# Intermolecular hydrogen bonding in organometallic-hormone derivatives. Crystal and molecular structures of .alpha.-[Cp*Ru(estradiol)][CF3SO3] and .alpha.-[Cp*Ru(3-O-(hydroxypropyl)estradiol)][CF3SO3]

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7-azabenzonorborandiene derivatives, it has been clearly demonstrated in this study that a fine-tuning of the electron-withdrawing substituent group on the bridging N atom gives fruitful information with regard to the nucleophilic attack on a coordinated CO. A strongly electron-releasing substituent or an H atom on the bridging N atom in 7-azabenzonorbornadiene, on the other hand, would cause the nucleophilic attack to proceed readily to a further stage such that the reaction of 7-azabenzonorbornadiene with $Fe_2(CO)_9$ failed to yield the analogous (olefin)$Fe(CO)_4$.[17]

(17) Sun, C. H.; Yang, C. Z. Unpublished results.

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**Registry No.** 1, 138234-34-1; 2, 138234-35-2; 3, 138234-36-3; $Fe_2(CO)_9$, 15321-51-4; 7-(methylsulfonyl)-7-azabenzonorbornadiene, 138234-31-8; 7-(*p*-chlorophenyl)-7-azabenzonorbornadiene, 138234-32-9; 7-*p*-tolyl-7-azabenzonorbornadiene, 138234-33-0.

**Supplementary Material Available:** Tables listing details of the data collection and refinement, final atomic coordinates, temperature factors, bond lengths and angles, and torsional angles for the compounds (17 pages); listings of observed and calculated structure factors (17 pages). Ordering information is given on any current masthead page.

# Intermolecular Hydrogen Bonding in Organometallic–Hormone Derivatives. Crystal and Molecular Structures of α-[Cp*Ru(estradiol)][$CF_3SO_3$] and α-[Cp*Ru(3-*O*-(hydroxypropyl)estradiol)][$CF_3SO_3$]

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*Summary:* The organometallic–hormone derivatives (α,β)-[Cp*Ru(estradiol)][$CF_3SO_3$] (**1a,b**) as well as (α,β)-[Cp*Ru(3-*O*-(hydroxypropyl)estradiol)][$CF_3SO_3$] (**2a,b**) were obtained in good yield and identified by spectroscopic methods. In particular, the crystal and molecular structures of **1a** and **2a** were determined by X-ray diffraction (monoclinic space groups $P2_1$, $P2_1$, $a$ = 8.596 (3), 8.533 (1) Å, $b$ = 16.005 (3), 16.483 (8) Å, $c$ = 10.674 (2), 11.798 (2) Å, $\beta$ = 100.77 (2), 102.37 (1)°, $Z$ = 2, 2, respectively), which reveal strong intermolecular hydrogen bonding in the solid state between the organometallic–hormone subunits, thus forming infinite chains, not a normal feature in steroid chemistry. Interestingly, the hydrogen donor and the hydrogen acceptor in **1a** and **2a** operate differently, and oppositely, depending on the nature of the hydroxyl group.

Hydrogen bonding plays a crucial role in the process of molecular recognition. This field has attracted considerable interest from both chemists and biochemists who are attempting to understand and explain the molecular basis of recognition.[1] Extensive research has been performed which shows that organic complexes and, more recently, organometallic complexes are capable of recognizing synthetic receptors[1,2] as well as natural and especially hormone receptors.[3] In the solid state, the "complex receptor" systems exhibit hydrogen bonding as a means of recognition.[4] Previously we have shown that the organometallic-labeled hormone α-[3-*O*-(hydroxypropyl)estradiol][$Cr(CO)_3$] is able to recognize the estradiol receptor with good binding affinities (relative binding affinity 28%);[3] however, the analogous α-[estradiol][$Cr(CO)_3$] was not studied, owing to its lack of stability. Consequently, we have become interested in preparing such stable complexes by direct introduction of the "Cp*Ru" (Cp* = $C_5Me_5$) adduct onto the A ring of estradiol but preserving the phenolic character. For comparison purposes, the [Cp*Ru(3-*O*-(hydroxypropyl)estradiol)][$CF_3SO_3$] derivative was also synthesized. It should be pointed out, however, that the presence of hydroxyl groups at C3 and C17 of β-estradiol is essential for effective binding, eventually by forming hydrogen bonds with the receptor sites.[5]

We have recently described the synthesis of some α-[Cp*Ru(estradiol)][$PF_6$] and (α,β)-[Cp*Ru(estradienonyl)] derivatives[6a] by following a one-pot reaction procedure.

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Table I. $^{13}C$ NMR Data ($\delta$, ppm) for Compounds 1a,b and 2a Recorded at 250 MHz in $CD_3CN$ or $CD_3COCD_3$ Solution

| | C1 | C2 | C3 | C4 | C5 | C10 | C18 | Cp* |
|---|---|---|---|---|---|---|---|---|
| | | | | (i) $CD_3CN$ Solution | | | | |
| free estradiol | 127.3 | 115.9 | 155.5 | 113.5 | 139.0 | 132.7 | 11.62 | |
| **1a** | 84.8 | 77.4 | 129.9 | 76.9 | 101.7 | 101.3 | 11.4 | 95.0, 10.1 |
| **1b** | 82.2 | 78.6 | 129.6 | 76.9 | 105.1 | 99.7 | 12.13 | 95.0, 10.6 |
| | | | | (ii) $CD_3COCD_3$ Solution | | | | |
| free 3-*O*-(hydroxypropyl)estradiol | 127.0 | 112.8 | 157.9 | 115.1 | 138.4 | 133.2 | 11.6 | |
| **2a** | 84.6 | 75.7 | 132.2 | 75.7 | 102.0 | 100.7 | 11.1 | 94.8, 9.8 |

However, problems arose in scaling up the reaction due to deposition of the starting material $[Cp^*RuCl_2]_2$[7] on zinc powder.[8] The introduction of the Cp*Ru moiety at the A ring of $\beta$-estradiol modifies the phenolic character of the ring to give the dienonylic form in 60% yield,[6a] but these compounds show a very weak recognition toward steroid receptors. Therefore, we were more interested in preparing an organometallic–hormone species in which the phenolic character of the A ring of $\beta$-estradiol would be preserved. We note that the compound [CpRu(3-*O*-methylestrone)]$PF_6$ and related species have been reported and, in particular, the X-ray structure of $\beta$-[CpRu(3-*O*-methylestrone)]$PF_6$ was determined.[6b,c]

Here we describe a selective route for the synthesis of ($\alpha$,$\beta$)-[Cp*Ru(estradiol)][$CF_3SO_3$] derivatives without formation of the corresponding dienonylic species. This method consists of introducing the tris(solvento) complex $[Cp^*Ru(MeCN)_3]^+[CF_3SO_3]^-$ at the A ring of $\beta$-estradiol according to the method of Fagan et al.[9] The crystal and molecular structures of $\alpha$-[Cp*Ru(estradiol)][$CF_3SO_3$] (**1a**) and $\alpha$-[Cp*Ru(3-*O*-(hydroxypropyl)estradiol)][$CF_3SO_3$] (**2a**) are also reported. Interestingly, these hormone derivatives exhibit strong intermolecular hydrogen bonding in the solid state between the O3, O33, and O17 atoms of these estradiol units, thus forming infinite chains, not a normal feature in steroid chemistry. The hydrogen donor and hydrogen acceptor in **1a** and **2a** operate differently, and oppositely, depending on the nature of the hydroxyl groups.

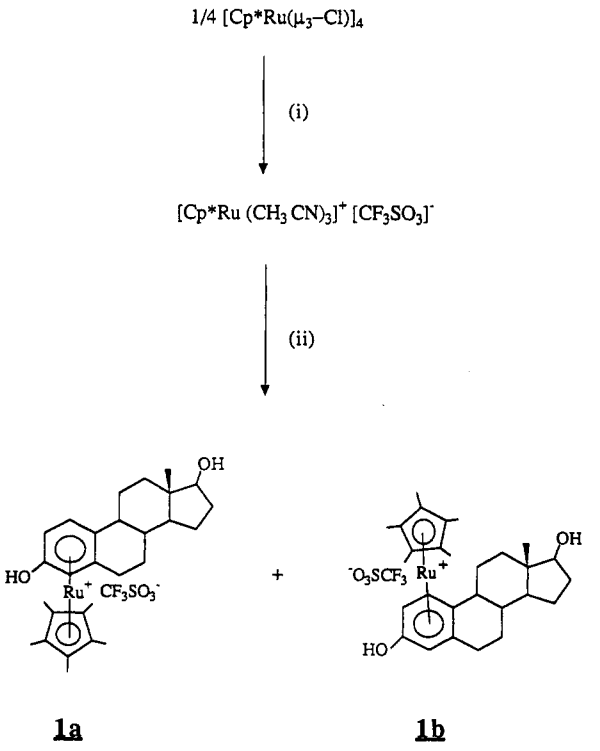
## Results and Discussion

Treatment of $[Cp^*Ru(MeCN)_3]^+[CF_3SO_3]^-$ with 1.2 equiv of estradiol in refluxing THF for 12 h gave a yellow solution which afforded the $\alpha$-isomer **1a** (Scheme I) upon addition of ether. The more soluble $\beta$-isomer **1b** was obtained from fractional crystallization of the supernatant phase, overall yield 65% ($\alpha/\beta$ ratio 85/15). Similarly, the above reaction was performed for 3-*O*-(hydroxypropyl)-estradiol, which led to the formation of ($\alpha$,$\beta$)-[Cp*Ru(3-*O*-(hydroxypropyl)estradiol)][$CF_3SO_3$] ($\alpha/\beta$ ratio 90/10) (**2a,b**) in 77% yield. Complexes **1a,b** and **2a** were isolated and characterized by spectroscopic methods, and satisfactory microanalyses were obtained for carbon and hydrogen.[11] The $^1H$ NMR spectra of **1a,b** recorded in $CD_3CN$ solution were most informative; they showed the upfield shift of the aromatic protons H1, H2, and H4 relative to the shifts in free estradiol. The stereochemistry of the Cp*Ru unit relative to the A ring is readily established by the chemical shifts of H2 and H4: these latter signals are permuted depending whether the compound is the $\alpha$- or $\beta$-isomer. The $^1H$ NMR spectra of the aromatic protons (H1, H2, H4) of **2a,b** recorded in $CD_3CN$ solution exhibit upfield shifts similar to those observed for **1a,b**. The pattern of the signals corresponding to H1, H2, and H4 is not preserved, however, and instead complex multiplets are obtained. The $^{13}C$ NMR spectra of **1a,b** and **2a** are presented in Table I. We note that the signals of aromatic carbons of the A ring are shifted to high field relative to those of free estradiol.

Interestingly, the **1a,b** salts obtained with a triflate counterion are more stable in solution than are the corresponding [Cp*Ru(estradiol)][$PF_6$] complexes, in terms of the transformation from the phenolic into the dienonylic species. In the presence of $NEt_3$, **1a,b** gives the corresponding ($\alpha$,$\beta$)-[Cp*Ru($\eta^5$-estradienonyl)] compound while when they are treated with $CF_3SO_3H$, the initial species were obtained, as previously reported for [Cp*Ru(estradiol)][$PF_6$].[6] Similar results were observed with the rhodium derivatives.[11]

Complexes **1a** and **2a** were crystallized from acetone/ether and $CH_2Cl_2$/ether, respectively, by following the

**Scheme I**[a]




**1a** **1b**

[a] Conditions and reagents: (i) THF/$CH_3CN$, AgOTf; (ii) estradiol, THF, reflux.

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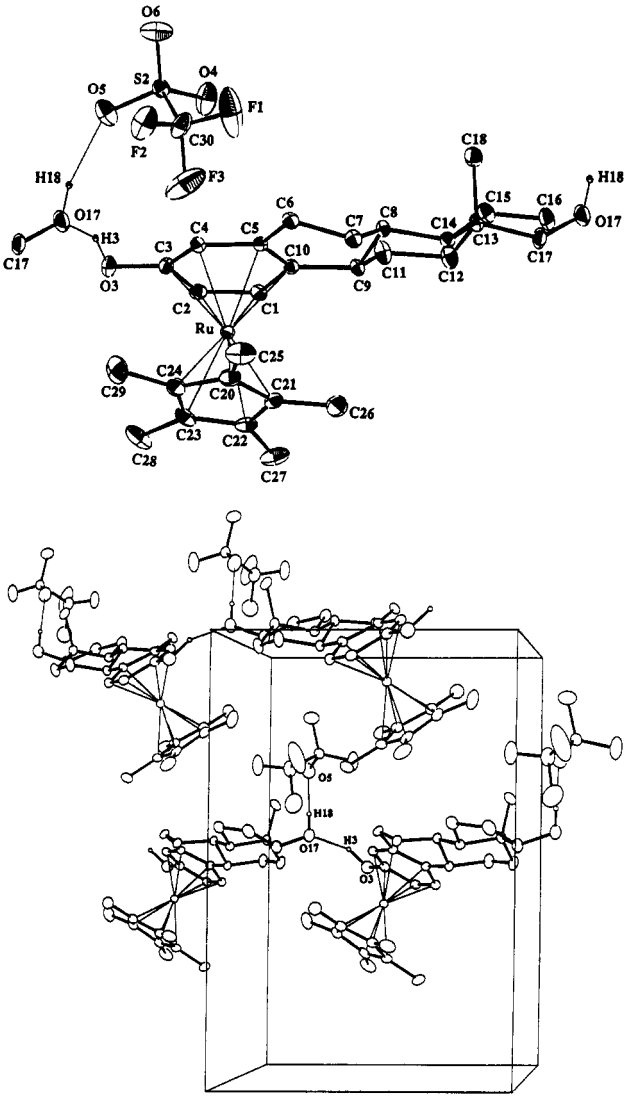


**Figure 1.** (a, top) Molecular structure of α-[Cp*Ru(estradiol)][$CF_3SO_3$] (**1a**). Selected bond distances (Å) and angles (deg): Ru1–C1 = 2.204 (5), Ru1–C2 = 2.203 (5), Ru1–C3 – 2.270 (5), Ru1–C4 = 2.187 (6), Ru1–C5 = 2.221 (6), Ru1–C10 = 2.268 (5), Ru1–C20 = 2.182 (5), Ru1–C21 = 2.197 (5), Ru1–C22 = 2.190 (7), Ru1–C23 = 2.183 (6), Ru1–C24 = 2.153 (6), C1–C2 = 1.398 (7), C2–C3 = 1.414 (7), C3–C4 = 1.400 (8), C4–C5 = 1.441 (8), C5–C10 = 1.418 (7), C10–C1 = 1.423 (7), C3–O3 = 1.328 (6); C10–C1–C2 = 120.8 (5), O3–C3–C2 = 119.1 (5), C4–C3–O3 = 123.4 (5), C10–C5–C4 = 118.8 (5), C3–C2–C1 = 121.8 (5), C4–C3–C2 = 117.2 (5), C5–C4–C3 = 122.3 (5). (b, bottom) ORTEP drawing of the one-dimensional infinite chains of the structure formed by hydrogen-bonding interactions between O3 and O17 of the organometallic–hormone subunits.

method of slow diffusion to give suitable crystals for X-ray structure analysis. Examination of the unit cell of either **1a** (Figure 1) or **2a** (Figure 2) shows that infinite chains of hormone derivatives are formed due to hydrogen bonding between O3–H3···O17 in **1a** and O33···H18–O17 in **2a**. These results are consistent with the IR spectra recorded for **1a** and **2a** (KBr disk), which show a broad peak due to ν(OH) at ca. 3415 and 3420 $cm^{-1}$, respectively, suggesting formation of intermolecular hydrogen bonding between the OH groups.

In complex **1a**, the O3···O17 distance is 2.672 (6) Å and O3–H3···O17 = 164°, with O3–H3 acting as the hydrogen donor and H3···O17 as the hydrogen acceptor. Furthermore, O17–H18 forms another hydrogen bond with one of the triflate counterions with O17···O(=S) = 2.849 (7) Å and O17–H18···O5 = 155°. For **2a**, the O33···O17 distance is

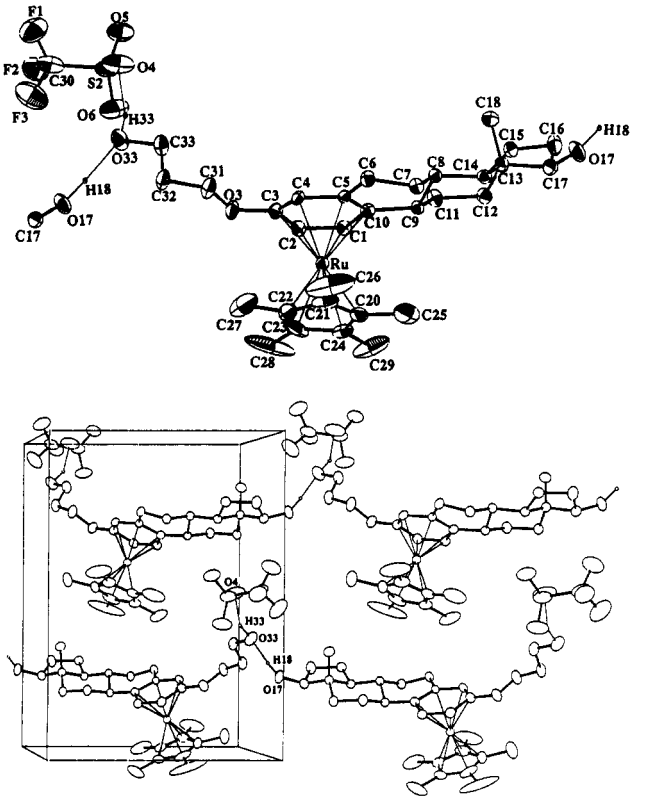


**Figure 2.** (a, top) X-ray structure of α-[Cp*Ru(3-*O*-(hydroxypropyl)estradiol)][$CF_3SO_3$] (**2a**). Selected bond distances (Å) and angles (deg): Ru1–C1 = 2.185 (7), Ru1–C2 = 2.191 (7), Ru1–C3 = 2.271 (8), Ru1–C4 = 2.200 (7), Ru1–C5 = 2.211 (7), Ru1–C10 = 2.242 (7), Ru1–C20 = 2.185 (9), Ru1–C21 = 2.14 (1), Ru1–C22 = 2.16 (1), Ru1–C23 = 2.14 (1), Ru1–C24 = 2.179 (9), C1–C2 = 1.403 (9), C2–C3 = 1.39 (1), C3–C4 = 1.38 (1), C4–C5 = 1.42 (1), C5–C10 = 1.407 (9), C10–C1 = 1.411 (9), C3–O3 = 1.351 (9); C10–C1–C2 = 120.3 (6), O3–C3–C2 = 116.9 (7), C4–C3–O3 = 123.6 (7), C10–C5–C4 = 119.8 (6), C3–C2–C1 = 120.7 (6), C4–C3–C2 = 119.4 (7), C5–C4–C3 = 120.7 (7). (b, bottom) ORTEP unit cell representation of **2a**. The intermolecular OH···O hydrogen bonds which link the molecules into one-dimensional infinite chains are indicated by thin lines.

2.830 (9) Å and O33···H18–O17 = 175°. Also, in contrast to what was observed for **1a**, O17–H18 acts as the hydrogen donor and O33···H18 as the hydrogen acceptor. Similarly, O33–H33 forms a hydrogen bond with one of the triflate counterions with O33···O(=S) = 2.777 (10) Å and O33–H33···O4 = 152°. Another important feature in these hormone derivative systems is the absence of water molecules in the unit cells. Hospital et al.[12] have reported the X-ray structure of free estradiol, where $H_2O$ plays an essential role by forming hydrogen bonds with O3 and O17 of two estradiol units. We note that the O3···O17 distance in **1a** is 2.672 (6) Å and is shorter than that reported for the free estradiol by 0.1 Å. This may indicate that α-[Cp*Ru(estradiol)][$CF_3SO_3$] has a stronger hydrogen-bonding system compared to that of free estradiol. This is due to the presence of the organometallic moiety Cp*Ru, which pulls out electronic density from the A ring and renders the phenolic group more acidic. The average C–C distance for the A ring of compound **1a** is 1.416 (4) Å compared to 1.39 (4) Å reported for the β-estradiol hemihydrate. The organometallic fragment Cp*Ru is bound symmetrically to the six carbons of the A ring of β-estradiol on the α-face trans to methyl C18 (Figure 1a), with an average Ru–C bond distance of 2.208 (5) Å. Similarly, the

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Cp*Ru moiety is coordinated to the A ring of 3-*O*-(hydroxypropyl)estradiol with an Ru–C distance of 2.217 (4) Å (Figure 2a). By comparison, in the X-ray structure of the analogous α-[Cp*Rh($\eta^5$-estradienonyl)][$BF_4$] derivative,[11] Cp*Rh is bound to only five carbons of the A ring with an average Rh–C distance of 2.225 (4) Å. We note that the C3–O3 distances are 1.328 (6) and 1.351 (9) Å in **1a** and **2a**, respectively, suggesting the presence of a single bond. These distances are longer than that observed for α-[Cp*Rh($\eta^5$-estradienonyl)][$BF_4$], reported to be 1.20 (1) Å, typical of a double bond. It is worth emphasizing that the dienonylic derivative α-[Cp*Rh($\eta^5$-estradienonyl)][$BF_4$] does not show any hydrogen bond between the organometallic–hormone subunits such as that observed in **1a** and **2a**. Preliminary results in hormone receptor binding assays with these complexes have shown that α-[Cp*Ru(estradiol)][$CF_3SO_3$] (**1a**) exhibits a reasonable binding affinity to the receptor site, while complex **2a** exhibits a weak interaction and the analogous α-[Cp*Rh($\eta^5$-estradienonyl)][$BF_4$] is inactive.

Research concerning the binding affinities of species **1a,b** and **2a,b** to the hormone receptor, as well as those of the rhodium and iridium derivatives, is currently underway in our laboratory. The effects of the charge, metal, and stereochemistry (i.e., α- or β-isomer) will be the subject of a forthcoming publication.

## Experimental Section

Manipulations were carried out under argon with use of standard Schlenk techniques. Solvents were purified and dried prior to use by conventional distillation techniques under argon. IR spectra were recorded as KBr pellets on a FT Bomen Michelson 100 spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM 250 instrument, and chemical shifts are relative to TMS ($^1H$, $^{13}C$); all $J$ values are given in Hz. The $^{13}C$ data are proton-decoupled and are reported downfield positive with respect to the reference standard Elemental analyses were performed by the microanalysis service of the CNRS, ICSN, Gif/Yvette, France.

**Preparation of (α,β)-[Cp*Ru(estradiol)][$CF_3SO_3$] (1a,b).** A red solution of 0.22 g (0.72 mmol) of recrystallized [Cp*Ru(μ-Cl)]$_4$[9] in a mixture of $CH_3CN$/THF (10 mL/10 mL) was maintained under reflux for 1 h under an argon atmosphere. AgOTf (0.22 g, 0.864 mmol) was then added, and the yellow solution was filtered. To the obtained solution was added β-estradiol (0.24 g, 0.936 mmol) in 10 mL of THF. After 12 h of reflux, the mixture was concentrated and complex **1a** (0.26 g, 0.38 mmol) was precipitated by addition of 40 mL of ether. **1b** (0.06 g, 0.091 mmol) was separated by fractional crystallization of the supernatant phase. Anal. Calcd: C, 52.97; H, 5.98. Found: C, 52.83; H, 5.94. IR (KBr, cm$^{-1}$): 3415 (vs, ν(OH) associated), 1547, 1466, 1447 (vs, phenyl ring), 1285–1260 (vs), 1031 (vs), 638 (vs) ($CF_3SO_3$). $^1H$ NMR (250 MHz, $CD_3CN$): free estradiol, δ 7.10 (d, $J$ = 7.5, H1), 6.53 (dd, $J$ = 7.5 and 2.5, H2), 6.49 (d, $J$ = 2.5, H4), 0.72 (s, Me 18); **1a**, δ 5.72 (d, $J$ = 6.5, H1), 5.50 (dd, $J$ = 6.5 and 2.5, H2), 5.42 (d, $J$ = 2.5, H4), 1.81 (s, Cp*), 0.70 (s, Me 18); **1b**, δ 5.69 (d, $J$ = 6.5, H1), 5.33 (dd, $J$ = 6.5 and 2.5, H2), 5.43 (d, $J$ = 6.5, H4), 1.87 (s, Cp*), 0.80 (s, Me 18).

**Preparation of (α,β)-[Cp*Ru(3-*O*-(hydroxypropyl)estradiol)][$CF_3SO_3$] (2a,b).** The above reaction was also performed with [Cp*Ru(μ-Cl)]$_4$ (0.27 g, 0.882 mmol) and of 3-*O*-(hydroxypropyl)estradiol (0.50 g, 1.323 mmol; prepared by heating β-estradiol with NaOH and $Br(CH_2)_3OH$).[10] After addition of ether, a mixture of **2a** and **2b** (0.55 g, 0.769 mmol) was obtained, and the α-isomer was recrystallized from $CH_2Cl_2$/ether. Anal. Calcd: C, 53.71; H, 6.39. Found: C, 53.95; H, 6.54. IR (KBr, cm$^{-1}$): 3420 (ν(OH) associated), 1541, 1470, 1465 (phenyl ring), 1281–1252 (vs), 1030 (vs), 638 (vs) ($CF_3SO_3$). $^1H$ NMR (250 MHz, $CD_3CN$): free 3-*O*-(hydroxypropyl)estradiol, δ 7.17 (dd, $J$ = 6.5, H1), 6.67 (dd, $J$ = 6.5 and 2.5, H2), 6.62 (d, $J$ = 2.5, H4), 0.72 (s, Me 18); **2a**, δ 5.75 (m, H1), 5.65 (m, H2), 5.64 (s, H4), 1.83 (s, Cp*), 0.71 (s, Me 18); **2b**, δ 5.60 (m, H1), 5.50 (m, H2), 5.75 (s, H4), 1.88 (s, Cp*), 0.80 (s, Me 18).

**X-ray Crystal Structures of Complexes 1a and 2a.** Crystal data for compound **1a** at 20 °C: space group $P2_1$, $a$ = 8.596 (3) Å, $b$ = 16.005 (3) Å, $c$ = 10.674 (2) Å, β = 100.77 (2)°, $V$ = 1443 (6) Å$^3$, $Z$ = 2, $\rho_{calcd}$ = 1.51 g cm$^{-3}$, 3596 unique reflections measured (Mo Kα, 2° < 2θ < 56°), 2870 reflections with $I > 3\sigma(I)$ and used in the solution, with standard Fourier–Patterson techniques and least-squares refinement of the structure. The final refinement (464 variables) gave $R$ = 0.028 and $R_w$ = 0.030. Crystal data for compound **2a** at 20 °C: space group $P2_1$, $a$ 8.5331 (8) Å, $b$ = 16.483 (8) Å, $c$ = 11.798 (2) Å, β = 102.37 (1)°, $V$ = 1621 (4) Å$^3$, $Z$ = 2, $\rho_{calcd}$ = 1.47 g cm$^{-3}$, 4039 unique reflections measured (Mo Kα, 2° < 2θ < 56°), 3023 reflections with $I > 3\sigma(I)$ used in the solution, with standard Fourier–Patterson techniques and least-squares refinement of the structure. The final refinement (464 variables) gave $R$ = 0.039 and $R_w$ = 0.040.

Computations were performed using CRYSTALS[13] adapted for a Microvax-II computer. Scattering factors and corrections for anomalous dispersion were from ref 14. Solutions of the structures were accomplished by using standard Patterson–Fourier techniques. For both compounds, all non-hydrogen atoms were refined anisotropically. For compound **1a**, hydrogen atoms (except the OH ones H3 and H18) were located on a difference-Fourier map and their coordinates refined with an overall refinable isotropic thermal parameter. For compound **2a**, a similar procedure was performed for all non-methyl hydrogens (except the OH ones H33 and H18). The methyl H atoms were included in the refinement as fixed contributors (with $U$(iso) = 1.2$U$(eq), of the bonded C atom) and recalculated after each cycle. For each compound, the hydroxyl H atoms, located on a difference-Fourier map, were put in the last refinement in fixed positions with approximately the same $U$(iso) value as the refined H atoms. In compound **2a**, the methyl carbons on the cyclopentadiene ring have relatively large ellipsoids.

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**Registry No.** **1a**, 137768-13-9; **1b**, 137821-43-3; **2a**, 137768-15-1; **2b**, 137821-45-5; $Br(CH_2)_3OH$, 627-18-9; [Co*Ru(μ-Cl)]$_4$, 113860-07-4; AgOTf, 2923-28-6; β-estradiol, 50-28-2; 3-*O*-(hydroxypropyl)estradiol, 21830-21-7.

**Supplementary Material Available:** Tables of crystal data, positional and thermal parameters, and complete bond distances and angles (14 pages); listings of calculated and observed structure factors (18 pages). Ordering information is given on any current masthead page.

(13) Watkin, D. J.; Carruthers, J. R.; Betteridge, P. W. *Crystals User Guide*; Chemical Crystallography Laboratory, University of Oxford: Oxford, England, 1986.

(14) *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.