Organometallic Complexes Containing 17-Ethynyl-17β-hydroxyandrost-4-en-3-one and Related Ethynyl Steroids

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Gold complexes of 17-ethynyl-17β-hydroxyandrost-4-en-3-one, 17-ethynyl-3-methoxyestra-1,3,5(10)-trien-17β-ol, and 17α-ethynylestra-1,3,5(10)-triene-3,17β-diol have been prepared and characterized. The title compounds were prepared by treatment of the parent ethynyl steroid with sodium bis(trimethylsilyl)-amide followed by the addition of R_3PAuCl. Using a variety of phosphorus donors, a total of 36 gold steroid compounds were readily prepared using this approach. Compounds containing basic low cone angle phosphines such as PMe_3 and PEt_3 exhibited broad signals in the $^{13}C\{^1H\}$ NMR spectrum for the alkyne moiety, while compounds containing triarylphosphines or moderately bulky trialkylphosphines exhibited sharp signals. Correlations between common measures of phosphine donor ability with $^2J_{CP}$ and $^3J_{CP}$ as well as changes in the ^{31}P chemical shift were made. While the use of low cone angle phosphines was successful, analogous reactions with trimesitylphosphine or tris(2,4,6-trimethoxyphenyl)phosphine resulted in intractable mixtures containing significant amounts of free phosphine. The incorporation of electron-withdrawing groups into the organic fragment of the phosphine donors was tolerated except for $P(C_6F_5)_3$, where displacement of the phosphine was observed. The molecular structures of five representative examples are presented and discussed. These determinations represent the first structurally characterized examples where the transition metal is σ-bound to the ethynyl fragment of the steroid.

Introduction

Over the past few decades, an intense amount of research has focused on new ways to introduce pharmaceuticals into cancerous tissues that are rich in estrogen receptors.[1] Recently, elegant work by Hanson demonstrated that 17α-phenylvinyl estradiols can be prepared using Stille coupling reactions involving vinyl tin steroids.[2] These steroid derivatives were attractive substrates for estrogen receptor therapy since they were shown to bind well to the ER−hormone binding domain.[2] Molecular modeling experiments corroborated the experimental studies by showing that the binding site can accommodate large groups in the 17α position of the steroid.[3] In addition to vinyl derivatives, a number of compounds have been prepared that retain the alkyne moiety. Arterburn has recently demonstrated that 17α-ethynyl estradiol derivatives can be prepared through Sonogashira coupling reactions.[4] In addition to organic derivatives, a number of transition metal complexes have been prepared using ethynyl steroids. Typically, the metal-containing compounds are synthesized by attaching functional groups to the alkyne moiety which act as ligands for transition metals.[5−7] Following this theme, Hannon prepared a series of pincer compounds that bind to several different metals including platinum and zinc,[8] and Jaouen has attached rhenium- and manganese-containing cyclopentadienyl fragments to 17α-ethynylestra-1,3,5(10)-triene-3,17β-diol (ethynyl estradiol).[9]

One of the simplest ways to bind ethynyl steroids to transition metals is through direct attachment of the metal to the acetylene group.[10] Recently, Osella attached two $Co(CO)_6$ fragments to

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17-ethynyl-17β-hydroxyandrost-4-en-3-one (ethisterone) through the π-system of the acetylene.[11] Examples of metal complexes that contain a σ-bound ethynyl steroid are extremely rare.[12] Bonati showed that PPh_3Au(imidazole) reacts with 17-ethynyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (mestranol) to generate PPh_3Au(mestranol).[13] In this example the coordinated imidazole was basic enough to deprotonate the acetylene fragment of the steroid to generate the gold(I) acetylide.

Gold is an attractive metal to incorporate into potential anticancer drugs due to the discovery that a number of inorganic and organometallic gold species inhibit the growth of tumors cells.[14] Some of the first gold compounds to be screened were the antiarthritis drug auranofin and simple gold(I) compounds of the type R_3PAuX (X = Cl, CN, SCH_3, SCN).[15,16] Recently, Che has shown that gold porphyrins are a promising new class of anticancer drugs, and Caruso demonstrated that a mixed phosphine species $[(Ph_2P(CH_2)_3PPh_2)Au(PPh_3)]Cl$ was active against MCF7 (breast cancer).[17] Due to the potential of gold(I) compounds to act as anticancer agents, we have synthesized and characterized a series of organometallic gold species bearing ethisterone, ethynyl estradiol, and mestranol (Figure 1).

Results and Discussion

A number of synthetic procedures have been developed for the preparation of alkynyl gold compounds.[18] Ligand-free oligomeric gold acetylides of the type $\{AuC{\equiv}CR\}_n$ have been prepared by treatment of gold salts with a terminal acetylene in the presence of a base such as Et_3N.[19] These ligand-free gold species react with Lewis bases such as phosphine donors to generate monomeric gold acetylides in high yields (**A**, Figure 2).[19] The mononuclear ethynyl gold compounds can be directly prepared by treatment of R_3PAuX (R = alkyl, aryl; X = Cl, Br) with a terminal acetylene in the presence of a base (**B**, Figure 2).[20]

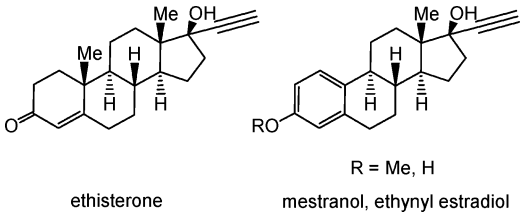

Figure 1. Ethynyl steroids used in the preparation of gold compounds.

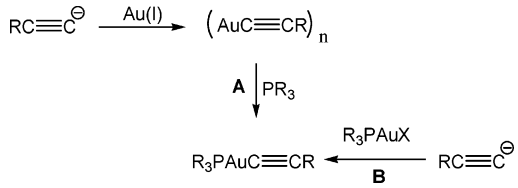

Figure 2. General methods for the preparation of gold(I) acetylide compounds.

Due to the availability of convenient precursors, treatment of R_3PAuX species with ethynyl steroids in the presence of a base was chosen as the synthetic pathway for the preparation of R_3PAu(steroid) compounds (**B**, Figure 2). To probe the effectiveness of this pathway, a series of screening reactions were carried out using ethisterone and Ph_3PAuX as model substrates. Initially, Ph_3PAuBr solutions were added to ethynyl steroid/base mixtures in THF at 25 °C with vigorous stirring. A number of bases were screened for activity, and while mild bases such as Et_3N and NaOEt were reported to give high yields of gold acetylide compounds, mixtures of Ph_3PAu(ethisterone), free ethisterone, and Ph_3PAuBr were observed by ^1H and ^{31}P NMR spectroscopy after the reaction was stirred for several days. Mineral bases such as Cs_2CO_3 were also inefficient and gave intractable mixtures. In contrast to these results, using sodium bis(trimethylsilyl)amide (NaHMDS) generated high yields of Ph_3PAu(ethisterone) within a few hours at 25 °C (eq 1). The gold acetylide species were isolated in analytically pure form after purification by column chromatography and drying under vacuum. Several variations of this theme were attempted in order to probe the scope of the methodology. The initial process involved the addition of Ph_3PAuBr solutions to a mixture created by the addition of NaHMDS to ethisterone in THF. However, this required isolation of the PR_3AuX species. To avoid isolating the R_3PAuX precursors, treatment of

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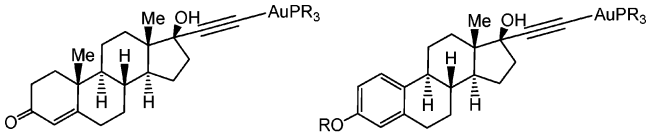
Table 1. Gold Steroid Complexes[a]

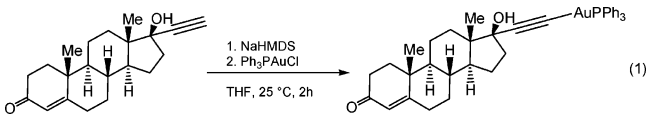


R = Me, H

R_3P-Au-steroid	#	yld[b]	δ ^{31}P[c]	$\Delta\delta$[d]	$^3J_{PC}$[e]	$^2J_{PC}$[e]	δ $C^1{\equiv}C-Au$[f]	δ $C{\equiv}C^2$-Au[f]	$\Delta\delta$ C^1[g]	$\Delta\delta$ C^2[g]
Me_3PAu(ethisterone)[h]	1	76.0	0.3	11.4	27.4	144.3	108.3	125.3	51.1	21.1
Me_3PAu(ethynyl estradiol)[i]	2	58.9	0.4	11.5	25.6	142.2	108.8	125.9	51.8	21.4
Me_3PAu(mestranol)[j]	3	55.0	0.3	11.4	25.6	143.9	108.5	125.2	51.2	21.0
Et_3PAu(ethisterone)[k]	4	84.5	36.5	5.9	25.3	136.0	107.4	128.4	54.2	20.2
Et_3PAu(ethynyl estradiol)[j]	5	65.4	36.5	5.9	26.0	135.9	107.8	128.8	54.7	20.4
Et_3PAu(mestranol)[j]	6	55.6	36.4	5.8	26.0	138.2	107.5	128.9	54.9	20.0
$(Me_2PhP)Au$(ethisterone)[k]	7	54.9	12.6	7.4	26.6	143.2	108.0	125.7	51.5	20.8
$(Me_2PhP)Au$(ethynyl estradiol)[j]	8	63.3	12.6	7.4	26.6	144.4	108.3	125.9	51.8	20.9
$(Me_2PhP)Au$(mestranol)[h]	9	62.0	12.5	7.3	26.5	144.0	108.3	125.9	51.9	20.8
$MePh_2PAu$(ethisterone)[k]	10	79.2	25.6	6.3	26.3	141.9	107.9	125.5	51.3	20.7
$MePh_2PAu$(ethynyl estradiol)[h]	11	55.5	25.6	6.3	26.2	141.1	108.1	125.7	51.6	20.7
$MePh_2PAu$(mestranol)[k]	12	43.0	25.6	6.3	26.4	144.5	108.1	125.7	51.9	20.7
Ph_3PAu(ethisterone)	13	85.6	40.7	8.7	25.7	142.0	107.4	125.9	51.7	20.2
Ph_3PAu(ethynyl estradiol)	14	87.1	41.3	9.2	25.9	141.7	107.8	125.8	51.7	20.4
Ph_3PAu(mestranol)	15	77.0	41.3	9.2	25.5	141.7	107.7	125.7	51.7	20.2
$(4\text{-}C_6H_4F)_3PAu$(ethisterone)	16	86.1	39.4	9.3	26.3	143.9	107.7	125.4	51.4	20.5
$(4\text{-}C_6H_4F)_3PAu$(ethynyl estradiol)	17	69.7	39.4	9.3	25.5	146.8	108.2	125.3	51.2	20.8
$(4\text{-}C_6H_4F)_3PAu$(mestranol)	18	76.0	39.5	9.3	26.0	144.4	108.0	125.2	51.2	20.5
Ph_2PyPAu(ethisterone)	19	90.4	40.5	9.3	25.4	140.3	107.3	126.2	52.0	20.1
Ph_2PyPAu(ethynyl estradiol)	20	78.2	40.5	9.3	25.0	144.7	107.7	126.1	52.0	20.3
Ph_2PyPAu(mestranol)	21	81.7	40.5	9.3	25.5	147.4	107.7	127.9	53.9	20.2
Cy_3PAu(ethisterone)	22	87.3	54.8	1.6	23.8	131.2	106.5	130.6	56.4	19.3
Cy_3PAu(ethynyl estradiol)	23	69.1	54.8	1.6	23.7	130.9	107.0	130.4	56.3	19.6
Cy_3PAu(mestranol)	24	83.4	54.8	1.6	23.8	131.3	106.8	130.4	56.4	19.3
$(ClCH_2CH_2O)_3PAu$(ethisterone)[j]	25	77.9	145.8	28.4	34.8	206.9	108.6	125.5	51.3	21.4
$(ClCH_2CH_2O)_3PAu$(ethynyl estradiol)[j]	26	82.7	145.8	28.4	37.8	207.3	109.0	126.6	52.5	21.6
$(ClCH_2CH_2O)_3PAu$(mestranol)[j]	27	73.0	145.8	28.4	36.7	207.3	109.0	126.6	52.6	21.5
$(OEt)_3PAu$(ethisterone)	28	83.2	143.7	30.2	36.5	204.1	108.2	127.0	52.8	21.0
$(OEt)_3PAu$(ethynyl estradiol)	29	80.0	144.1	30.4	36.9	203.9	108.6	126.9	52.8	21.2
$(OEt)_3PAu$(mestranol)	30	55.0	144.1	30.4	36.1	205.1	108.6	126.8	52.8	21.1
$(furyl)_3PAu$(ethisterone)[h]	31	65.2	−17.9	12.9	27.1	149.1	107.2	123.9	49.7	20.0
$(furyl)_3PAu$(ethynyl estradiol)[h]	32	65.3	−18.0	12.8	27.6	150.3	107.6	124.0	49.9	20.2
$(furyl)_3PAu$(mestranol)[h]	33	58.0	−18.1	12.7	27.5	149.2	107.5	123.8	49.8	20.0
$(pyrr)_3PAu$(ethisterone)	34	49.3	111.2	25.0	31.4	169.7	107.7	130.3	56.1	20.5
$(pyrr)_3PAu$(ethynyl estradiol)	35	86.7	111.3	25.1	31.1	169.2	108.3	130.3	56.2	20.9
$(pyrr)_3PAu$(mestranol)	36	55.1	111.4	25.2	30.9	169.4	108.0	130.1	56.1	20.5

[a] $CDCl_3$ at 25 °C unless stated. [b] Isolated material based upon gold. [c] Reported in ppm and relative to external 85% phosphoric acid. [d] $\Delta\delta$ refers to the change in the ^{31}P chemical shift between R_3PAuCl and $R_3P-Au-C{\equiv}C$steroid. [e] Hertz. [f] Chemical shift (ppm) in the ^{13}C spectrum of the alkyne carbons. [g] $\Delta\delta$ refers to the change in the chemical shift between the alkyne carbons in **1**−**36** relative to the free ethynyl steroid ($CDCl_3$): ethisterone ($C^1 = 87.2$, $C^2 = 74.2$), ethynyl estradiol ($C^1 = 87.4$, $C^2 = 74.1$), mestranol ($C^1 = 87.5$, $C^2 = 74.0$). The carbon spectrum is reported at the temperature that gave the highest resolution of the alkyne carbons. [h] $^{13}C\{^1H\}$ data recorded at −23 °C. [i] $^{13}C\{^1H\}$ data recorded at −13 °C. [j] $^{13}C\{^1H\}$ data recorded at −33 °C. [k] $^{13}C\{^1H\}$ data recorded at −43 °C.

Me_2SAuCl with 1 equiv of a trialkyl- or triarylphosphine was found to be a convenient way to generate R_3PAuCl species in situ. In addition to the stepwise addition reaction, moderate yields of the R_3PAu(steroid) species were obtained when the reaction was carried out in a "one-pot" fashion where all of the solids were added to the reactor vessel prior to the addition of the solvent and base.



(1)

After the screening experiments were completed, the chemistry was extended to other phosphines and phosphites as well as other ethynyl steroids. The preparative yields and selected spectroscopic data for the isolated R_3PAu(steroid) complexes prepared in this study are listed in Table 1. A number of compounds containing basic trialkylphosphines with low cone angles such as PMe_3 and PEt_3 (cone angles = 118° and 132°) were readily prepared.[21] Slightly bulkier trialkylphosphines such as PCy_3 (cone angle = 170°) also gave high yields of the R_3PAu(steroid) species. The use of phosphorus donors containing heteroatoms such as oxygen and nitrogen was also successful (Table 1; **19**−**21**, **25**−**36**). Compounds **19**−**21** are particularly attractive since transition metal compounds bearing Ph_2PyP have been used to prepare bimetallic species.[22] Compounds **1**−**36** are robust white solids that exhibit high solubility in a variety of common solvents. In contrast to many gold acetylides that are shock sensitive or explosive,[18b,23] these gold steroids are

(20) Cross, R. J.; Davidson, M. F.; McLennan, A. J. *J. Organomet. Chem.* **1984**, *265*, C37. (b) Bruce, M. I.; Horn, E.; Matisons, J. G.; Snow, M. R. *Aust. J. Chem.* **1984**, *37*, 1163. (c) Bruce, M. I.; Duffy, D. N. *Aust. J. Chem.* **1986**, *39*, 1697. (d) Bruce, M. I.; Grundy, K. R.; Lidell, M. J.; Snow, M. R.; Tiekink, R. T. *J. Organomet. Chem.* **1988**, *344*, C49. (e) Bruce, M. I.; Hall, B. C.; Skelton, B. W.; Smith, M. E.; White, A. H. *J. Chem. Soc., Dalton Trans.* **2002**, 995. (f) Coates, G. E.; Parkin, C. *J. Chem. Soc.* **1962**, 3220. (g) Johnson, A.; Puddephatt, R. J. *J. Chem. Soc., Dalton Trans.* **1977**, 1384. (h) Irwin, M. J.; Vittal, J. J.; Puddephatt, R. J. *Organometallics* **1997**, *16*, 3541.

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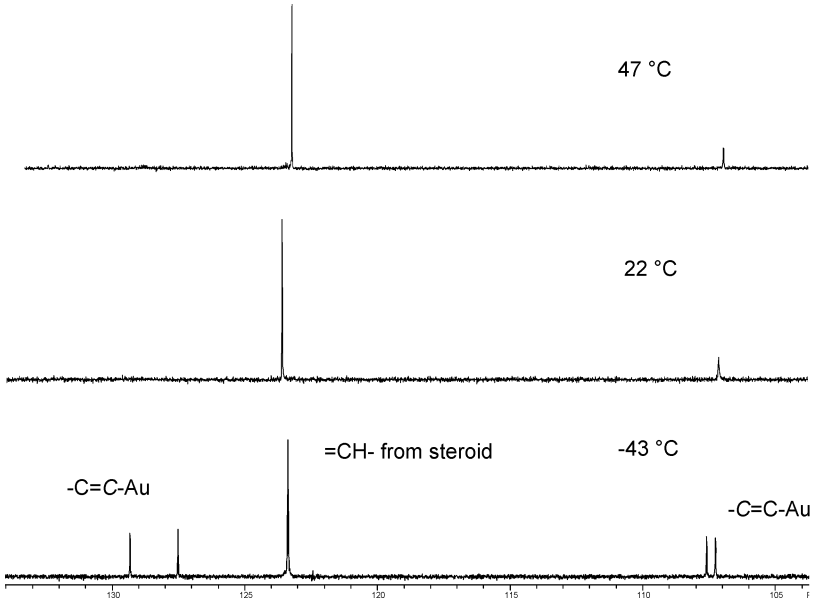

Figure 3. $^{13}C\{^1H\}$ NMR spectra of Et_3PAu(ethisterone) (alkyne carbon region) between −43 and 47 °C.

stable up to 200 °C under vacuum. Although a number of compounds were successfully prepared with a variety of small to moderately large phosphine donors, analogous reactions involving bulky phosphines such as Mes_3P (cone angle = 212°) and $(2,4,6\text{-}C_6H_2(OMe)_3)_3P$ were problematic. Analysis of the crude residues from these reactions with $^{31}P\{^1H\}$ NMR spectroscopy revealed free Mes_3P and $(2,4,6\text{-}C_6H_2(OMe)_3)_3P$. Additionally, reactions using weakly basic phosphine donors such as $P(C_6F_5)_3$ were unsuccessful. Similar to reactions involving bulky phosphine donors, analysis of the reaction mixtures revealed free phosphine, and no $(C_6F_5)_3PAu$(steroid) compounds were observed. Although extremely bulky and weakly basic phosphines presented synthetic challenges, the scope of the reaction chemistry is broad, and several dozen new gold steroid compounds were prepared.

NMR Spectroscopic Characterization of Gold Steroids. The gold steroids exhibited a singlet in the $^{31}P\{^1H\}$ NMR spectrum with line widths between 1.5 and 4.0 Hz. The only exceptions were complexes bearing $furyl_3P$ (**31**−**33**; line widths > 40 Hz) and $(4\text{-}C_6H_4F)_3P$ (**16**−**18**). The latter exhibited a multiplet in the $^{31}P\{^1H\}$ NMR spectrum due to coupling to ^{19}F. For **31**−**33**, recording the data at low temperature resulted in sharp signals. Typically, the signal in the $^{31}P\{^1H\}$ NMR spectrum for the R_3PAu(steroid) complexes appeared to higher frequency than the R_3PAuCl precursors, with the magnitude of the change (Table 1: $\Delta\delta = \delta_{acetylide} - \delta_{chloride}$) ranging from 1.6 ($PCy_3$) to 30.4 ppm ($P(OEt)_3$). The $\Delta\delta$ follows the Tolman electronic parameter[24] with the σ-donor donors exhibiting larger $\Delta\delta$ values, while σ-donor/π-acceptor donors displayed smaller $\Delta\delta$ values. The $\Delta\delta$ also displayed moderate correlations with other measures of phosphine donor ability (E_B,[25] C_B,[25] E_B/C_B,[25] and $E°$,[26] Supporting Information).

In all cases the carbon atoms of the steroid framework were resolved in the $^{13}C\{^1H\}$ NMR spectrum. For carbon atoms removed from the point of attachment to gold, small changes in the chemical shifts were observed between **1**−**36** and free ethisterone, ethynyl estradiol, and mestranol. In contrast, significant changes were observed for the alkyne carbons upon coordination of gold (Table 1). Both alkyne carbons appeared at higher frequency (relative to the free ethynyl steroid) with the terminal alkyne carbon shifting over 49 ppm in **1**−**36**, while the internal alkyne carbon shifted over 18 ppm.

In the course of this work we observed that the alkyne carbons were often broad in the $^{13}C\{^1H\}$ NMR spectrum at or above 25 °C (Figure 3). This dynamic solution behavior was typically observed in compounds with small basic phosphines (**1**−**12**). Compounds incorporating slightly bulkier phosphine donors (PCy_3; **22**−**24**) as well as triarylphosphines (**13**−**21**) gave sharp resonances in the $^{13}C\{^1H\}$ NMR spectrum at 25 °C. The broadened signals exhibited by **1**−**12** could be due to a trace amount of free phosphine that exchanged with the bound phosphine, or intermolecular phosphine exchange between gold steroid compounds. Both possibilities have been reported for two-coordinate gold compounds.[27] Identical solution behavior was observed when the X-ray crystals were used for the NMR analysis. In all cases cooling the solutions resulted in sharp resonances for the alkyne carbons. Additionally, the line width of the singlet in the $^{31}P\{^1H\}$ NMR spectrum of **1**−**12** was sharp (<5 Hz) between 25 and −43 °C, and no additional phosphine resonances were observed in the $^{31}P\{^1H\}$ NMR spectra of **1**−**12**

(22) Wang, Q.-M.; Lee, Y.-A.; Crespo, O.; Deaton, J.; Tang, C.; Gysling, H. J.; Concepcion Gimeno, M.; Larraz, C.; Villacampa, M. D.; Laguna, A.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 9488. (b) Newkome, G. R. *Chem. Rev.* **1993**, *93*, 2067. (c) Francio, G.; Scopelliti, R.; Arena, C. G.; Bruno, G.; Drommi, D.; Faraone, F. *Organometallics* **1998**, *17*, 338. (d) Chan, W.-H.; Zhang, Z.-Z.; Mak, T. C. W.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1998**, 803. (e) Kuang, S.-M.; Xue, F.; Zhang, Z.-Z.; Xue, W.-M.; Che, C.-M.; Mak, T. C. W. *J. Chem. Soc., Dalton Trans.* **1997**, 3409. (f) Kuang, S.-M.; Cheng, H.; Sun, L.-J.; Zhang, Z.-Z.; Zhou, Z. Y.; Wu, B.-M.; Mak, T. C. W. *Polyhedron* **1996**, *15*, 3417. (g) Xie, L. Y.; James, B. R. *Inorg. Chim. Acta* **1994**, *217*, 209. (h) De Munno, G.; Bruno, G.; Arena, C. G.; Drommi, D.; Faraone, F. *J. Organomet. Chem.* **1993**, *450*, 263. (i) Reinhard, G.; Hirle, B.; Schubert, U.; Knorr, M.; Braunstein, P.; De Cian, A.; Fischer, J. *Inorg. Chem.* **1993**, *32*, 1656. (j) Zhang, Z.-Z.; Xi, H.-P.; Zhao, W.-J.; Jiang, K.-Y.; Wang, R.-J.; Wang, H.-G.; Wu, Y. *J. Organomet. Chem.* **1993**, *454*, 221. (k) Arena, C. G.; Faraone, F.; Fochi, M.; Lanfranchi, M.; Mealli, C.; Seeber, R.; Tiripicchio, A. *J. Chem. Soc., Dalton Trans.* **1992**, 1847. (l) Rotondo, E.; Bruno, G.; Nicolo, F.; Lo Schiavo, S.; Piraino, P. *Inorg. Chem.* **1991**, *30*, 1195. (m) Maisonnat, A.; Farr, J. P.; Omstead, M. M.; Hunt, C. T.; Balch, A. L. *Inorg. Chem.* **1982**, *21*, 3961. (n) Alcock, N. W.; Moore, P.; Lampe, P. A. *J. Chem. Soc., Dalton Trans.* **1982**, 207.

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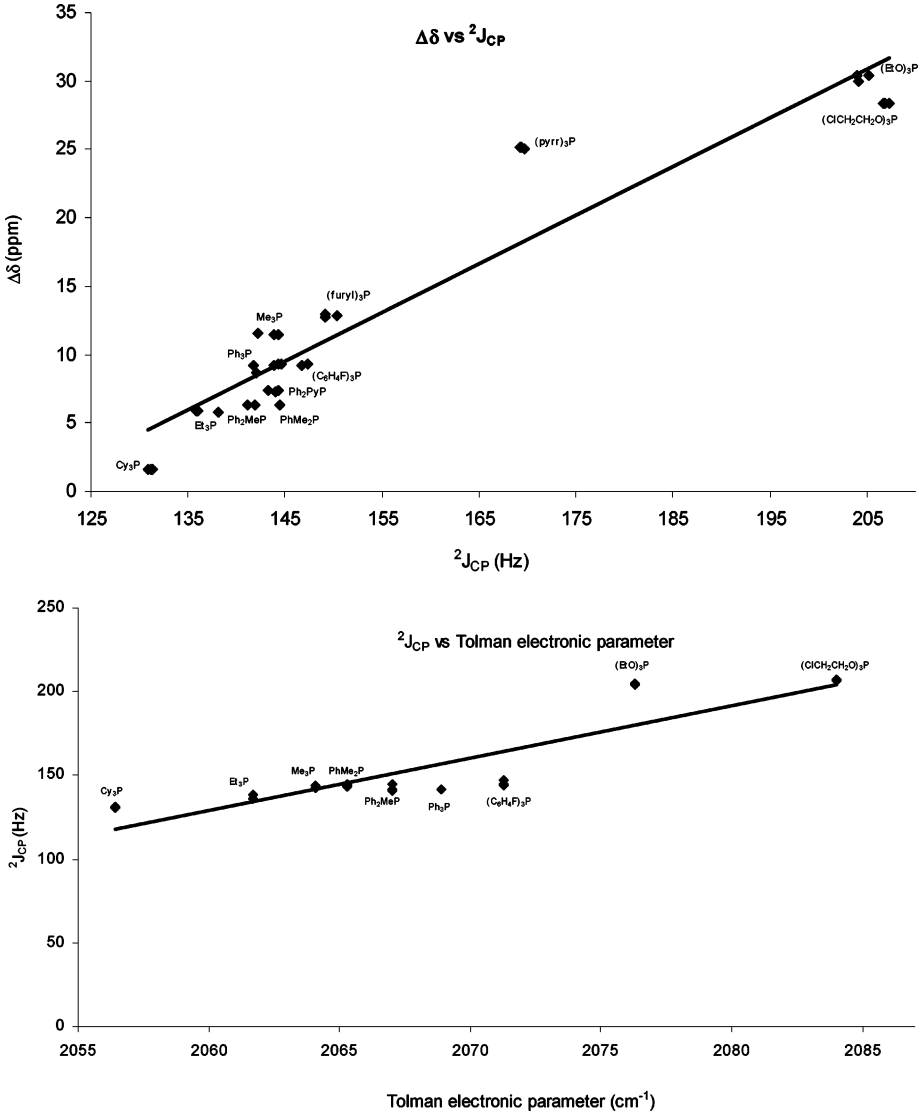

Figure 4. Selected correlations of the spectral data. Tolman electronic parameter υ (cm^{-1}); $\Delta\delta$ refers to the change in the ^{31}P chemical shift between R_3PAuCl and R_3PAu(steroid). Further analyses are given in the Supporting Information.

at the lower temperature where the alkyne carbons were sharp. This evidence supports an intermolecular phosphine exchange mechanism; however, we cannot rule out the presence of a trace amount of phosphine that is below the level of detection of the NMR and X-ray experiments. Compounds incorporating (furyl)$_3$P (**31**−**33**) also displayed dynamic solution behavior; however, in contrast to solutions of **1**−**12**, both the singlet in the ^{31}P{^{1}H} NMR spectrum and the resonances for the alkyne carbon atoms in the ^{13}C{^{1}H} NMR spectrum were broad at room temperature and sharpened upon cooling with no new signals observed. This behavior could be explained by a process similar to the one described above or by the interconversion of several rotamers due to slow rotation of the furyl substituent.

In the static NMR spectrum, the alkyne carbons were observed as doublets (Table 1, Figure 3). In some cases a $^4J_{CP}$ (1−2 Hz) between a quaternary carbon (C17) of the steroid and phosphorus was also observed. The magnitude of the $^2J_{CP}$ and $^3J_{CP}$ was found to correlate moderately well with the Tolman electronic parameter as well as other measures of phosphine donor ability such as E_B,[25] C_B,[25] E_B/C_B,[25] and E°[26] (Figure 4 and Supporting Information). The $\Delta\delta$ (vide supra) was found to have a good correlation ($R^2 > 0.90$) with the $^2J_{CP}$ and $^3J_{CP}$ values for compounds **1**−**36** (Figure 4). The $^2J_{CP}$ also showed a high correlation with the $^3J_{CP}$ ($R^2 = 0.97$, Supporting Information).

Molecular Structures of Gold Steroid Compounds. The solid-state structures of **1**, **4**, **22**, **24**, and **25** have been determined by X-ray diffraction. The molecular diagrams of these compounds are shown in Figure 5, and selected bond distances and angles are listed in Table 2. The crystallographic data are listed in Table 3. A few transition metal−steroid compounds have been structurally characterized (vide infra); however, to the best of our knowledge, no known examples contain a σ-bond between the transition metal and the ethynyl fragment. Thus, these represent the first structural determinations of such organometallic species. Compounds **22** and **24** crystallize in the chiral space group $P2_12_12_1$. The packing in these compounds is dominated by the bulky steroid and cyclohexyl rings and results in long gold···gold separations (5.667 and 6.192 Å for **22** and **24**). These gold···gold separations are outside of the range for an aurophilic interaction.[28] The P−Au distances in **22** and **24** (Table 2) are longer than in Cy$_3$PAuCl (2.242(4) Å)[29] due to the increased *trans* influence of the acetylide

(28) For a recent review see: Pyykko, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4412.

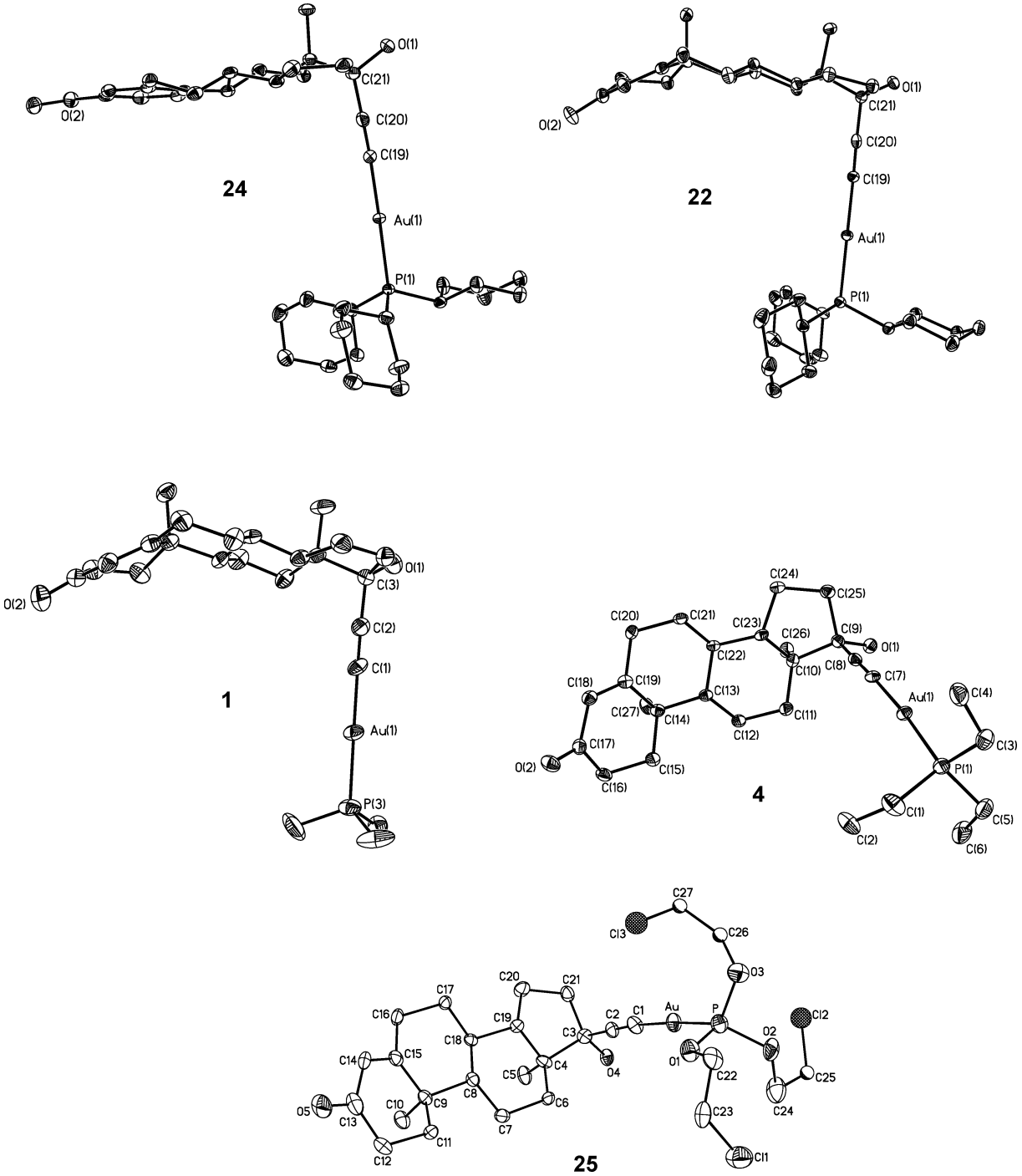

Figure 5. Molecular structures of **1**, **4**, **22**, **24**, and **25**. Thermal ellipsoids are shown at 50% probability for all structures except for **1**, which is at 30%. The orientation of the projection is perpendicular to the −C≡C−Au unit for **1**, **22**, and **24**. The orientation of the projection for **4** and **25** is along the P−Au−C≡C− fragment to illustrate the steroid framework.

Table 2. Selected Bond Distances and Angles for 1, 4, 22, 24, and 25

compound	Au−P (Å)	Au−C (Å)	C≡C (Å)	P−Au−C (deg)	Au−C≡C (deg)
Me_3PAu(ethisterone)	2.266(3)	1.986(10)	1.209(14)	179.2(3)	179.2(10)
Et_3PAu(ethisterone)	2.2833(8)	2.001(3)	1.208(5)	174.52(16)	174.2(4)
Cy_3PAu(ethisterone)	2.2875(8)	1.999(3)	1.204(5)	177.38(10)	177.1(3)
$(ClCH_2CH_2O)_3PAu$(ethisterone)	2.240(2)	1.989(8)	1.207(11)	176.3(2)	174.4(7)
Cy_3PAu(mestranol)	2.2834(5)	1.995(2)	1.204(3)	174.61(6)	175.9(2)

substituent. The −C≡C− triple bond is lengthened in **22** (1.204(5) Å) and **24** (1.204(3) Å) relative to free ethisterone (1.171 Å),[30] mestranol (1.176 Å),[31] and 17α-[(cyclopentadienyltricarbonylrhenium)ethynyl]-11β-(chloromethyl)estra-1,3,5-(10)-triene-3,17β-diol (1.17 Å)[9] and is similar to the −C≡C− in [$Co_2(CO)_6$-ethisterone], where two hexacarbonyl fragments are π-bound to the alkyne fragment of ethisterone (1.283 Å).[11a] The P−Au−C angle in **22** and **24** approaches linearity (**22**,

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Table 3. Crystallographic Data for 1, 4, 22, 24, and 25

	22	4	1	24	25
formula	$C_{39}H_{60}AuO_2P\cdot1.63THF$	$C_{27}H_{42}AuO_2P$	$C_{24}H_{38}AuO_2P\cdot H_2O$	$C_{39}H_{58}AuO_2P$	$C_{27}H_{39}AuCl_3O_5P$
fw	788.81	626.54	602.48	786.79	777.87
cryst syst	orthorhombic	monoclinic	monoclinic	orthorhombic	monoclinic
space group	$P2_12_12_1$	C_2	$P2_1$	$P2_12_12_1$	$P2_1$
a (Å)	11.3424(16)	20.196(3)	7.6458(7)	10.1375(4)	9.2578(9)
b (Å)	15.052(2)	9.4385(16)	11.6381(13)	10.2855(4)	9.5100(10)
c (Å)	25.423(4)	16.166(3)	14.1742(11)	33.7384(14)	17.5077(18)
α (deg)	90	90	90	90	90
β (deg)	90	118.964 (2)	102.252(7)	90	105.1200(10)
γ (deg)	90	90	90	90	90
temp (K)	100(2)	100(2)	273(2)	100 (2)	100(2)
V (Å^3)	4340.5(10)	2696.1(8)	1232.5(2)	3517.9(2)	1488.0(3)
Z	4	4	2	4	2
θ_{max} (deg)	26.36	26.43	28.50	26.37	26.39
D(calcd) (Mg m^{-3})	1.207	1.544	1.623	1.486	1.736
no. reflns collected	35 669	22 305	4574	51 072	21 833
no. indep reflns	8850	5514	3537	7123	6066
R ($I > 2\sigma(I)$)	0.0245	0.0203	0.0374	0.0140	0.0409
GOF	1.053	1.071	1.040	1.061	0.991

177.38(10)°; **24**, 174.61(6)°, respectively). Complex **22** exhibits an extended hydrogen-bonding network with the individual molecules linked by a hydrogen bond between the 17-OH of one gold steroid species and the carbonyl oxygen of an adjacent molecule (Figure 6). Complex **24** did not exhibit a hydrogen-bonding network. The packing diagram of **24** is shown in Figure 7 and illustrates the shortest Au···Au distance found in the structure of **24**. Complex **4** crystallizes in the chiral space group C_2 with four molecules per unit cell. The Au−P distance in **4** (2.2833(8) Å) is similar to the Au−P distance in **22** and **24** and is lengthened relative to Et_3PAuCl (2.232(9) Å).[32] The remaining distances and angles about the gold center are listed in Table 2. An analysis of the packing of **4** revealed a hydrogen bond between the 17-OH of one gold steroid species and the carbonyl carbon in an adjacent molecule, but in contrast to the hydrogen-bonding network found in **22**, the steroid framework of one molecule of **4** is folded over the analogous fragment of the adjacent molecule (Figure 8). The shortest Au···Au separation in the structure of **4** is the closest one found in the structures of **1**, **4**, **22**, **24**, and **25**, but it is still outside the normal range for an aurophilic interaction at 4.138 Å. The packing of **4** is significantly different from **22** and **24** and gives rise to unequal Au···Au distances between adjacent molecules (Supporting Information). Compounds **1** and **25** crystallize in the chiral space group $P2_1$. The Au−P bond length in **1** (2.266(3) Å) is longer than in the analogous chloride (Me_3PAuCl, 2.234 Å),[33] and the shortest Au···Au separations in **1** and **25** are 6.192 and 6.276 Å. The remaining distances and angles about the gold center in **1** and **25** are similar to those found in **4**, **22**, and **24**.

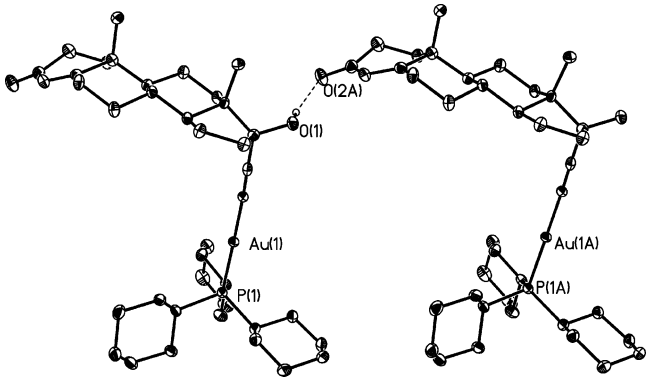

Figure 6. Hydrogen bonding between the 17-OH and the carbonyl oxygen of an adjacent molecule of **22** forming a hydrogen-bonded network of gold steroids.

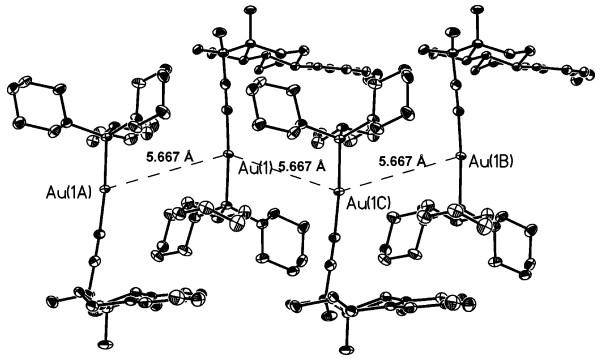

Figure 7. Packing of **24** showing the shortest Au···Au distance. No hydrogen-bonding interactions were found in the extended structure.

The relative binding affinities of selected ethynyl estradiol derivatives (**35**, **32**, **17**, **8**, **23**) to the ERα-ligand binding domain were determined by competitive binding experiments against [^{3}H]E_2. The results of these experiments are summarized in Table 4. In general the gold derivatives displayed significant binding to the ERα-LBD. Additionally, changing the donor ability and polarity of the phosphine did not drastically affect the binding affinity (28−52%).

In summary, a series of gold steroid complexes incorporating a variety of phosphorus donors have been prepared and characterized. These compounds were synthesized by treatment of the parent ethynyl steroid with sodium bis(trimethylsilyl)-amide followed by the addition of R_3PAuCl. These compounds were remarkably robust and could be heated to several hundred degrees with no decomposition. Although the gold steroids were thermally stable, a number of the compounds displayed dynamic solution behavior. Correlations between common measures of phosphine donor ability with $^2J_{CP}$ and $^3J_{CP}$ as well as changes in the ^{31}P chemical shift were made. The discrete structures of five gold steroid complexes show similarities in bond distances and angles; however, significant differences were observed in the extended structures, where two different hydrogen-bonding motifs were found.

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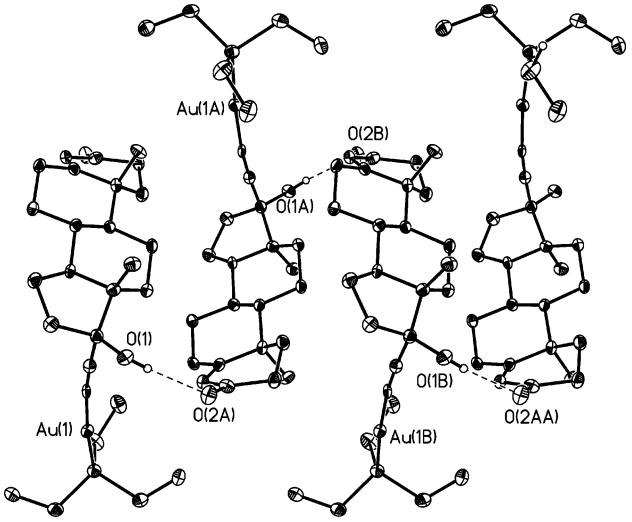

Figure 8. Hydrogen bonding between the 17-OH and the carbonyl oxygen of an adjacent molecule in the extended structure of **4** forming a hydrogen-bonded network of gold steroids.

Table 4. Relative Binding Affinity of Selected Gold Steroids to the Ligand Binding Domain of ERα[a]

entry	compound	ERα-LBD (RBA)
1	E_2	100
2	**35**	58 ±10
3	**32**	47 ± 12
4	**17**	47 ± 13
5	**8**	28 ± 11
6	**23**	28 ± 8

[a] RBA = relative binding affinity where $E_2 = EC_{50} = 1.5 \pm 0.3$ nM = 100%. Data are averages ± SD.

Experimental Section

General Considerations. Diethyl ether, dichloromethane, and hexane were dried using a Grubbs-type solvent purification system. THF was dried by distillation from Na/benzophenone. Mestranol, ethynyl estradiol, ethisterone, and all of the phosphine ligands used in this study were obtained from Aldrich and used as received. The R_3PAuCl precursors were prepared by treatment of Me_2SAuCl with 1 equiv of the phosphine in THF. All yields are based upon isolated material. Elemental analyses were performed by Midwest Microlabs. ^1H and ^{13}C chemical shifts were determined by reference to residual protonated solvent resonances. All coupling constants are given in hertz. $^{31}P\{^1H\}$ NMR spectra were referenced to external H_3PO_4 (0 ppm). Ionizable hydrogens were identified using acetone-d_6 or dmso-d_6 as the solvent. Representative examples of the experimental procedures are included below. The remaining experimental procedures and characterization data are included in the Supporting Information.

Preparation of Gold Steroid Compounds. General Method A. A 10 mL reaction flask was charged with R_3PAuX (X = Cl or Br) and ethynyl steroid. After sealing, evacuating, and refilling with nitrogen, THF was added by syringe. Alternatively, the PR_3AuCl precursor could be generated in situ by the combination of PR_3 and Me_2SAuCl. The reaction was stirred for 10 min, and NaHMDS (1.0 solution in THF) was added dropwise with vigorous stirring. After stirring for 2 h in the dark, the reaction mixture was centrifuged. After removal of the volatiles from the supernatant, the title compounds were purified by column chromatography.

General Method B. A 10 mL reaction flask was charged with R_3PAuCl. After sealing, evacuating, and refilling with nitrogen, THF was added by syringe. Alternatively, the PR_3AuCl precursor could be generated in situ by the combination of PR_3 and Me_2SAuCl. In a separate flask, NaHMDS (1.0 solution in THF) was added dropwise to a THF solution of the steroid. After stirring for 20 min, the two solutions were combined with vigorous stirring, and the resulting solution was stirred in the dark. After stirring for 2 h, the reaction mixture was centrifuged, and the title compound was purified by column chromatography.

Preparation of 1. Method A was followed using Me_2SAuCl (0.10 g, 0.34 mmol), PMe_3 (0.34 mL of a 1.0 M toluene solution), ethisterone (0.106 g, 0.34 mmol), and NaHMDS (0.34 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.15 g, 76%) after purification by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O). Anal. Calcd for $C_{24}H_{36}O_2PAu$: C, 49.32; H, 6.21. Found: C, 49.38; H, 6.11. ^1H NMR (acetone-d_6, 25 °C): δ 5.62 (s, 1H, =CH−), 3.39 (s, 1H, −OH), 2.65−0.80 (m, 19H, −CH−, $-CH_2-$), 1.55 (d, 9H, $-CH_3$), 1.25 (s, 3H, $-CH_3$), 0.85 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 5.71 (s, 1H, =CH−), 2.51−2.20 (m, 5H, −CH−, $-CH_2-$), 2.10−0.09 (m, 14H, −CH−, $-CH_2-$), 1.48 (d, 9H, $-CH_3$), 1.18 (s, 3H, $-CH_3$), 0.86 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, −23 °C): δ 200.7 (s, quat), 172.7 (s, quat), 125.3 (d, J = 144.3, ≡C−), 123.4 (s, =CH−), 108.3 (d, J = 27.4, ≡C−), 80.0 (s, quat), 52.6 (s, −CH−), 49.3 (s, −CH−), 46.0 (s, quat), 39.2 (s, $-CH_2-$), 38.4 (s, −CH−), 35.7 (s, quat), 35.2 (s, $-CH_2-$), 33.8 (s, $-CH_2-$), 32.7 (s, $-CH_2-$), 32.4 (s, $-CH_2-$), 30.9 (s, $-CH_2-$), 22.8 (s, $-CH_2-$), 20.3 (s, $-CH_2-$), 17.1 (s, $-CH_3$), 15.3 (d, J = 36.6, $-CH_3$), 12.7 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 0.3 (s).

Preparation of 5. Method B was followed using Me_2SAuCl (0.20 g, 0.68 mmol), PEt_3 (99.7 μL, 0.68 mmol), ethynyl estradiol (0.20 g, 0.68 mmol), and NaHMDS (0.68 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.27 g, 65.4%) after purification of the crude residue by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O) and recrystallization from THF/hexane. Anal. Calcd for $C_{26}H_{38}O_2PAu$: C, 51.15; H, 6.27. Found: C, 51.38; H, 6.15. ^1H NMR (acetone-d_6, 25 °C): δ 7.86 (s, 1H, −OH), 7.08 (d, 1H, J = 8.5, Ar−H), 6.55 (dd, 1H, J = 8.4, 2.2, Ar−H), 6.48 (d, 1H, J = 2.2, Ar−H), 3.38 (s, 1H, OH), 2.72 (m, 2H, −CH−, $-CH_2-$), 2.38 (m, 1H, −CH−, $-CH_2-$), 2.22−0.90 (m, 18H, −CH−, $-CH_2-$), 1.13 (dt, 9H, J = 18.2, 7.5, $-CH_3$), 0.79 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.14 (d, 1H, J = 8.4, Ar−H), 6.65 (d, 1H, J = 8.4, Ar−H), 6.58 (s, 1H, Ar−H), 5.13 (s, 1H, −OH), 2.78 (m, 2H, −CH−, $-CH_2-$), 2.43−2.05 (m, 4H, −CH−, $-CH_2-$), 1.91−1.68 (m, 15H, −CH−, $-CH_2-$), 1.18 (dt, 9H, $-CH_3$), 0.86 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, −33 °C): δ 153.3 (s, quat), 138.1 (s, quat), 132.1 (s, quat), 128.8 (d, J = 135.9, ≡C−), 126.5 (s, Ar−C), 115.1 (s, Ar−C), 112.5 (s, Ar−C), 107.8 (d, J = 26.0, ≡C−), 80.7 (s, quat), 48.8 (s, −CH−), 46.7 (s, quat), 42.9 (s, −CH−), 39.2 (s, $-CH_2-$), 39.1 (s, −CH−), 32.8 (s, $-CH_2-$), 29.6 (s, $-CH_2-$), 26.8 (s, $-CH_2-$), 26.2 (s, $-CH_2-$), 22.6 (s, $-CH_2-$), 16.9 (d, J = 33.4, $-CH_2-$), 12.8 (s, $-CH_3$), 8.6 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 36.5 (s).

Preparation of 7. Method A was followed using Me_2SAuCl (0.20 g, 0.68 mmol), Me_2PhP (96.2 μL, 0.68 mmol), ethisterone (0.21 g, 0.68 mmol), and NaHMDS (0.68 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.24 g, 54.9%) after purification of the crude residue by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O). Anal. Calcd for $C_{29}H_{38}O_2PAu$: C, 53.87; H, 5.92. Found: C, 53.77; H, 6.26. ^1H NMR (acetone-d_6, 25 °C): δ 7.88−7.81 (m, 2H, Ar−H), 7.58−7.55 (m, 3H, Ar−H), 5.64 (s, 1H, =CH−), 3.46 (s, 1H, −OH), 2.48−1.20 (m, 17H, −CH−, $-CH_2-$), 1.86 (d, 6H, J = 9.6, $-CH_3$), 1.25 (s, 3H, $-CH_3$), 1.10−0.88 (m, 2H, −CH−, $-CH_2-$), 0.87 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.74−7.67 (m, 2H, Ar−H), 7.52−7.45 (m, 3H, Ar−H), 5.72 (s, 1H, =CH−), 2.50−2.20 (m, 5H, −CH−, $-CH_2-$), 2.15−1.20 (m, 12H, −CH−, $-CH_2-$), 1.74 (d, 6H, J = 9.6, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.18−0.95 (m, 2H, −CH−, $-CH_2-$), 0.88 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, −43 °C): δ 200.7 (s, quat), 172.7 (s, quat), 131.9 (d, J = 13.7, Ar−C), 131.7 (d, J = 2.3, Ar−C), 131.4 (d, J = 60.0, quat), 129.0 (d, J =

11.3, Ar−C), 125.7 (d, J = 143.2, ≡C−), 23.4 (s, =CH−), 108.0 (d, J = 26.6, ≡C−), 80.0 (s, quat), 52.5 (s, −CH−), 49.3 (s, −CH−), 46.1 (s, quat), 39.2 (s, $-CH_2-$), 38.4 (s, quat), 35.8 (s, −CH−), 35.2 (s, $-CH_2-$), 33.9 (s, $-CH_2-$), 32.7 (s, $-CH_2-$), 32.4 (s, $-CH_2-$), 30.9 (s, $-CH_2-$), 22.8 (s, $-CH_2-$), 20.4 (s, $-CH_2-$), 17.1 (s, $-CH_3$), 15.2 (d, J = 36.0, $-CH_3$), 12.7 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 12.6 (s).

Preparation of 11. Method B was followed using Me_2SAuCl (0.20 g, 0.68 mmol), $MePh_2P$ (126.0 μL, 0.68 mmol), ethynyl estradiol (0.20 g, 0.68 mmol), and NaHMDS (0.68 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.26 g, 55.5%) after purification of the reaction residue by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O) and recrystallization from THF/pentane. Anal. Calcd for $C_{33}H_{36}O_2PAu$: C, 57.23; H, 5.24. Found: C, 57.12; H, 5.34. ^1H NMR (acetone-d_6): δ 7.93 (s, 1H, −OH), 7.78−7.70 (m, 4H, Ar−H), 7.60−7.51 (m, 6H, Ar−H), 7.12 (d, 1H, J = 8.4, Ar−H), 6.60 (dd, 1H, J = 8.4, 2.6, Ar−H), 6.53 (d, 1H, J = 2.5, Ar−H), 3.51 (s, 1H, −OH), 2.77 (m, 2H, −CH−, $-CH_2-$), 2.34−2.28 (m, 1H, −CH−, $-CH_2-$), 2.22−2.10 (m, 3H, −CH−, $-CH_2-$), 2.21 (d, 3H, J = 9.3, $-PCH_3$), 2.10−1.80 (m, 3H, −CH−, $-CH_2-$), 1.79−1.61 (m, 2H, −CH−, $-CH_2-$), 1.49 − 1.20 (m, 4H, −CH−, $-CH_2-$), 0.85 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$): δ 7.65−7.57 (m, 4H, Ar−H), 7.51−7.40 (m, 6H, Ar−H), 7.16 (d, 1H, J = 8.4, Ar−H), 6.63 (dd, 1H, J = 8.4, 2.6, Ar−H), 6.56 (d, 1H, J = 2.6, Ar−H), 4.80 (s, 1H, −OH), 2.80 (m, 2H, −CH−, $-CH_2-$), 2.43−2.20 (m, 3H, −CH−, $-CH_2-$), 2.17−1.98 (m, 2H, −CH−, $-CH_2-$), 2.03 (d, 3H, J = 9.1, −CH−, $-CH_2-$), 1.90−1.70 (m, 4H, −CH−, $-CH_2-$), 1.58−1.25 (m, 4H, −CH−, $-CH_2-$), 0.87 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, −23 °C): δ 153.1 (s, quat), 138.3 (s, quat), 132.7 (d, J = 13.5, Ar−C), 132.5 (s, quat), 131.4 (d, J = 2.3, Ar−C), 131.0 (d, J = 56.1, quat), 129.0 (d, J = 11.3, Ar−C), 126.6 (s, Ar−C), 125.7 (d, J = 141.1, ≡C−), 115.0 (s, Ar−C), 112.4 (s, Ar−C), 108.1 (d, J = 26.2, ≡C−), 80.5 (s, quat), 49.0 (s, −CH−), 46.7 (s, quat), 43.0 (s, −CH−), 39.4 (s, $-CH_2-$), 39.1 (s, −CH−), 32.9 (s, $-CH_2-$), 29.6 (s, $-CH_2-$), 26.8 (s, $-CH_2-$), 26.3 (s, $-CH_2-$), 22.7 (s, $-CH_2-$), 13.8 (d, J = 35.8, $-PCH_3$), 12.7 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 25.6 (s).

Preparation of 15. Method A was followed using PPh_3AuBr (0.20 g, 0.37 mmol), mestranol (0.12 g, 0.37 mmol), and NaHMDS (0.37 mL of a 1.0 M solution). The title compound was isolated as a white solid (0.22 g, 77%) after purification by column chromatography (silica gel; 1:1 CH_2Cl_2/ether). Anal. Calcd for $C_{39}H_{40}O_2PAu$: C, 60.94; H, 5.25. Found: C, 60.74; H, 4.82. ^1H NMR (dmso-d_6, 25 °C): δ 7.64−7.47 (m, 15H, Ar−H), 7.17 (d, 1H, J = 8.6, Ar−H), 6.66 (dd, 1H, J = 8.2, 2.5, Ar−H), 6.59 (d, 1H, J = 2.5, Ar−H), 4.86 (s, 1H, −OH), 3.68 (s, 3H, −OMe), 2.76 (m, 2H, −CH− or $-CH_2-$), 2.28 (m, 1H, −CH− or $-CH_2-$), 2.10−1.56 (m, 9H, −CH− or $-CH_2-$), 1.27 (m, 3H, −CH− or $-CH_2-$), 0.72 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.56−7.42 (m, 15H, Ar−H), 7.23 (d, 1H, J = 8.6, Ar−H), 6.71 (dd, 1H, J = 8.5, 2.8, Ar−H), 6.64 (d, 1H, J = 2.8, Ar−H), 3.78 (s, 3H, $-OCH_3$), 2.85 (m, 2H, −CH−, $-CH_2-$), 2.47−2.28 (m, 3H, −CH−, $-CH_2-$), 2.22−2.12 (m, 2H, −CH−, $-CH_2-$), 1.94−1.73 (m, 4H, −CH−, $-CH_2-$), 1.51−1.34 (m, 4H, −CH−, $-CH_2-$), 0.89 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 157.2 (s, quat), 138.1 (s, quat), 134.3 (d, J = 13.7, Ar−H), 133.1 (s, quat), 131.5 (s, Ar−H), 129.7 (d, J = 55.7, quat), 129.1 (d, J = 11.2, Ar−H), 126.4 (s, =CH), 125.7 (d, J = 141.7, ≡C−), 113.7 (s, Ar−H), 111.4 (s, Ar−H), 107.7 (d, J = 25.5, ≡C−), 80.5 (s, quat), 55.2 (s, −OMe), 49.3 (s, −CH−), 47.0 (s, quat), 43.3 (s, −CH−), 39.9 (s, $-CH_2-$), 39.6 (s, −CH−), 33.2 (s, $-CH_2-$), 30.0 (s, $-CH_2-$), 27.1 (s, $-CH_2-$), 26.6 (s, $-CH_2-$), 22.9 (s, −CH2−), 12.9 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 41.3 (s).

Preparation of 16. Method A was followed using Me_2SAuCl (0.10 g, 0.34 mmol), $P(C_6H_4F)_3$ (0.107 g, 0.34 mmol), ethisterone (0.106 g, 0.34 mmol), and NaHMDS (0.34 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.24 g, 86.1%) after purification of the crude reaction residue by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O). Anal. Calcd for $C_{39}H_{39}F_3O_2PAu$: C, 56.80; H, 4.77. Found: C, 57.15; H, 4.85. ^1H NMR (acetone-d_6, 25 °C): δ 7.74−7.62 (m, 6H, Ar−H), 7.41−7.36 (m, 6H, Ar−H), 5.61 (s, 1H, =CH−), 3.56 (s, 1H, −OH), 2.50−1.20 (m, 19H, −CH−, $-CH_2$), 1.23 (s, 3H, $-CH_3$), 0.86 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.53−7.44 (m, 6H, Ar−H), 7.20−7.14 (m, 6H, Ar−H), 5.72 (s, 1H, =CH−), 2.50−2.18 (m, 5H, −CH−, CH_2-), 2.18−0.80 (m, 14H, −CH−, CH_2-), 1.20 (s, 3H, $-CH_3$), 0.89 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 199.7 (s, quat), 171.7 (s, quat), 164.9 (dd, J = 255.1, 2.4, quat), 136.3 (dd, J = 45.6, 8.7, Ar−C), 125.4 (d, J = 143.9, ≡C−), 125.2 (dd, J = 58.41, 3.6, quat), 123.7 (s, Ar−C), 116.8 (dd, 21.8, 12.6, Ar−C), 107.7 (d, J = 26.3, ≡C−), 80.3 (d, J = 2.1, quat), 53.2 (s, −CH−), 49.8 (s, −CH−), 46.5 (s, quat), 39.8 (s, $-CH_2-$), 38.7 (s, quat), 36.4 (s, −CH−), 35.7 (s, $-CH_2-$), 34.0 (s, $-CH_2-$), 32.9 (s, $-CH_2-$), 32.8 (s, $-CH_2-$), 31.5 (s, $-CH_2-$), 23.1 (s, $-CH_2-$), 20.8(s, $-CH_2-$), 17.4 (s, $-CH_3$), 12.9 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 39.4 (m).

Preparation of 20. Method B was followed using Me_2SAuCl (0.10 g, 0.34 mmol), Ph_2PyP (0.090 g, 0.34 mmol), ethynyl estradiol (0.10 g, 0.34 mmol), and NaHMDS (0.34 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.20 g, 78.2%) after purification of the reaction residue by column chromatography (silica gel; 1:1 THF/ether) and recrystallization from THF/hexane. Anal. Calcd for $C_{37}H_{37}NO_2PAu$: C, 58.81; H, 4.94. Found: C, 58.50; H, 4.71. ^1H NMR (acetone-d_6, 25 °C): δ 8.80 (d, 1H, J = 4.4, Ar−H), 7.97−7.94 (m, 1H, Ar−H), 7.91 (s, 1H, −OH), 7.82 (t, 1H, J = 7.1, Ar−H), 7.74−7.67 (m, 4H, Ar−H), 7.56 (m, 7H, Ar−H), 7.11 (d, 1H, J = 8.4, Ar−H), 6.59 (dd, 1H, J = 8.3, 2.3, Ar−H), 6.52 (d, 1H, J = 2.2, Ar−H), 3.55 (s, 1H, −OH), 2.75 (m, 2H, −CH−, $-CH_2-$), 2.40−1.80 (m, 7H, −CH−, $-CH_2-$), 1.78−1.60 (m, 2H, −CH−, $-CH_2-$), 1.33−1.28 (m, 4H, −CH−, $-CH_2-$), 0.85 (m, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 8.78 (d, 1H, J = 4.1, Ar−H), 7.96 (t, 1H, J = 7.9, Ar−H), 7.76−7.65 (m, 5H, Ar−H), 7.49−7.36 (m, 7H, Ar−H), 7.17 (d, 1H, J = 8.4, Ar−H), 6.64 (dd, 1H, J = 8.4, 2.4, Ar−H), 6.57 (d, 1H, J = 2.4, Ar−H), 4.81 (s, 1H, −OH), 2.80 (m, 2H, −CH−, $-CH_2-$), 2.46−2.29 (m, 3H, −CH−, $-CH_2-$), 2.20−2.03 (m, 2H, −CH−, $-CH_2-$), 1.91−1.73 (m, 4H, −CH−, $-CH_2-$), 1.53−1.30 (m, 4H, −CH−, $-CH_2-$), 0.89 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 155.2 (d, J = 76.5, quat), 153.2 (s, quat), 151.3 (d, J = 14.6, Ar−C), 138.3 (s, quat), 136.4 (d, J = 10.8, Ar−C), 134.6 (d, J = 13.8, Ar−C), 133.1 (s, quat), 131.6 (d, J = 32.8, Ar−C), 131.6 (d, J = 2.3, Ar−C), 129.4 (d, J = 60.3, quat), 128.9 (d, J = 11.5, Ar−C), 126.6 (s, Ar−C), 126.1 (d, J = 144.7, ≡C−), 125.0 (d, J = 2.2, Ar−C), 115.2 (s, Ar−C), 112.6 (s, Ar−C), 107.7 (d, J = 22.2, ≡C−), 80.6 (s, quat), 49.3 (s, −CH−), 47.0 (s, quat), 43.3 (s, −CH−), 39.9 (s, $-CH_2-$), 39.6 (s, −CH−), 33.2 (s, $-CH_2-$), 29.8 (s, $-CH_2-$), 27.1 (s, $-CH_2-$), 26.6 (s, $-CH_2-$), 22.9 (s, $-CH_2-$), 12.9 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 40.5 (s).

Preparation of 24. Method A was followed with Cy_3PAuCl (0.49 g, 0.96 mmol), mestranol (0.298 g, 0.96 mmol), and NaHMDS (0.96 mL of a 1.0 M solution). The title compound was isolated as a white solid (0.63 g, 83.4%) after purification by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O) and trituration with hexane. Anal. Calcd for $C_{39}H_{58}O_2PAu$: C, 59.53; H, 7.43. Found: C, 59.71; H, 7.50. ^1H NMR (dmso-d_6, 25 °C): δ 7.16 (d, 1H, J = 8.6, Ar−H), 6.69 (dd, 1H, J = 8.5, 2.5, Ar−H), 6.61 (d, 1H, J = 2.5, Ar−H), 4.80 (s, 1H, −OH), 3.69 (s, 3H, −OMe), 2.74 (m, 2H, −CH−, $-CH_2-$), 2.29−2.25 (m, 1H, −CH−, $-CH_2-$), 2.20−1.10 (m, 45H, −CH−, $-CH_2-$), 0.74 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.23 (d, 1H, J = 8.6, Ar−H), 6.71 (dd, 1H, J = 8.5, 2.2, Ar−H), 6.63 (d, 1H, J = 2.2, Ar−H), 3.78 (s, 3H, $-OCH_3$), 2.83 (m, 2H, −CH−, $-CH_2-$), 2.40 (m, 3H, −CH−,

$-CH_2-$), 2.20−1.23 (m, 44H, −CH−, $-CH_2-$), 0.86 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 157.3 (s, quat), 138.1 (s, quat), 133.1 (s, quat), 130.4 (d, J = 131.3, ≡C−), 126.4 (s, Ar−C), 113.7 (s, Ar−C), 111.4 (s, Ar−C), 106.8 (d, J = 23.8, ≡C−), 80.5 (d, J = 2.0, quat), 55.2 (s, −OMe), 49.2 (s, −CH−), 46.9 (s, quat), 43.3 (s, −CH−), 39.9 (s, $-CH_2-$), 39.6 (s, −CH−), 33.2 (d, J = 27.8, −CH−), 33.2 (s, $-CH_2-$), 30.6 (s, $-CH_2-$), 29.9 (s, $-CH_2-$), 27.2 (s, $-CH_2-$), 27.1 (d, J = 11.7, $-CH_2-$), 26.6 (s, $-CH_2-$), 25.8 (d, J = 1.0, $-CH_2-$), 22.9 (s, $-CH_2-$), 12.9 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 54.8 (s).

Preparation of 25. Method A was followed using Me_2SAuCl (0.20 g, 0.68 mmol), $P(OCH_2CH_2Cl)_3$ (137.3 μL, 0.68 mmol), ethisterone (0.21 g, 0.68 mmol), and NaHMDS (0.68 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.41 g, 77.9%) after purification of the reaction residue by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O) and trituration with hexane. Anal. Calcd for $C_{27}H_{39}Cl_3O_5PAu$: C, 41.69; H, 5.05. Found: C, 42.06; H, 5.15. ^1H NMR (acetone-d_6, 25 °C): δ 5.63 (s, 1H, ═CH−), 4.49 (m, 6H, $-CH_2-$), 3.92 (t, 6H, J = 5.3, $-CH_2-$), 3.62 (s, 1H, −OH), 2.50−1.26 (m, 17H, −CH−, $-CH_2-$), 1.24 (s, 3H, $-CH_3$), 1.08−0.80 (m, 2H, −CH−, $-CH_2-$), 0.86 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 5.72 (s, 1H, ═CH−), 4.37 (m, 6H, $-CH_2-$), 3.72 (t, 6H, J = 5.6, $-CH_2-$), 2.43−2.20 (m, 5H, −CH−, $-CH_2-$), 2.10−1.99 (m, 2H, −CH−, $-CH_2-$), 1.90−1.80 (m, 2H, −CH−, $-CH_2-$), 1.77−1.54 (m, 5H, −CH−, $-CH_2-$), 1.50−1.22 (m, 3H, −CH−, $-CH_2-$), 1.20 (s, 3H, $-CH_3$), 1.11−0.95 (m, 2H, −CH−, $-CH_2-$), 0.87 (m, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, −23 °C): δ 200.4 (s, quat), 172.2 (s, quat), 125.5 (d, J = 206.9, ≡C−), 123.5 (s, ═CH−), 108.6 (d, J = 34.8, ≡C−), 80.0 (s, quat), 66.0 (s, $-CH_2-$), 52.8 (s, −CH−), 49.5 (s, −CH−), 46.3 (s, quat), 42.7 (d, J = 8.0, $-CH_2-$), 39.3 (s, $-CH_2-$), 38.5 (s, quat), 35.9 (s, −CH−), 35.3 (s, $-CH_2-$), 33.4 (s, $-CH_2-$), 32.7 (s, $-CH_2-$), 32.4 (s, $-CH_2-$), 31.1 (s, $-CH_2-$), 22.9 (s, $-CH_2-$), 20.5 (s, $-CH_2-$), 17.2 (s, $-CH_3$), 12.7 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 145.8 (s).

Preparation of 29. Method B was followed using Me_2SAuCl (0.20 g, 0.68 mmol), $P(OEt)_3$ (116.4 μL, 0.68 mmol), ethynyl estradiol (0.20, 0.68 mmol), and NaHMDS (0.68 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.36 g, 80%) after purification by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O) and recrystallization from THF/hexane. Anal. Calcd for $C_{26}H_{38}O_5PAu$: C, 47.42; H, 5.82. Found: C, 47.07; H, 5.94. ^1H NMR (acetone-d_6, 25 °C): δ 7.90 (s, 1H, −OH), 7.12 (d, 1H, J = 8.5, Ar−H), 6.59 (d, 1H, J = 8.4, Ar−H), 6.51 (s, 1H, Ar−H), 4.17 (m, 6H, $-OCH_2CH_3$), 3.56 (s, 1H, −OH), 2.75 (m, 2H, −CH−, $-CH_2-$), 2.35 (m, 1H, −CH−, $-CH_2-$), 2.20−1.98 (m, 3H, −CH−, $-CH_2-$),1.95−1.80 (m, 2H, −CH−, $-CH_2-$), 1.78−1.55 (m, 2H, −CH−, $-CH_2-$), 1.31 (m, 14H, −CH−, $-CH_2-$, $-CH_3$), 0.84 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.17(d, 1H, J = 8.4, Ar−H), 6.64 (dd, 1H, J = 8.4, 2.5, Ar−H), 6.57 (d, 1H, J = 2.5, Ar−H), 4.13 (m, 6H, $-OCH_2CH_3$), 2.80 (m, 2H, −CH−, $-CH_2-$), 2.41−2.20 (m, 3H, −CH−, $-CH_2-$), 2.15−1.90 (m, 2H, −CH−, $-CH_2-$), 1.90−1.55 (m, 4H, −CH−, $-CH_2-$), 1.50−1.30 (m, 4H, −CH−, $-CH_2-$), 1.34 (t, 9H, J = 7.0, $-OCH_2CH_3$), 0.87 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ153.2 (s, quat), 138.4 (s, quat), 133.0 (s, quat), 126.9 (s, J = 203.9, ≡C−), 126.6 (s, Ar−C), 115.2 (s, Ar−C), 112.6 (s, Ar−C), 108.6 (d, J = 36.9, ≡C−), 80.4 (s, quat), 62.3 (s, $-OCH_2CH_3$), 49.3 (s, −CH−), 46.9 (s, quat), 43.4 (s, −CH−), 39.8 (s, $-CH_2-$), 39.5 (s, −CH−), 33.1 (s, $-CH_2-$), 29.7 (s, $-CH_2-$), 27.1 (s, $-CH_2-$), 26.6 (s, $-CH_2-$), 22.8 (s, $-CH_2-$), 16.3 (d, J = 6.8, $-OCH_2CH_3$), 12.8 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 144.1 (s).

Preparation of 32. Method B was followed using Me_2SAuCl (0.20 g, 0.68 mmol), P(furyl)$_3$ (0.16, 0.68 mmol), ethynyl estradiol (0.20 g, 0.68 mmol), and NaHMDS (0.68 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.32 g, 65.3%) after purification by column chromatography (silica gel; 1:1 CH_2Cl_2/Et_2O) and recrystallization from THF/hexane. Anal. Calcd for $C_{32}H_{32}O_5PAu$: C, 53.05; H, 4.45. Found: C, 52.73; H, 4.40. ^1H NMR (acetone-d_6, 25 °C): δ 8.04 (m, 3H, Ar−H), 7.89 (s, 1H, −OH), 7.25 (t, 3H, J = 4.0, Ar−H), 7.13 (d, 1H, J = 8.5, Ar−H), 6.69 (m, 3H, Ar−H), 6.60 (dd, 1H, J = 8.4, 2.6, Ar−H), 6.53 (d, 1H, J = 2.5, Ar−H), 3.64 (s, 1H, −OH), 2.75 (m, 2H, −CH−, $-CH_2-$), 2.37−2.06 (m, 4H, −CH−, $-CH_2-$), 2.05−1.65 (m, 5H, −CH−, $-CH_2-$), 1.42−1.31 (m, 4H, −CH−, $-CH_2-$), 0.87 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.79 (m, 3H, Ar−H), 7.18 (m, 4H, Ar−H), 6.69 (dd, 1H, J = 8.4, 2.5, Ar−H), 6.62 (d, 1H, J = 2.5, Ar−H), 6.51 (m, 3H, Ar−H), 5.62 (s, 1H, −OH), 2.80 (m, 2H, −CH−, $-CH_2-$), 2.47−2.24 (m, 3H, −CH−, $-CH_2-$), 2.16−2.07 (m, 2H, −CH−, $-CH_2-$), 1.85−1.70 (m, 4H, −CH−, $-CH_2-$), 1.50−1.32 (m, 4H, −CH−, $-CH_2-$), 0.87 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, −23 °C): δ 153.1 (s, quat), 149.9 (d, J = 5.7, Ar−C), 141.8 (d, J = 80.4, quat), 138.3 (s, quat), 132.5 (s, quat), 126.6 (s, Ar−C), 125.2 (d, J = 113.1, Ar−C), 124.0 (d, J = 150.3, ≡C−), 115.1 (s, Ar−C), 112.5 (s, Ar−C), 111.4 (d, J = 9.9, Ar−C), 107.6 (d, J = 27.6, ≡C−), 80.6 (d, J = 2.2, quat), 49.1 (s, −CH−), 46.8 (s, quat), 43.0 (s, −CH−), 39.4 (s, $-CH_2-$), 39.2 (s, −CH−), 32.9 (s, $-CH_2-$), 29.7 (s, $-CH_2-$), 26.8 (s, $-CH_2-$), 26.3 (s, $-CH_2-$), 22.7 (s, $-CH_2-$), 12.8 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, −23 °C): δ −18.0 (s).

Preparation of 36. Method A was followed using Me_2SAuCl (0.20 g, 0.68 mmol), P(pyrr)$_3$ (155.6 μL, 0.68 mmol), mestranol (0.21 g, 0.68 mmol), and NaHMDS (0.68 mL of a 1.0 M solution in THF). The title compound was isolated as a white solid (0.21 g, 55.1%) after purification of the crude residue by column chromatography (silica gel; 1:1 CH_2Cl_2/ether) and trituration with hexane. Anal. Calcd for $C_{33}H_{49}O_2PN_3Au$: C, 53.01; H, 6.61. Found: C, 53.08; H, 6.80. ^1H NMR (acetone-d_6, 25 °C): δ 7.22 (d, 1H, J = 8.6, Ar−H), 6.68 (dd, 1H, J = 2.5, Ar−H), 6.60 (d, 1H, J = 2.4, Ar−H), 3.73 (s, 3H, $-OCH_3$), 3.40 (s, 1H, −OH), 3.17 (m, 12H, $-CH_2-$), 2.40−2.30 (m, 1H, −CH−, $-CH_2-$), 2.28−1.52 (m, 22H, −CH−, $-CH_2-$), 1.50 − 1.22 (m, 4H, −CH−, $-CH_2-$), 0.84 (s, 3H, $-CH_3$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.23 (d, 1H, J = 8.6, Ar−H), 6.71 (dd, 1H, J = 8.5, 2.5, Ar−H), 6.63 (d, 1H, J = 2.5, Ar−H), 3.78 (s, 3H, $-OCH_3$), 3.17 (m, 12H, $-CH_2-$), 2.84 (m, 2H, −CH, $-CH_2-$), 2.43−2.28 (m, 3H, −CH, $-CH_2-$), 2.19−2.00 (m, 2H, −CH, $-CH_2-$), 1.87 (m, 16H, −CH, $-CH_2-$), 1.54−1.35 (m, 4H, −CH, $-CH_2-$), 0.87 (s, 3H, $-CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 157.3 (s, quat), 138.1 (s, quat), 133.2 (s, quat), 130.1 (d, J = 169.4, ≡C−), 126.4 (s, Ar−C), 113.7 (s, Ar−C), 111.4 (s, Ar−C), 108.0 (d, J = 30.9, ≡C−), 80.5 (s, quat), 55.2 (s, $-OCH_3$), 49.2 (s, −CH−), 47.5 (d, J = 8.5, $-CH_2-$), 46.9 (s, quat), 43.3 (s, −CH−), 39.9 (s, $-CH_2-$), 39.6 (s, −CH−), 33.2 (s, $-CH_2-$), 30.0 (s, $-CH_2-$), 27.2 (s, $-CH_2-$), 26.6 (s, $-CH_2-$), 26.1 (d, J = 7.3, $-CH_2-$), 22.9 (s, $-CH_2-$), 12.9 (s, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 111.4 (s).

Preparation of (pyrr)$_3$PAuCl. A round-bottom flask was charged with Me_2SAuCl (0.20 g, 0.68 mmol) and a magnetic stirring bar. After evacuating the flask and refilling with nitrogen, THF (5.0 mL) and (pyrr)$_3$P (155.6 μL, 0.68 mmol) were added by syringe. The reaction mixture was stirred in the absence of light for 30 min and dried under vacuum to afford 0.27 g (84.2%) of the title compound as a white solid. ^1H NMR ($CDCl_3$, 25 °C): δ 3.06 (m, 6H, $-CH_2-$), 1.72 (m, 6H, $-CH_2-$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 47.6 (d, J = 8.37, $-CH_2-$), 26.0 (d, J = 7.6, $-CH_2-$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 86.2 (s).

Preparation of (ClCH$_2$CH$_2$O)$_3$PAuCl. A round-bottom flask was charged with Me_2SAuCl (0.20 g, 0.68 mmol) and a magnetic stirring bar. After evacuating the flask and refilling with nitrogen, THF (5.0 mL) and $(ClCH_2CH_2O)_3P$ (137.3 μL, 0.68 mmol) were added by syringe. The reaction mixture was stirred in the absence

of light for 30 min and dried under vacuum to afford 0.31 g (90.1%) of the title compound as a light tan oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ 4.42 (m, 6H, $-CH_2-$), 3.75 (t, 6H, $J = 5.5$, $-CH_2-$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 67.0 (s, $-CH_2-$), 42.3 (d, $J = 8.03$, $-CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 117.4 (s).

X-ray Crystallographic Studies. Crystals suitable for X-ray diffraction studies of **1**, **4**, **22**, **24**, and **25** were grown by slow diffusion of pentane into THF solutions of the gold steroid complex. Compound **1** was mounted on the tip of a glass fiber using glue and mounted at 22 °C in the goniometer and optically centered. Data collection was performed using a Bruker P-4 diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å). The positions and anisotropic thermal parameters of the non-hydrogen atoms were refined on F^2 using direct methods with the SHELXTL97 package. One disordered methyl group was refined as two partial atoms (C23, C23B), and the hydrogen atoms were placed in calculated positions. For **4**, **22**, **24**, and **25**, a suitable crystal was selected and mounted on the tip of a nylon loop. The crystal was mounted in a stream of cold nitrogen at 100(2) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo Kα ($\lambda = 0.71073$ Å) radiation and the diffractometer to crystal distance of 4.9 cm. The structures were solved using direct methods and refined on F^2. All non-hydrogen atoms were located and anisotropically refined. In **25**, several atoms are disordered over two positions in the following ratios: Cl2 86:14, Cl3 67:33, C27 67:33. The following atoms were refinied isotropically: Cl2, Cl2a, Cl3, Cl3a, C25, C26, C27, C27a. Soft restraints and constraints were applied to groups containing disordered atoms.

Competitive Binding to the Human Estrogen Receptor Alpha Ligand Binding Domain (ERα-LBD). Binding to ERα-LBD was measured as we have previously described,[34] by displacement of [^{3}H]E_2 (~1 nM) in incubations performed at room temperature overnight with lysates of *Escherichia coli* in which the LBD of human ERα (M_{250}-V_{595})(2) is expressed.[35] For assay, the lysates were incubated with nonradioactive E_2 and the E_2 analogues over a range of concentrations from 10^{-6} to 10^{-12} M. Binding affinity (RBA) relative to E_2 was determined by analysis of the binding curves by the curve-fitting program Prism (GraphPad Software inc., San Diego, CA 92130). The results, averages of eight separate experiments performed in duplicate, are shown in Table 4.

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Supporting Information Available: Packing diagrams, correlations of NMR spectral data with common measures of phosphine donor ability, experimental crystallographic descriptions, and crystallographic information files are available free of charge on the Internet at http://pubs.acs.org.

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