C(25)	123.5(7)
C(2)−Ir(1)−C(25)	149.4(8)	C(4)−Ir(1)−C(25)	143.5(8)
C(5)−Ir(1)−C(25)	118.2(8)	C(10)−Ir(1)−C(25)	109.5(7)
C(21)−Ir(1)−C(25)	38.5(8)	C(22)−Ir(1)−C(23)	37.7(8)
C(22)−Ir(1)−C(24)	63.7(9)	C(23)−Ir(1)−C(24)	39.2(10)
C(22)−Ir(1)−C(25)	63.8(8)	C(23)−Ir(1)−C(25)	65.9(8)
C(24)−Ir(1)−C(25)	39.7(8)	Ir(1)−C(1)−C(2)	71.6(11)
Ir(1)−C(1)−C(10)	71.8(12)	C(2)−C(1)−C(10)	122.8(18)
Ir(1)−C(2)−C(1)	70.1(12)	Ir(1)−C(2)−C(3)	83.9(13)
C(1)−C(2)−C(3)	120.2(21)	O(1)−C(3)−C(2)	124.7(24)
O(1)−C(3)−C(4)	127.3(21)	C(2)−C(3)−C(4)	107.3(20)
Ir(1)−C(4)−C(3)	86.8(13)	Ir(1)−C(4)−C(5)	73.3(12)
C(3)−C(4)−C(5)	128.1(21)	Ir(1)−C(5)−C(4)	69.1(11)
Ir(1)−C(5)−C(6)	126.0(14)	C(4)−C(5)−C(6)	120.4(18)
Ir(1)−C(5)−C(10)	71.3(11)	C(4)−C(5)−C(10)	118.0(19)
C(6)−C(5)−C(10)	121.3(19)	C(5)−C(6)−C(7)	115.6(16)
C(6)−C(7)−C(8)	108.0(18)	C(7)−C(8)−C(9)	109.2(15)
C(7)−C(8)−C(14)	113.1(18)	C(9)−C(8)−C(14)	104.1(15)
C(8)−C(9)−C(10)	110.1(16)	C(9)−C(9)−C(11)	110.8(15)
C(10)−C(9)−C(11)	113.6(17)	Ir(1)−C(10)−C(1)	69.8(11)
Ir(1)−C(10)−C(5)	71.1(11)	C(1)−C(10)−C(5)	116.6(18)
Ir(1)−C(10)−C(9)	127.5(13)	C(1)−C(10)−C(9)	121.8(16)
C(5)−C(10)−C(9)	121.6(17)	C(9)−C(11)−C(12)	111.7(16)
C(11)−C(12)−C(13)	111.7(20)	C(12)−C(13)−C(14)	112.3(19)
C(12)−C(13)−C(17)	116.1(18)	C(14)−C(13)−C(17)	97.4(16)
C(12)−C(13)−C(18)	111.3(20)	C(14)−C(13)−C(18)	112.9(17)
C(17)−C(13)−C(18)	106.1(17)	C(8)−C(14)−C(13)	111.6(16)
C(8)−C(14)−C(15)	119.6(18)	C(13)−C(14)−C(15)	106.1(19)
C(14)−C(15)−C(16)	104.6(20)	C(15)−C(16)−C(17)	105.2(18)
O(2)−C(17)−C(13)	116.5(19)	O(2)−C(17)−C(16)	110.9(18)
C(13)−C(17)−C(16)	104.6(15)	Ir(1)−C(21)−C(22)	69.9(10)
Ir(1)−C(21)−C(25)	71.8(10)	C(22)−C(21)−C(25)	108.8(18)
Ir(1)−C(21)−C(26)	126.7(15)	C(22)−C(21)−C(26)	128.6(21)
C(25)−C(21)−C(26)	122.6(21)	Ir(1)−C(22)−C(21)	72.9(11)
Ir(1)−C(22)−C(23)	71.0(10)	C(21)−C(22)−C(23)	111.9(19)
Ir(1)−C(22)−C(27)	125.7(15)	C(21)−C(22)−C(27)	124.5(22)
C(23)−C(22)−C(27)	123.5(23)	Ir(1)−C(23)−C(22)	71.2(11)
Ir(1)−C(23)−C(24)	70.6(11)	C(22)−C(23)−C(24)	106.5(20)
Ir(1)−C(23)−C(28)	128.0(14)	C(22)−C(23)−C(28)	130.2(28)
C(24)−C(23)−C(28)	122.9(27)	Ir(1)−C(24)−C(23)	70.2(12)
Ir(1)−C(24)−C(25)	72.4(12)	C(23)−C(24)−C(25)	108.4(23)
Ir(1)−C(24)−C(29)	128.6(18)	C(23)−C(24)−C(29)	130.5(23)
C(25)−C(24)−C(29)	120.7(22)	Ir(1)−C(25)−C(21)	69.7(11)
Ir(1)−C(25)−C(24)	67.9(11)	C(21)−C(25)−C(24)	104.3(19)
Ir(1)−C(25)−C(30)	130.9(16)	C(21)−C(25)−C(30)	128.0(20)
C(24)−C(25)−C(30)	127.4(22)		
F(1)−B(1)−F(2)	108.2(27)	F(1)−B(1)−F(3)	107.4(29)
F(2)−B(1)−F(3)	113.2(29)	F(1)−B(1)−F(4)	112.5(30)
F(2)−B(1)−F(4)	106.3(25)	F(3)−B(1)−F(4)	109.3(26)

the order of C_{11} and C_{12} was considered to be unchanged relative to the free hormone and thus appeared at 29.8 and 37.6 ppm. Only C_{13} was not observed.

4. Oxidative Demetalation and Regioselective Ortho-Functionalization of 5,6,7,8-Tetrahydro-2-naphthol (3) and β-Estradiol (1). When a CH_3CN solution of **8a** was exposed to iodine and the mixture was stirred for 15 min, a red solution was obtained. Workup of the reaction mixture followed by separation on silica gel plates gave 2-methoxyestradiol (**2**) in 90% yield. Similar results were obtained for the iridium cyclohexadienone derivatives [Cp*Ir{η^4-($C_{10}H_{11}O$)(OMe)}] (**7a**), affording after iodine oxidation the free 3-methoxy-5,6,7,8-tetrahydro-2-naphthalenol (**9**) (Table 4). We have also isolated the organometallic complex [Cp*IrI_2]$_2$, as a deep brown microcrystalline solid. The formation of [Cp*IrI_2]$_2$ was confirmed by elemental analysis; further, the ^{1}H NMR spectrum shows a singlet at 1.84 ppm, which corresponds to the η^5-Cp* units.[10] Therefore, our organometallic starting material can be recovered in the form of [Cp*IrI_2]$_2$ in 60% overall yield. This is a rare example of a recyclable transition metal directed to organic synthesis.

Scheme 3. Oxidative Demetalation of 8a and Formation of 2-Methoxyestradiol (2)



The formation of 2-methoxyestradiol (**2**) is no doubt the result of keto-enol tautomerism of the free cyclohexadienone intermediate to give the more stable substituted phenol species **2** (Scheme 3). It should be mentioned that activation and functionalization of naphthol and β-estradiol toward electrophiles was illustrated by Harman[5] using the $Os(NH_3)_5^{2+}$ unit. The Os system is completely different from the Ir one because the electron-rich $Os(NH_3)_5^{2+}$ moiety blocks one of the double bonds of the arene and activates the free diene part to an electrophilic Michael addition reaction. In the Os system the electrophilic attacks occur at C(4) and C(10) of the β-estradiol.

The preparation of 2-methoxyestradiol (**2**) from β-estradiol (**1**) *via* the organic methods has been reported first by Fishman in 1958.[11] Later on, other groups published different organic procedures.[12,13] We include here the alternative literature procedure for its synthesis[13] (Scheme 4). The procedure consists of five steps. (a) Formylation of β-estradiol (**1**) with hexamethylenetetramine affords the two isomers 2- and 4-formylestradiol. (b) Benzylation of the two hydroxyl groups of 2-formylestradiol under basic conditions with benzyl bromide provides dibenzyl ether. 2-Methoxyestradiol (**2**) was then obtained by (c) Baeyer−Villiger oxidation, (d) methylation of the phenol (e) and debenzylation. The overall yield of 2-methoxyestradiol is 5%.

Concluding Remarks

In this paper we have reported the high-yield syntheses of cationic (oxo-η^5-dienyl)iridium complexes where

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(13) (a) He, H.-M.; Cushman, M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1725. (b) Cushman, M.; He, H.-M.; Katzenellenbogen, J. A.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1995**, *38*, 2041 and references therein.

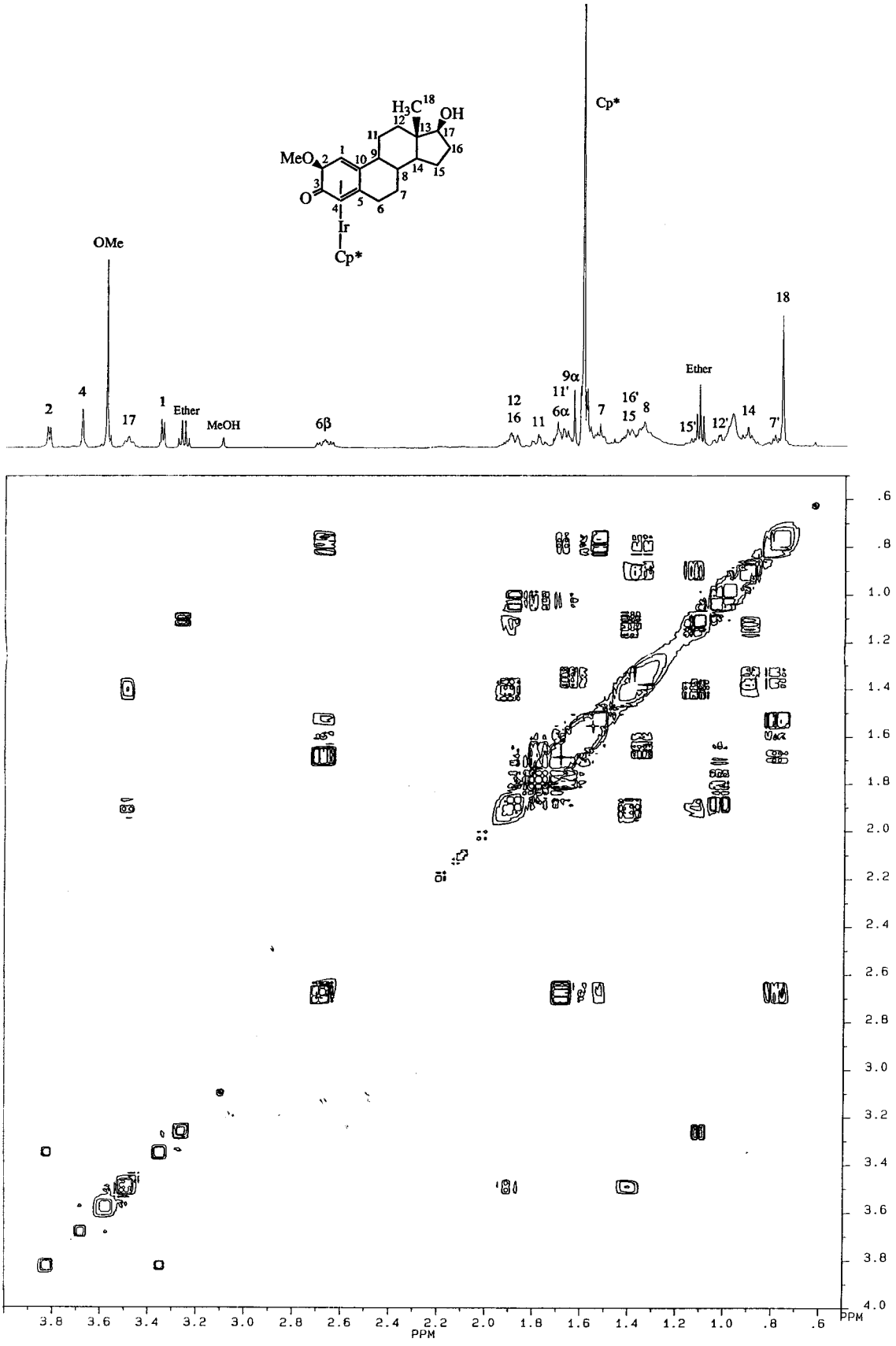
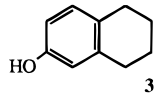
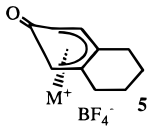
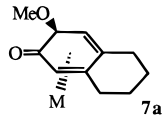
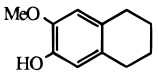
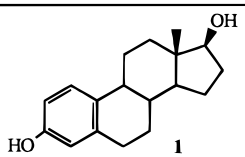
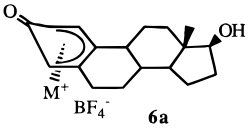
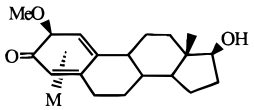
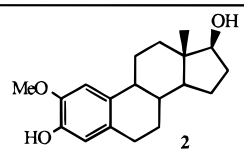


Figure 4. 500-MHz ^{1}H NMR COSY (C_6D_6) spectrum at 298 K of compound **8a**.

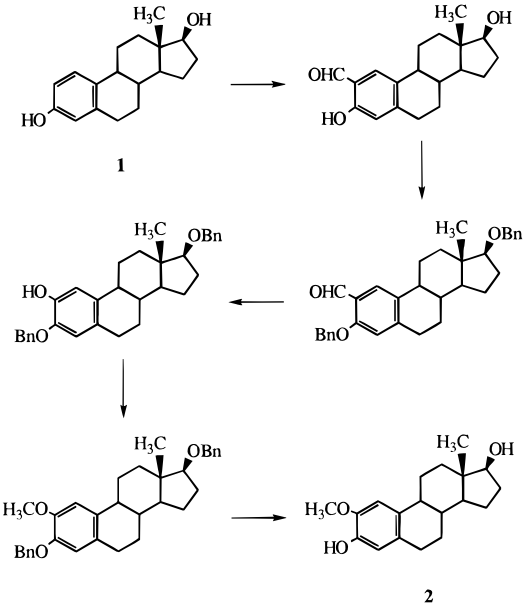
the oxo-dienyl unit is the corresponding η^5-phenoxo form of 5,6,7,8-tetrahydro-2-naphthol and β-estradiol. The X-ray structure of **6a** was included and showed that the Cp*Ir fragment coordinates to only five carbons of the A-ring. The most pertinent results are that we showed the first example of ortho functionalization of β-estradiol by MeO^-, promoted by the Cp*Ir moiety, and we demonstrated that subsequent oxidative decomplexation provides 2-methoxyestradiol in high yield. This efficient organometallic route affords 2-methoxyestradiol (**2**) from β-estradiol (**1**) in three steps in 60% overall yield. The present synthesis is more efficient than the classical

Table 4. Reactants and Products of Reactions

Starting materials	Oxo-η^5-dienyl-Ir derivatives	η^4-dienone-Ir derivatives	I_2 Oxidation / Products
 **3**	 **5**	 **7a**	 **9**
 **1**	 **6a**	 **8a**	 **2**

M =Cp*Ir

Scheme 4. Classical Organic Strategy for the Synthesis of 2-Methoxyestradiol (2)[13]



organic procedure, which requires five steps starting from β-estradiol and produces **2** in an overall yield of 5%. Our method is a unique addition to the steroid literature and should increase availability of rare steroids and other oxygenated compounds of use to chemists and biochemists who are interested in this area.

Experimental Section

General Procedures. All manipulations were carried out under an argon atmosphere using Schlenk techniques. Solvents were purified and dried prior to use by conventional distillation techniques. MeOH was distilled over traces of Na and used freshly in the preparation of NaOMe solutions. All reagents obtained from commercial sources were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 500 and 250 MHz instruments. ^{1}H-NMR chemical shifts are reported in parts per million referenced to the residual solvent proton resonance. Infrared spectra were obtained on a Bruker IR 45 spectrometer from samples prepared on KBr disks. All absorptions are expressed in wave numbers (cm^{-1}). Elemental analyses were performed by the Microanalytical Laboratory of the University of Paris VI.

Synthesis of [Cp*Ir(η^5-$C_{10}H_{11}O$)][BF_4] (5). A solution of $AgBF_4$ (100 mg, 0.51 mmol) in acetone (5 mL) was added to $[Cp^*IrCl_2]_2$ (100 mg, 0.12 mmol) in acetone (10 mL), to give rapidly a white precipitate of AgCl. The reaction mixture was stirred for 15 min; then the resulting orange solution of $[Cp^*Ir(acetone)_3][BF_4]_2$ was filtered into a dry Schlenk tube kept under argon. To this orange solution was then added 5,6,7,8-tetrahydro-2-naphthol (110 mg, 0.74 mmol) in 5 mL of CH_2Cl_2, and the mixture was stirred for 12 h, during which time the solution was decolorized and a white precipitate was obtained. The reaction mixture was treated with NEt_3 (200 μL) for 15 min. Then the light yellow solution was reduced under vacuum and subsequent addition of Et_2O (40 mL) afforded a white precipitate. This compound was washed several times with Et_2O and dried under vacuum. Overall yield: 86% (120 mg). IR (KBr disk); ν(C=O) 1623, ν(B−F) 1054. Anal. Calcd for $C_{20}H_{26}BF_4IrO$: C, 42.78; H, 4.67. Found: C, 42.76; H: 4.72. ^{1}H NMR (CD_3CN, 500 MHz): δ 6.08 (d, J = 7.3 Hz, 1H, H_1), 5.40 (dd, J = 7.3, 1.9 Hz, 1H, H_2), 5.37 (d, J = 1.9 Hz, 1H, H_4), 2.93 and 2.34 (m, 2H gem, H_6 or H_9), 2.87 and 2.38 (m, 2H gem, H_9 or H_6), 2.06 (s, 15H, Cp*), 1.81 and 1.54 (m, 2H gem, H_7 or H_8), 1.81 and 1.67 (m, 2H gem, H_8 or H_7). ^{13}C NMR (CD_3CN, 62.9 MHz): δ 163.8 (C_3), 112.0 and 100.1 (C_5 and C_{10}), 99.6 (η^5-Cp), 94.0 (C_1), 80.7 (C_2), 79.7 (C_4), 27.1, (C_6 or C_9), 25.7 (C_9 or C_6), 21.5 (C_7 or C_8), 21.9 (C_8 or C_7), 9.6 (Me-Cp).

Synthesis of [Cp*Ir(η^5-$C_{18}H_{23}O_2$)][BF_4] (6a,b). A solution of $AgBF_4$ (400 mg, 2.05 mmol) in THF (10 mL) was added to $[Cp^*IrCl_2]_2$ (400 mg, 0.50 mmol) in acetone (20 mL), to give rapidly a white precipitate of AgCl. The reaction mixture was stirred for 15 min; then the orange solution of $[Cp^*Ir(acetone)_3][BF_4]_2$ was filtered into a dry Schlenk tube kept under argon. To this orange solution was then added β-estradiol (305 mg, 1.12 mmol) in THF (20 mL), and the mixture was stirred for 4 h, during which time the solution was decolorized. A white precipitate obtained by filtration was identified as the α-isomers of η^6-phenolic and η^5-phenoxo forms of the coordinated steroid, analogous to these obtained for the rhodium steroid derivatives.[6a] The supernatant phase afforded the β-isomers as the major species. Separation of the α- from the β-isomer in the supernatant phase was performed by fractional crystallization, the β-isomer being more soluble in THF. Addition of NEt_3 (300 μL) to the α-species (η^5-phenoxo and η^6-phenol) allowed complete deprotonation and gave the target complex α-[Cp*Ir(η^5-$C_{18}H_{23}O_2$)][BF_4] (**6a**). Yield: 74% (508 mg). Similarly, the isomer β-[Cp*Ir(η^5-$C_{18}H_{23}O_2$)][BF_4] (**6b**) was prepared. Yield: 8% (56 mg). IR of **6a** (KBr disk): ν(C=O) 1619, ν(B−F) 1054. Anal. Calcd for **6a** $C_{28}H_{38}BF_4IrO_2$: C, 49.05; H, 5.58. Found: C, 49.07; H, 5.43.^{1}H NMR for **6a**, (CD_3CN, 500 MHz): δ 6.68 (d, J = 7.3 Hz, 1H, H_1), 5.42 (dd, J = 7.3, 2.0 Hz, 1H, H_2), 5.34 (d, J = 2.0 Hz, 1H, H_4), 3.61 (m, 1H, H_{17}), 3.13 and 2.32 (m, 2H, H_6), 2.10 and 1.64 (m, 2H, H_{11}), 2.05 (s, 15H, Cp*), 2.00 and 1.46 (m, 2H, H_{16}), 1.88 (m, 1H, H_9), 1.88 and 1.30 (m, 2H, H_{12}), 1.88 and 0.96 (m, 2H, H_7) 1.64 and 1.35 (m, 2H, H_{15}), 1.57 (m, 1H, H_8), 1.23 (m, 1H, H_{14}), 0.76 (s, 3H, CH_3). ^{13}C NMR (CD_3CN, 62.9 MHz): δ 164.4 (C_3), 111.6 and 102.9 (C_5 and C_{10}), 99.6 (η^5-Cp*), 92.5 (C_1), 80.2 (C_2), 81.5 (C_{17}), 78.7 (C_4), 49.9 (C_{14}), 44.0 (C_{13}), 42.0 (C_9), 38.5 (C_8), 37.1

(C_{12}), 30.8 (C_{16}), 27.7 (C_{11}), 28.4 (C_6), 26.1 (C_7), 23.5 (C_{15}), 11.5 (C_{18}), 9.5 (Me-Cp).

Synthesis of [Cp*Ir{η^4-$C_{10}H_{11}O$(OMe)}] (7a). A methanolic solution of NaOMe (0.75 mmol; freshly prepared from NaH (18 mg) in methanol (4 mL)) was added to a solution of [Cp*Ir(η^5-$C_{10}H_{11}O$)][BF_4] (**5**; 78 mg, 0.14 mmol) in MeOH (10 mL). The reaction mixture was stirred for 8 h at −40 °C; then the solvent was removed completely and the residue dried under vacuum. The residue was then extracted by Et_2O (2 × 50 mL), and the extracts were filtered into a dry Schlenk tube kept under argon. Diethyl ether was removed under vacuum, affording an off-white microcrystalline solid. Yield: 95% (67 mg). IR (KBr disk): ν(C=O) 1617. Anal. Calcd for $C_{21}H_{29}IrO_2$: C, 49.88; H, 5.78. Found: C, 49.74; H, 5.73. ^{1}H NMR (C_6D_6, 500 MHz): δ 3.81 (dd, J = 5.5 Hz, 1 Hz, 1H, H_2), 3.65 (d, J = 1 Hz, 1H, H_4), 3.59 (s, 3H, OMe), 3.03 (d, J = 5.5 Hz, 1H, H_2), 2.62 and 1.61 (m, 2H gem, H_6 or H_9), 2.45 and 1.75 (m, 2H gem, H_9 or H_6), 1.56 (s, 15H, Cp*), 1.44 and 1.23 (m, 2H gem, H_7 or H_8), 1.34 (m, 2H gem, H_8 or H_7). ^{13}C NMR (C_6D_6, 62.9 MHz): δ 184.5 (C_3), 88.6 (η^5-Cp), 85.4 and 82.5 (C_5 and C_{10}), 77.5 (C_2), 59.3 (C_4), 57.7 (OMe), 40.5 (C_1), 27.3 (C_6 or C_9), 26.6 (C_9 or C_6), 22.8, (C_7 and C_8), 9.3 (Me-Cp).

Synthesis of [Cp*Ir{η^5-$C_{18}H_{23}O_2$(OMe)}] (8a). Complex **8a** was synthesized in a way similar to that described for **7a**. This iridium dienone complex was obtained as an off-white microcrystalline solid in 91% yield. IR (KBr disk): ν(C=O) 1609. Anal. Calcd for $C_{29}H_{41}IrO_3$: C, 55.30; H, 6.56. Found: C, 55.10; H, 6.75. ^{1}H NMR (C_6D_6, 500 MHz): δ 3.82 (dd, J = 5.4 Hz, 1.0 Hz, 1H, H_2), 3.68 (d, J = 1.0 Hz, 1H, H_4), 3.58 (s, 3H, OMe), 3.49 (s, 1H, H_{17}), 3.35 (d, J = 5.4 Hz, 1H, H_1), 2.68 (m, 1H, $H_{6\beta}$), 1.92 and 1.41 (m, 2H, H_{16}), 1.89 and 1.03 (m, 2H, H_{12}), 1.79 and 1.71 (m, 2H, H_{11}), 1.67 (m, 1H, $H_{6\alpha}$), 1.62 (m, 1H, H_9), 1.60 (s, 15H, Cp*), 1.53 and 0.80 (m, 2H, H_7), 1.41 and 1.15 (m, 2H, H_{15}), 1.34 (m, 1H, H_8), 0.92 (m, 1H, H_{14}), 0.77 (s, 3H, CH_3). ^{13}C NMR (C_6D_6, 62.9 MHz): δ 186.4 (C_3), 88.7 (η^5-Cp*), 85.7 and 83.8 (C_5 and C_{10}), 81.6 (C_{17}), 77.0 (C_2), 58.5 (C_4), 57.7 (OMe), 50.2 (C_{14}), 43.7 (C_9), 40.2 (C_8), 38.7 (C_1), 37.6 (C_{12}), 30.9 (C_{16}), 29.8 (C_{11}), 29.2 (C_6), 26.6 (C_7), 23.3 (C_{15}), 11.5 (C_{18}), 9.4 (Me-Cp).

Oxidation of [Cp*Ir{η^5-$C_{10}H_{23}O_2$(OMe)}] (7a) by Iodine and Formation of 3-Methoxy-5,6,7,8-tetrahydro-2-naphthalenol (9). A solution of [Cp*Ir{η^5-$C_{10}H_{23}O_2$(OMe)}] (**7a**; 10 mg, 0.02 mmol) in CH_3CN (0.5 mL) was exposed to iodine (20 mg, 0.08 mmol) in CH_3CN (2 mL), and the reaction mixture was stirred for 15 min. The solvent was removed under vacuum. Analysis of the solution mixture by ^{1}H NMR showed quantitative formation of (**9**)[14] and the disappearance of **7a**. We also noted the presence of a singlet at 1.84 ppm, which corresponds to the chemical shift of $[Cp^*IrI_2]_2$ as reported in the literature.[10] ^{1}H NMR for **9** ($CDCl_3$, 200 MHz): δ 6.62 (s, 1H), 6.54 (s, 1H), 5.40 (s, 1H), 3.84 (s, 3H), 2.61 (m, 4H), 1.74 (m, 4H).

Oxidation of [Cp*Ir{η^5-$C_{18}H_{23}O_2$(OMe)}] (8a) by Iodine and Formation of 2-Methoxyestradiol (2). A solution of α-[Cp*Ir{η^4-$C_{18}H_{23}O_2$(OMe)}] (**8a**; 70 mg, 0.11 mmol) in CH_3-CN (5 mL), was exposed to iodine (42 mg, 0.16 mmol) in CH_3-CN (5 mL) and the reaction mixture was stirred for 15 min. The solvent was removed under vacuum, and the residue was eluted on a silica gel plate (20 × 20 cm) using Et_2O as eluent. The organic material **2** was obtained as a pale yellow solid.[13b] Yield: 90% (30 mg). The organometallic material $[Cp^*IrI_2]_2$ was obtained in 90% yield (115 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.81 (s, 1H), 6.65 (s, 1H), 5.43 (br s, 1H), 3.87 (s, 3H), 3.75 (t, 1H, J = 8.5 Hz), 2.77 (m, 2H), 2.20 (m, 3H), 1.99 (m, 1H), 1.87 (m, 1H), 1.69 (m, 1H), 1.35 (m, 8H), 0.80 (s, 3H).

X-ray Crystallography. Suitable crystals of α-[Cp*Ir(η^5-$C_{18}H_{23}O_2$)][BF_4] (**6a**) were obtained by recrystallization from acetone/Et_2O solution. The selected crystal was glued on the top of a glass stick. Accurate cell dimensions and orientation matrix were obtained by least-squares refinements of 25 accurately centered reflections. No significant variations were observed in the intensities of two check reflections during data collection. Complete crystallographic data and collection parameters are listed in Tables 1−3. The data were corrected for Lorentz and polarization effects. Computations were performed by using the PC version of CRYSTALS.[15] Scattering factors and corrections for anomalous dispersion were taken from ref 16. The structure was solved by standard Patterson and Fourier techniques and refined by full-matrix least squares with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were introduced in calculated positions in the last refinements and were allocated an overall refinable isotropic thermal parameter.

Acknowledgment. We thank Professor D. B. Grotjahn and Dr. M. Stephan for a loan of $IrCl_3 \cdot xH_2O$. The CNRS is gratefully acknowledged for supporting this work.

Supporting Information Available: Anisotropic displacement parameters (Table S1) and fractional parameters (Table S2) for **6a** (2 pages). Ordering information is given on any current masthead page.

OM961079C

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