Synthesis and Binding Affinities of Novel Re-Containing 7α-Substituted Estradiol Complexes: Models for Breast Cancer Imaging Agents

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The diagnosis and staging of breast cancer could be improved by the development of imaging radiopharmaceuticals that provide a noninvasive determination of the estrogen receptor status in the tumor cells. Toward this goal, we have synthesized a number of novel Re-containing 7α-substituted estradiol complexes. The introduction of the 7α side chain involves the alkylation of tetrahydropyranyloxy-protected 6-keto estradiol. The methods used to introduce the rhenium metal involve "3 + 1" and "4 + 1" mixed ligand complexes (**2a**−**c** and **5**, respectively), tricarbonyl dithioether complexes (**3**), and the cyclopentadienyltricarbonylmetal organometallic system (**4ab**, **6**, **7)**. These complexes showed binding affinities for the estrogen receptor (as high as 45% for the "3 + 1" complex **2c)** when compared to the native ligand estradiol. The polarity of some complexes (**4ab**) was modified to improve biodistribution properties by introducing (poly)ether linkages into the 7α side chain (**6**, **7**). These complexes provide a further refinement of our understanding of ligand structure-binding affinity correlations for the estrogen receptor, and they furnish the synthetic groundwork for the synthesis of the analogous Tc-99m complexes for evaluation as breast tumor imaging agents.

Introduction

Breast cancer is the most prevalent form of diagnosed cancer of women in the United States and is the second leading cause of cancer death in women.[1] As with most cancers, early diagnosis is imperative for long-term survival. In addition to early detection, the ability to determine the estrogen receptor (ER) content of the breast tumor is essential for making the most appropriate choice of treatment for the patient. Tumors with a relatively high concentration of the ER are termed ER+ tumors and can often be treated successfully with antiestrogen hormone therapy.[2] Tumors with a relatively low concentration of the ER are accordingly dubbed ER−. Such ER− tumors often respond poorly to hormone therapy and must be treated by more invasive means, such as surgical removal of the tumor, oophorectomy, and/or cytotoxic chemotherapy.

One way to determine the ER content of cells would be to image breast tumors, using positron emission tomography (PET) or single photon emission computerized tomography (SPECT). These techniques utilize the emission characteristics of certain radiolabeled receptor-binding pharmaceuticals that have appropriate distribution properties to image tissues.

In our ongoing effort to develop imaging agents for ER+ breast cancer, we have focused on the design of ligands bearing Tc-99m as the radionuclide. Although considerable advances have been made in the development of steroids labeled with either fluorine-18 for PET imaging[3−14] or iodine-123 for SPECT imaging,[14−19] a large effort continues to be made toward the use of Tc-99m as the radionuclide, because of its convenient 6-h half-life and its wide availability.

There are two basic paradigms used to incorporate Tc-99m into steroids, the "integrated" design and the "pendant" or "conjugated" design. Although progress has

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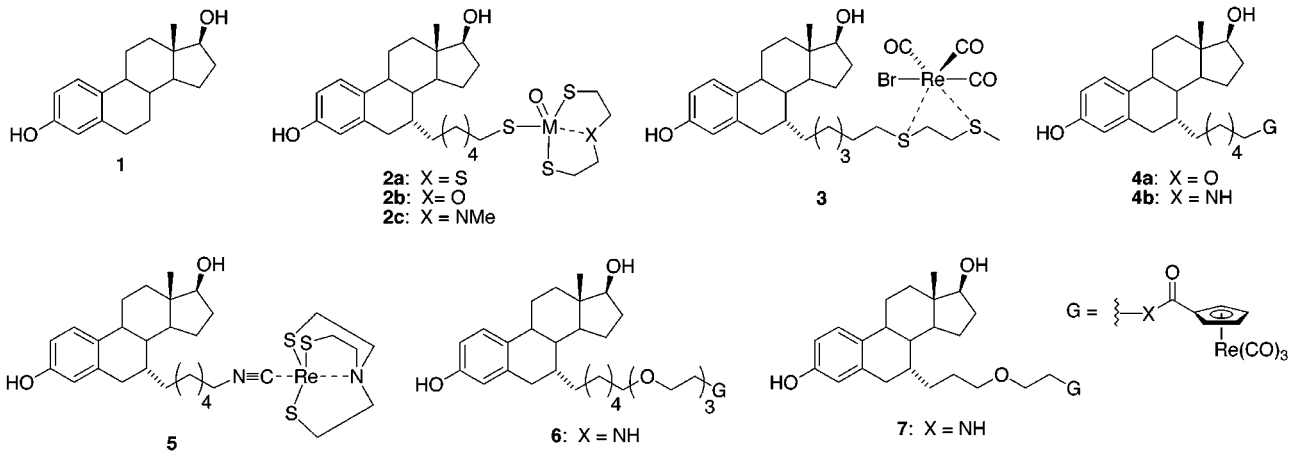

Figure 1. Estradiol and Re-containing estradiol complexes.

been made in the synthesis of integrated estrogen mimics (where part of the steroid is replaced with the requisite metal chelate),[20−24] the resulting chelates have generally either been too unstable or exhibited low binding affinity to the ER. In the conjugated design, a metal-containing moiety is tethered to an existing steroid, such as progesterone or estradiol (**1**).[25−33] The binding affinities of these complexes can remain quite high when attached to an appropriate position known to tolerate steric bulk.

We report here the synthesis and binding affinity of nine rhenium-labeled estradiol complexes based on the conjugated design (Figure 1). Because of the well-known chemical similarity of Re to Tc, these mimics should be effective models for Tc-99m-containing imaging agents for breast cancer. The 7α position of estradiol was chosen because of the well-known tolerance of the ER for bulky substituents at this site.[34] Three of these complexes (**2a**−**c**) take advantage of the "3 + 1" approach, in which a tridentate ligand and monodentate ligand stabilize an oxorhenium(V) core.[35] Four others (**4a,b**, **6**, **7**) are based on the cyclopentadienyltricarbonylmetal (CpTM) organometallic system for complexing the metal.[36] Both the "3 + 1" and CpTM paradigms were chosen for their well-established stability, as well as their known facility for being prepared at the tracer level.[35,37] Two other complexes are based on dithioether-carbonyl (**3**) and "4 + 1" mixed ligand designs (**5**).[35,38] The dithioether-carbonyl design utilizes the recently reported low valence Re(I) carbonyl precursor $[M(Hal)_3(CO)_3]^{2-}$.[39] In the "4 + 1" system, a tripodal NS_3 ligand and an isocyanide ligand chelate a Re(III) center. The lipophilicities of these complexes tend to be lower than their "3 + 1" oxorhenium counterparts, and hence their biological properties are expected to be different as well.[40]

Results and Discussion

Synthesis of 7α-Substituted Estrogens 2−5. A number of factors entered into our choice of the type of "spacer" to be used to bridge the metal-containing moiety and the steroid in compounds **2**−**5**. It is known that short chains with bulky substituents at the 7α position attenuate binding affinity, whereas excessively long chains can detrimentally increase the lipophilicity and molecular weight of the compound.[34] Therefore, a hexyl spacer of intermediate length was chosen.

The synthesis of the alcohol, amine, and thiol precursors for mimics **2**−**5** began with tetrahydropyranyloxy-(THP)-protected estradiol (**8**, Scheme 1). The 6-keto functionality was introduced using a previously published method[41] to provide steroid **9** in good yield. The 7α-substituted alkene **10** was synthesized in 53% yield by treating the potassium enolate of **9** with 6-iodohexene, using BEt_3 as an additive to help stabilize the enolate and prevent O-alkylation.[42] The yields for introducing long side chains at the 7α-position using this method are

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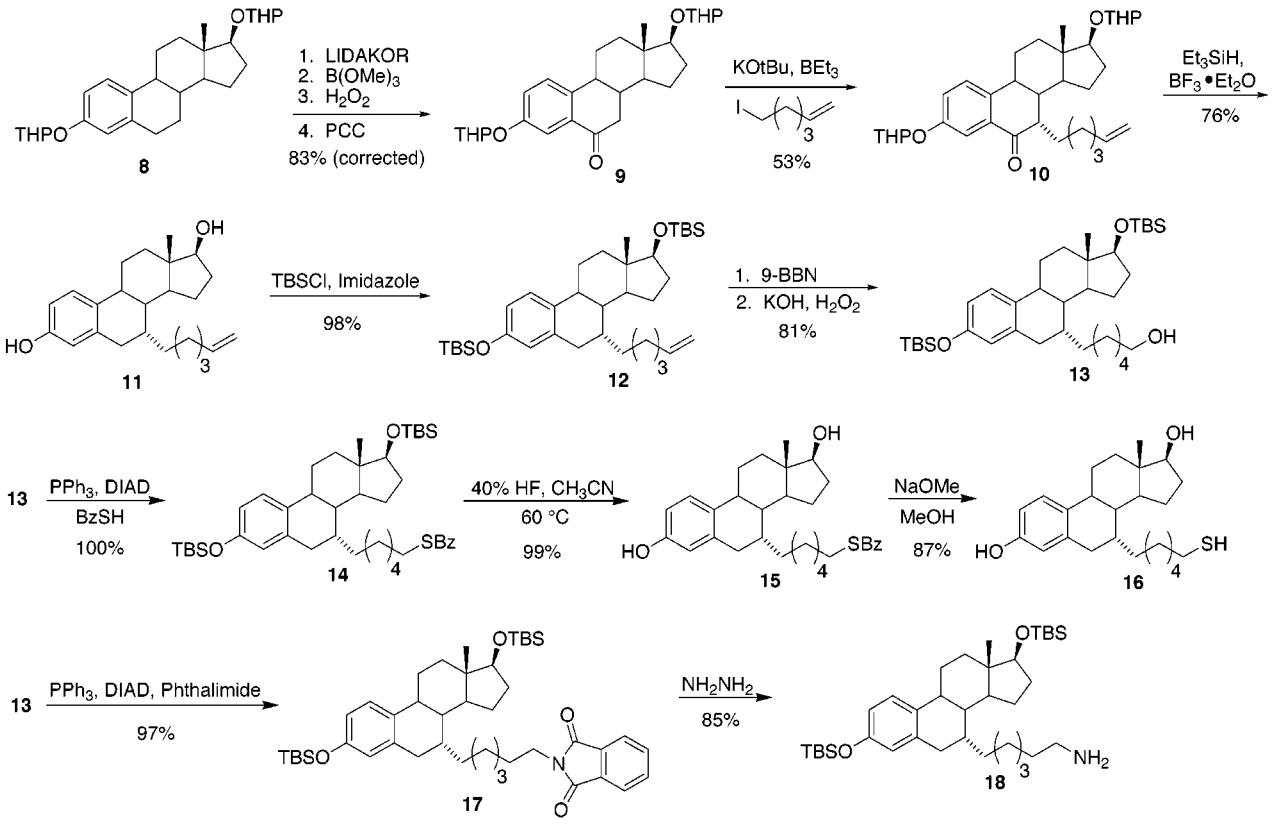
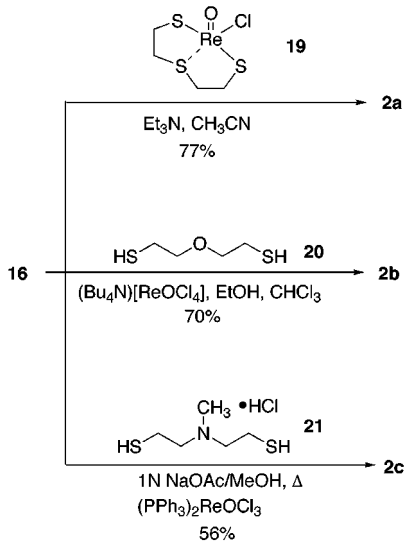
Scheme 1



generally quite low, but this is one of the highest *uncorrected* yields reported for an alkyl substituent of this size. Yields corrected for recovered **9** were as high as 64% for this reaction. Deprotection of the THP groups and deoxygenation of the 6-keto functionality can be accomplished simultaneously with $BF_3{\cdot}OEt_2/Et_3SiH$ to afford alkene **11**, although in later reactions it was found that deprotecting the 3 and 17 positions first was necessary to prevent the product from prematurely precipitating from solution. Reprotection of the free hydroxyls with *tert*-butyldimethylsilyl (TBS) groups provides TBS-protected alkene **12**, and subsequent hydroboration-oxidation gave alcohol **13** in a 27% overall uncorrected yield from **8**. Thiol **16** can be prepared by converting alcohol **13** to thiobenzoate **14** using Mitsunobu conditions,[43] followed by acidic deprotection to diol **15** and saponification of the thiobenzoate. We chose HF as the deprotecting agent at both sites because of the well-known stability of 17β-silyl groups toward tetrabutylammonium fluoride (TBAF).[44] Mitsunobu conditions were also used to convert alcohol **13** into phthalimide **17**. Subsequent hydrazinolysis provided amine **18** in excellent yield.

Thiol **16** was then used to prepare all three "3 + 1" mixed ligand complexes (Scheme 2). These complexes differ only in the nature of the central donor atom on the tridentate ligand. The "SSS" complex **2a** was prepared in good yield by reacting thiol **16** with rhenium precursor **19** in which the tridentate ligand is already

Scheme 2



attached to the metal center.[45] The "SOS" complex **2b** was synthesized in good yield by reacting thiol **16** in a 1:1:1 ratio with the tridentate ligand **20** and $(Bu_4N)[ReOCl_4]$[39] as the source of rhenium. The synthesis of the N-containing "3 + 1" complex **2c** required more vigorous conditions, in which thiol **16**, bis(2-mercaptoethyl)methylamine HCl (**21**),[46] rhenium precursor $(PPh_3)_2ReOCl_3$, and MeOH are refluxed together in the presence of NaOAc. Complexes **2a** and **2b** were isolated as red foams,

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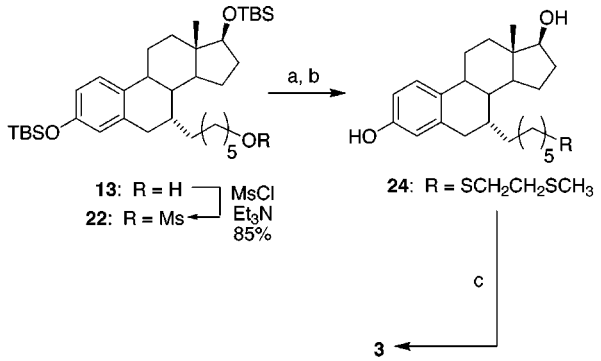
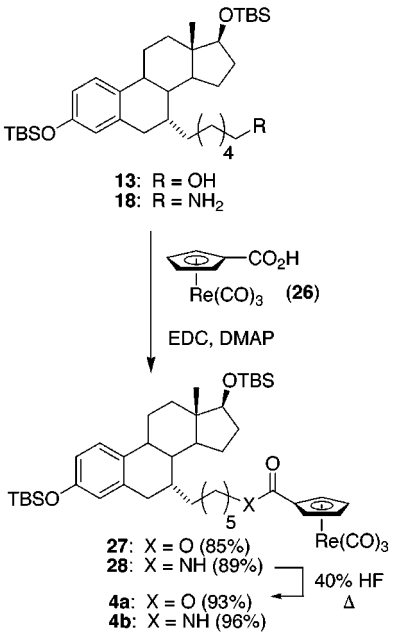
Scheme 3



(a) KOtBu, $HS(CH_2)_2SCH_3$ (**23**); (b) 40% HF, Δ, (49%, 2 steps) (c) $(NEt_4)_2[ReBr_3(CO)_3]$ (**25**), MeOH (79%)

Scheme 4



whereas complex **2c** was isolated as a green foam. All complexes were stable in aqueous media and to column chromatography.

Synthesis of the dithioether-carbonyl complex **3** begins with the conversion of alcohol **13** to methanesulfonate (mesylate) **22** (Scheme 3). Mesylate **22** is then displaced with thiol **23** (readily prepared from 2-(mercaptomethyl)-ethanol in two steps, see the Experimental Section). The resulting protected dithioether is then deprotected with HF, providing dithioether **24** in modest yield. Reaction of dithioether **24** with Re(I) precursor **25** at room temperature provides the desired dithioether-carbonyl rhenium complex **3** in good yield.

The protected CpTR ester **27** and amide **28** were prepared by the coupling of cyclopentadienylrheniumtricarbonyl carboxylic acid (**26**)[36] with either alcohol **13** or amine **18**, respectively, using 1-(3-dimethylaminopropyl)-3-ethylamine carbodiimide HCl (EDC) as the coupling agent (Scheme 4). Deprotection with HF affords the desired CpTR ester **4a** and CpTR amide **4b** in good yields.

The "4 + 1" complex **5** requires the synthesis of the terminal isocyanide from amine **18** (Scheme 5). This can be easily accomplished by reacting amine **18** with ethyl formate to produce amide **29** in good yield. The generation of the required isocyanide was accomplished during

Scheme 5

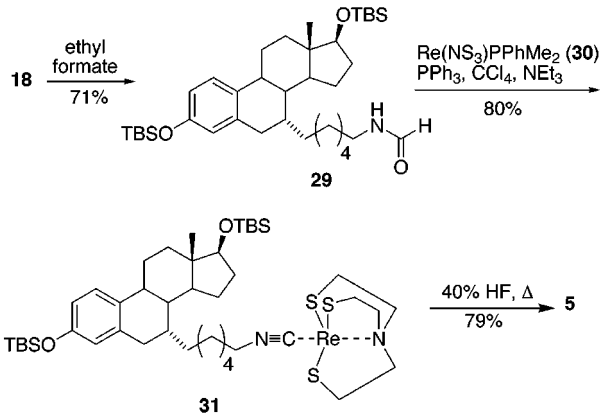
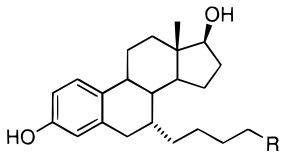


Table 1. Relative Binding Affinity (RBA) and log $P_{o/w}$ Values of Rhenium Complexes



complex/ligand	RBA (0 °C)	RBA (25 °C)	log P
1	100	100	3.74
R = CH=CH_2	102	26	N/A
R = $(CH_2)_2OH$	48	14	N/A
R = $(CH_2)_2SH$	107	18	N/A
R = DTE[a]	24	28	N/A
2a	11	21	5.73
2b	43	20	5.95
2c	10	45	5.52
3	12	15	6.29
4a	5	8	7.31
4b	29	24	6.88
5	14	15	5.13

[a] DTE = $CH_2CH_2S(CH_2)_2SCH_3$.

the complexation step by the in situ dehydration of amide **29** with the $PPh_3/CCl_4/NEt_3$[47] system. This isocyanide immediately underwent complexation with the phosphine-containing rhenium(III) precursor **30**[48] to afford complex **31**. Deprotection with HF gave the final "4 + 1" complex **5** in good yield.

Estrogen Receptor Binding Affinities and log $P_{o/w}$ Measurements of 7α-Substituted Estrogens 2−5. The ER binding affinities and lipophilicities of complexes **2**−**5**, as well as some of the free ligands, were measured (Table 1). The affinities are expressed as relative-binding affinity values (RBA), where estradiol has a value of 100.

Most of the binding affinities of the 7α-substituted compounds are moderate to high, even for extremely bulky substituents (e.g., tripodal rhenium moiety in **5**), confirming the high tolerance of the ER toward bulky substituents at this position. Although binding affinity values determined at 0 °C are reported for the sake of comparison, the emphasis should be placed on the 25 °C RBA values, as this is a temperature more representative of physiological conditions and the one that gives complete equilibration and the most reproducible binding affinity values for the complexes. Thus, the highest RBA at 25 °C for the inorganic complexes is that of "SNS"

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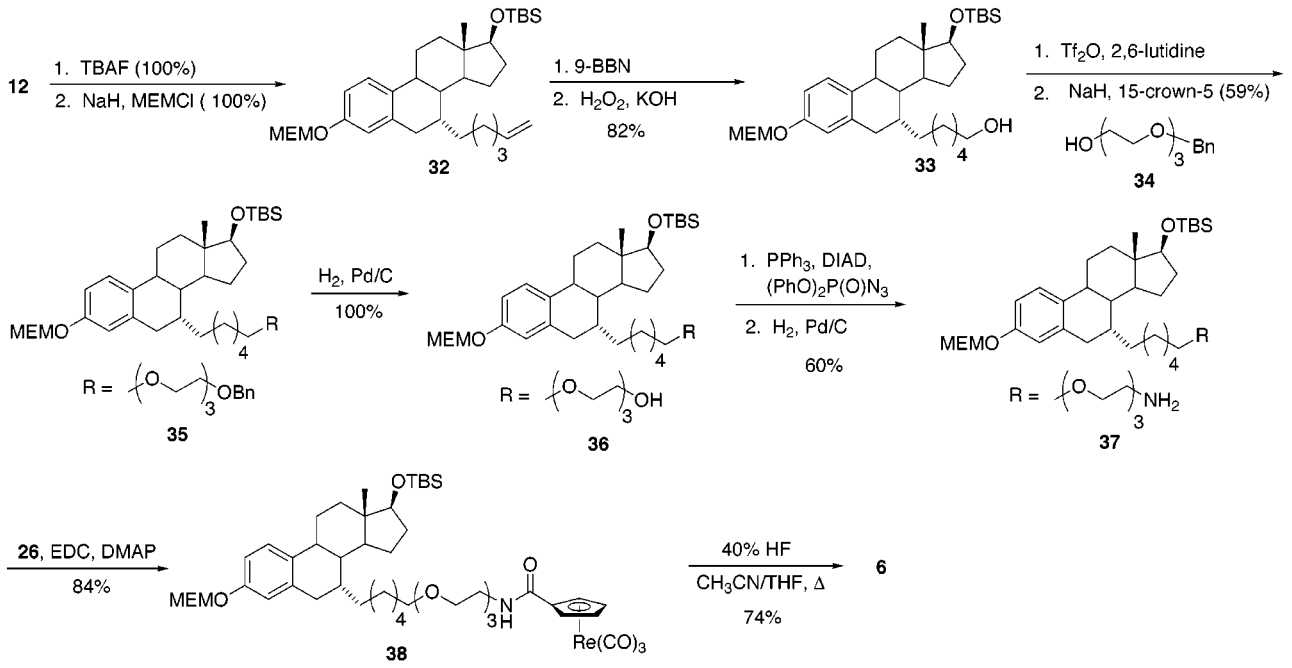
Scheme 6



complex **2c**, with an RBA of 45%. This is also the highest RBA value reported for a rhenium-labeled estradiol complex containing no auxiliary functional groups that promote receptor binding (e.g., 11β CH_2Cl).[29] The highest of the organometallic series (**4a**, **4b**) is the CpTR amide **4b**, with an RBA of 24%.

It is unclear what accounts for the rise in binding affinity when a nitrogen is added to the 7α side chain in **2c** and **4b**. For **2c**, it is known that the more basic nitrogen lengthens and hence weakens the Re=O bond, making it more polarized. This is evident from a drop in IR stretching frequency for this bond (e.g., 961 cm^{-1} for **2a**, 949 cm^{-1} for **2c**). Molecular modeling studies also suggest that the 7α substitutents of **2c** and **4b** remain in the binding pocket of the ER. One could hypothesize that the ability of this moiety to interact with the amino acid residues in the 7α pocket of the ER is the reason for the dramatic jump in binding affinity for **2c**. An analogous explanation could be given for the rise in binding affinity of **4b** vs that of **4a**. Amides (e.g., **4b**) do have more single bond character in the C=O bond than do esters (e.g., **4a**), creating a more polarized C=O bond in **4b**. Again, this is evident from the IR stretching frequencies of the C=O bond (1723 cm^{-1} for **4a**, 1644 cm^{-1} for **4b**). Amide **4b** also possesses more hydrogen bond donating capability than ester **4a**, as well as more restricted rotation about the N−CO bond, both of which may also play a role in its greater affinity for the ER than that of **4a**.

As expected, the attachment of a lipophilic side chain increased the respective log $P_{o/w}$ values of the complexes vs that of estradiol itself (log $P_{o/w}$ = 3.74). The change is most dramatic for that of the CpTR complexes **4a** and **4b** (7.31 and 6.88, respectively) and dithioether carbonyl **3** (6.29). Tissue distribution studies on the Tc-99m analogues of **2c** and **4b** have shown that these complexes, although stable in aqueous media, show rather low target tissue uptake selectivity and high nonspecific uptake,[49] probably as a result of their high lipophilicities. Thus, we extended our effort to synthesize more polar varieties of these complexes, focusing our efforts on CpTR amide **4b**.

Synthesis of 7α-Substituted Estrogens 6 and 7. To increase the polarity of CpTR amide **4b**, we decided to introduce ether linkages into the side chain (**6** and **7**). This modification keeps the steroid backbone intact, thereby preserving binding affinity. The long-chain ether **6** has the advantage of possessing a lower molecular weight, whereas the short-chain ether **7** has the advantage of placing the polar polyether farther away from the steroid backbone.

The synthesis of long-chain ether **6** begins with TBS-protected alkene **12** (Scheme 6). It became evident to us that the 3-TBS group was unstable under the basic Williamson ether-type conditions required for the conversion of alcohol **33** to ether **35**. Therefore, the 3-TBS group was replaced with the base-stable MEM group to give **32** quantitatively. Efforts to attach polyether unit **34**[50] using the mesylate, tosylate, or tresylate of alcohol **33** failed to give consistent yields above 20%. The use of a variety of bases and solvents was also unsuccessful. This step was finally accomplished by using the trifluromethanesulfonate (triflate), under conditions similar to those of Nicolaou and co-workers in the synthesis of β-D-glucose ethers.[51] This resulted in the formation of polyether steroid **35** in 59% yield. The benzyl group was then removed by hydrogenolysis to provide alcohol **36** quantitatively. The azide functionality was introduced under Mitsunobu conditions, followed by hydrogenation of the azide to amine **37** in 60% yield over two steps. Efforts to introduce the amine in this substrate via the phthalimide (vide supra) were unsuccessful. The protected CpTR amide **38** was then formed in good yield by coupling

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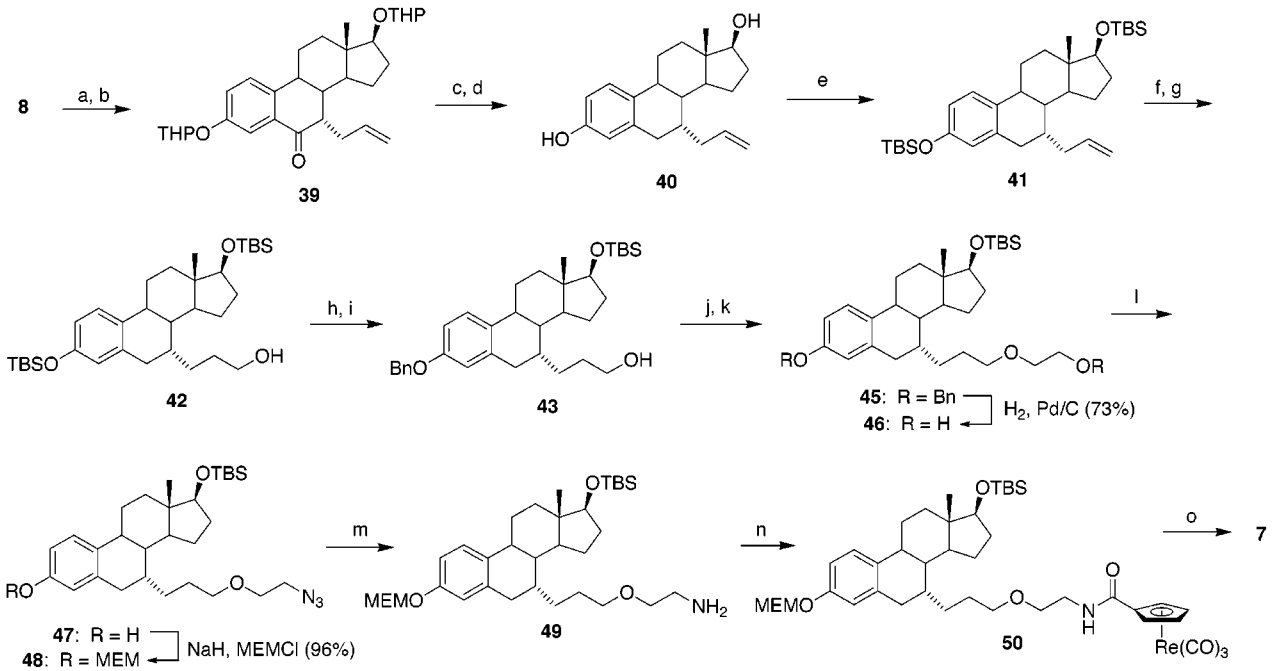
Scheme 7



(a) KOtBu, allyl iodide, THF, -78 °C; (b) NaOMe (77%, corrected); (c) HCl; (d) $BF_3 \cdot OEt_2$, Et_3SiH (83%); (e) TBSCl, imidazole, DMF (90%); (f) 9-BBN; (g) H_2O_2, KOH (87%, corrected); (h) TBAF (100%); (i) BnBr, K_2CO_3 (100%); (j) Tf_2O, 2,6-lutidine (k) NaH, 15-crown-5, $HO(CH_2)_2OBn$ (**44**) (59%); (l) PPh_3, DIAD, $(PhO)_2P(O)N_3$ (74%); (m) H_2, Pd/C (96%); (n) **26**, EDC, DMAP (80%); (o) 40% HF, CH_3CN/THF, Δ (73%)

amine **37** to CpTR acid **26** in the presence of EDC. Deprotection of the 3 and 17 hydroxyls then leads to the desired amide **6**.

The synthesis of short-chain ether **7** begins with THP-protected estradiol **8** (Scheme 7). The conditions used to introduce the allyl side chain were analogous to those used to form **10**, except that the higher reactivity of the allyl iodide erodes the α/β selectivity in the C(7) alkylation and also increases the amount of dialkylated product.

The erosion of selectivity can be attributed to the earlier transition state of the allyl iodide alkyation relative to that of the reaction involving the less reactive 6-iodohexene. Selectivities for endocyclic enolate alkylations of six-membered rings involving late transition states depend on the torsional strain of the six-membered ring as the electophile approaches from the α or β face.[52] For this system, an axial approach of the electrophile from the 7α face involves a less strained chairlike transition state, whereas an electrophile approaching axially from the 7β face involves a more strained boatlike transition state; hence, the α product is preferred for alkylation with 6-iodohexene. The much more reactive allyl iodide involves an earlier, more reactant-like transition state, and therefore the selectivity between faces is attenuated. The angular 18-CH_3 group may also play a role in increasing the α-selectivity for the more bulky 6-iodohexene.

In contrast to the alkylation conditions used for the formation of alkene **10**, BEt_3 had little effect on this reaction. It was found that by lowering the temperature to −78 °C and using THF as the solvent, we could ensure that virtually no dialkylated product was formed. Even though the 7β epimer is produced exclusively in this reaction, conversion to the 7α epimer product is readily accomplished by stirring the reaction product with NaOMe at room temperature for several hours to produce alkene **39** in good yield.

Deoxygenation, reprotection of the free hydroxyls with TBS groups, and hydroboration-oxidation generated alcohol **42**, using conditions similar to those reported for the synthesis of hexyl-spaced alcohol **13**. Also in this case, the 3-TBS group on alcohol **42** was removed and the phenol was protected as a benzyl ether prior to etherification under basic conditions with monobenzylated ethylene glycol **44**,[50] providing ether **45** in good yield. The reaction sequence to produce amide **7** from ether **45** proceeds analogously to that reported for the synthesis of amide **6** from ether **35**. However, protection of the 3 hydroxyl group was necessary prior to the coupling step. Amide **7** was formed in a 29% six-step yield from ether **45**.

Table 2. RBA and log $P_{o/w}$ Values of 6 and 7

mimic	RBA (0 °C)	RBA (25 °C)	log *P*
6	7	23	6.94
7	35	20	5.40

Estrogen Receptor Binding Affinities and log $P_{o/w}$ Measurements of 7α-Substituted Estrogens 6 and 7. The RBA and log $P_{o/w}$ values for amides **6** and **7** were measured and are shown in Table 2. It is encouraging to note that the binding affinities at 25 °C for **6** (23%) and **7** (20%) are relatively unchanged from that of the original amide **4b**. As expected, the introduction of ether functionalities in the side chain did change the log $P_{o/w}$ values relative to that of the amide. Surprisingly, the log $P_{o/w}$ for the polyether **6** (6.94) is actually higher than that for the original amide, even though calculations suggested that there would be a 5-fold decrease in lipophilicity.[53] It is possible that the log $P_{o/w}$ predictions might not be

(52) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*, 1st ed.; Wiley-Interscience: New York, 1994; p 1267.

(53) log $P_{o/w}$ calculations were performed on ChemDraw Ultra using the benzamide analogues of **4a**, **4b**, **6**, and **7**.

as accurate for compounds like **6** with a very high molecular weight. The log $P_{o/w}$ for **7** (5.40), however, did show a 30-fold increase in polarity relative to that of **4b** (6.90). Thus, the log $P_{o/w}$ value for **7** seems to suggest that we were successful in increasing the polarity of amide **4b** by introducing an ether linkage into the side chain. It should be noted, however, that while the log $P_{o/w}$ for **6** is still quite high, the extra oxygens in the side chain offer more hydrogen bond accepting sites; as a result, this compound might be more soluble in aqueous media than amide **4b**. Therefore, the biodistribution experiments of the Tc-99m analogues of both **6** and **7** are being investigated.

Conclusions

We have described the synthesis of a number of novel Re-containing 7α-substituted estrogen complexes, and we have determined their lipophilicities and binding affinities for the ER. To our knowledge, this is the first time the 7α-position of estradiol has been labeled with rhenium. The highest affinity ligand in the inorganic complex series (**2**, **3**, **5**) is the "SNS 3 + 1" complex **2c**, with an RBA of 45%. The highest affinity ligand in the original organometallic series (**4**) was that of the amide **4b**, with an RBA of 24%. The lipophilicities of these two complexes proved to be too high for an acceptable biodistribution profile.

This prompted us to increase the polarity of these complexes by modifying the side chain with ether linkages. We focused on modifying amide **4b**, synthesizing both the long-chain polyether **6** and short-chain ether **7**. The critical step was the attachment of the poly(ethylene glycol) moieties. The final CpTR amides **6** and **7** showed good binding affinity—essentially unchanged from that of the original amide **4b**. Although the log $P_{o/w}$ of **6** was unexpectedly high, the log $P_{o/w}$ of **7** (an order of magnitude lower than that of **4b**) demonstrates that we were successful in lowering the log $P_{o/w}$ of **4b** by introducing an ether linkage in the 7α side chain. Efforts to synthesize the Tc-99m analogues of **6** and **7** are currently underway. A favorable biodistribution would suggest the usefulness of these compounds as effective imaging agents for ER+ breast cancer.

Experimental Section

General. All reagents and solvents were obtained from Aldrich, Acros, Alfa Aesar, Fisher, Fluka, or Mallinckrodt. All reactions were performed under a nitrogen atmosphere unless otherwise indicated. The synthesis of 3,17β-bis(2-tetrahydropyranyloxy)-estra-1,3,5(10)-triene (**8**) has already been described.[41] THF and DME were distilled from sodium/benzophenone immediately prior to use. Methylene chloride and toluene were distilled from CaH_2 prior to use. Triethylamine was dried by distillation from CaH_2 and stored over KOH. Diisopropylamine was distilled from powdered KOH and stored over KOH pellets. Dimethylformamide was dried with BaO and distilled from and stored over 4 Å molecular sieves. MeOH was distilled from Mg/I_2 and stored over 3 Å molecular sieves. Acetone was distilled from $CaSO_4$ and stored over 4 Å molecular sieves. Hexanes were distilled from $CaSO_4$ (Drierite) before use in flash chromatography.

Reaction progress was monitored by analytical thin-layer chromatography (Analtech scored 10 cm × 20 cm hard TLC plates, glass). Silica gel used in flash chromatography was 32−63 μm. TLC plates were visualized using short wave UV light (254 nm), potassium permanganate, ninhydrin, or phosphomolybdic acid.

^1H and ^{13}C NMR were obtained at 400 or 500 MHz and are reported in parts per million relative to tetramethylsilane or the incomplete deuteration signal of the NMR solvent. The signals generated from diastereomeric mixtures (due to the presence of the tetrahydropyranyloxy group) are reported as two numbers separated by a comma (x, x) and the 1H multiplicity is indicated as a double signal (e.g., 2d = two doublets). Melting points are uncorrected. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois.

3,17β-Bis(2-tetrahydropyranyloxy)estra-1,3,5(10)-triene-6-one (9). To a −78 °C solution of 1.3 M *n*-BuLi in hexanes (56 mL, 72.6 mmol) in THF (100 mL) was added diisopropylamine (10.2 mL, 72.6 mmol), followed by 1 M KO*t*-Bu in THF (72.6 mL, 72.6 mmol). After 5 min, a solution of **8** (8.00 g, 18.2 μmol) in THF (40 mL) was slowly added via cannula. The solution turned a dark red color, and stirring was continued for 3 h at −78 °C. The dry ice/IPA bath was replaced with an ice bath, and trimethylborate (27 mL) was slowly added. The mixture became turbid, and after the reaction was stirred for an additional 2 h, the stir bar was removed and replaced by a mechanical stirrer. To this was added 30% H_2O_2 (50 mL), and the reaction was stirred for 1 h at room temperature. The reaction was cooled to 0 °C, and 10% $Na_2S_2O_3$ (100 mL) was added. After extraction with EtOAc, drying over Na_2SO_4/Na_2CO_3, and evaporation in vacuo, a pale yellow foam of the 6-hydroxy compound was obtained (7.70 g, 93%).

The 6-hydroxy compound (6.50 g, 14.2 mmol) was dissolved in CH_2Cl_2 (80 mL). At 0 °C, PCC (5.4 g, 24.8 mmol) was added in portions within 15 min. After 15 min at 0 °C, the mixture was allowed to warm to room temperature, and after 1.5 h, the reaction was diluted with ether (80 mL). The black-brown mixture was filtered through Florisil to remove the chromium salts. The yellow solution was evaporated in vacuo, and the residue was purified by flash chromatography (25% EtOAc/Hex) to yield **9** as a white foam (4.20 g, 65%, 83% when corrected for recovered SM). IR (KBr): 1685 cm^{-1} (s, C=O). ^1H NMR ($CDCl_3$, 500 MHz): δ 0.80, 0.81 (2s, 3H), 2.32−2.36 (m, 2H), 2.44−2.49 (m, 1H), 2.72 (dd, J = 16.8, 3.3 Hz, 1H), 3.48−3.51 (m, 1H), 3.58−3.61 (m, 2H), 3.71, 3.74 (2t, J = 8.4 Hz, 1H), 3.85−3.93 (m, 2H), 4.63−4.68 (m, 1H), 5.46−5.47 (m, 1H), 7.21, 7.22 (2dd, J = 8.6, 2.7 Hz, 1H), 7.33, 7.34 (2d, J = 7.9 Hz, 1H), 7.70, 7.71 (2d, J = 3.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.52, 11.54; 18.71; 19.34, 19.73; 22.75, 22.86; 25.10; 25.48, 25.56; 27.07; 28.62; 30.18; 30.98, 31.05; 36.66, 37.19; 39.76, 39.80; 39.86, 39.89; 42.60, 42.90; 42.96, 43.04, 43.07; 43.97, 44.03; 44.06, 44.11; 49.84, 49.98; 61.92, 62.09; 62.12, 62.60; 83.82, 86.25; 96.30, 96.34; 96.70, 99.35; 113.99, 114.02; 122.49, 122.58; 126.45, 126.50; 133.43; 140.47; 155.40; 197.87, 197.94. MS (CI, CH_4): m/z 455 ($M + H^+$, 14), 371 (85), 85 (100). HRMS (CI, CH_4) calcd for $C_{28}H_{39}O_5$: 455.2898. Found: 455.2800. Anal. Calcd for $C_{28}H_{38}O_5$: C, 73.98; H, 8.42. Found: C, 74.00; H, 8.57.

3,17β-Bis(2-tetrahydropyranyloxy)-7α-(5-hexen-1-yl)-estra-1,3,5(10)-triene-6-one (10). A 1 M solution of KO*t*-Bu in THF (5.80 mL, 5.80 mmol) was added to a solution of ketone **9** (2.40 g, 5.28 mmol) in DME (25 mL). After 10 min, 1 M BEt_3 in THF (6.60 mL, 6.60 mmol) was added, and stirring was continued for 1 h at room temperature. A solution of 6-iodohexene (1.33 g, 6.60 mmol, prepared from 6-bromo-1-hexene and NaI in acetone) in DME (2 mL) was then added to the enolate. After 30 min an additional equivalent of KO*t*-Bu was added, and the mixture was stirred overnight. The reaction was quenched with water, extracted with $CHCl_3$, and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography (10% EtOAc/Hex) to afford **10** as a white foam (1.50 g, 53%). IR (KBr): 1683 (s, C=O). ^1H NMR ($CDCl_3$, 500 MHz): δ 0.79, 0.80 (2s, 3H), 2.35−2.37 (m, 2H). 2.42−2.45 (m, 1H), 2.67−2.71 (m, 1H), 3.48−3.51 (m, 1H), 3.60−3.63 (m, 1H), 3.74, 3.76 (2t, J = 8.4 Hz, 1H), 3.87−3.93 (m, 2H), 4.63−4.68 (m, 1H), 4.89−4.97 (m, 2H), 5.45−5.47 (m, 1H), 5.76 (2ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 7.19, 7.22 (2dd, J = 8.6, 2.7 Hz, 1H), 7.30, 7.32 (2d, J = 7.7 Hz, 1H), 7.68, 7.69 (2d, J = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.52; 18.79, 18.88; 19.37, 19.75; 22.19, 22.32;

23.46, 23.52; 25.16; 25.51, 25.61; 26.61, 26.79, 27.01; 28.60, 28.94; 30.25, 30.30; 31.00, 31.07; 36.95, 37.40; 37.49; 42.23, 42.27; 42.31, 42.36; 42.78, 43.26; 45.25, 45.34; 48.59, 48.67, 48.75; 61.93, 62.18; 62.32, 62.61; 83.89, 86.31; 96.33, 96.49; 96.70, 99.35; 114.36, 114.58, 114.67; 122.37, 127.05; 132.33; 138.85; 139.42, 139.55; 155.50; 200.86. MS (CI, CH_4): *m/z* 537 ($M + H^+$, 73), 453 (100), 85 (57). HRMS (CI, CH_4) calcd for $C_{34}H_{49}O_5$: 537.3580. Found: 537.3583. Anal. Calcd for $C_{34}H_{48}O_5$: C, 76.08; H, 9.01. Found: C, 75.84; H, 8.98.

7α-(5-Hexen-1-yl)-estra-1,3,5(10)-triene-3,17β-diol (11). Et_3SiH (30 mL) was added to a solution of steroid **10** (1.40 g, 2.60 mmol) in CH_2Cl_2 (100 mL). The mixture was cooled to 0 °C and BF_3·Et_2O (100 mL) was added dropwise. The yellow-green solution was warmed to room temperature and stirred overnight. The reaction was carefully hydrolyzed with 10% K_2CO_3 (500 mL) and then passed through a plug of silica. The aqueous layer was washed with CH_2Cl_2, and the organic fractions were then combined and dried over Na_2SO_4. Following evaporation of the CH_2Cl_2, the residue was purified by flash chromatography (40% EtOAc/Hex) to give **11** as a white solid (700 mg, 76%). IR(KBr): 3410 (s, OH), 1639 (s, C=O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.70 (d, *J* = 16.8 Hz, 1H), 2.86 (dd, *J* = 16.8, 4.6 Hz, 1H), 3.75 (t, *J* = 8.4 Hz, 1H), 4.82 (bs, 1H), 4.90−4.98 (m, 2H), 5.78 (ddtd, *J* = 17.1, 10.3, 6.7, 1.5 Hz, 1H), 6.54 (s, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.07, 22.63, 25.42, 27.24, 27.62, 29.15, 30.52, 33.13, 33.85, 34.53, 36.85, 38.01, 41.91, 43.36, 46.43, 82.03, 112.79, 114.25, 116.10, 127.07, 131.89, 137.12, 139.01, 153.34. MS (EI, 70 eV): *m/z* 354 (M, 100). HRMS (EI, 70 eV) calcd for $C_{24}H_{34}O_2$: 354.2559. Found: 354.2564. Anal. Calcd for $C_{24}H_{34}O_2$·H_2O: C, 77.38; H, 9.74. Found: C, 77.60; H, 9.55.

3,17β-Bis(*t*-butyldimethylsilanyloxy)-7α-(5-hexen-1-yl)-estra-1,3,5(10)-triene (12). A solution of TBSCl (841 mg, 5.58 mmol) in DMF (4 mL) was added to a cooled solution (0 °C) of imidazole (844 mg, 12.4 mmol) in DMF (10 mL). After the reaction was stirred for 30 min, a solution of steroid **11** (400 mg, 1.24 mmol) in DMF (2 mL) was added all at once. The reaction was stirred overnight and then hydrolyzed with 0.1% K_2CO_3, followed by extraction with CH_2Cl_2. The extracts were flushed through a silica plug and then concentrated in vacuo to give **12** as a colorless oil (700 mg, 98%). IR ($CHCl_3$): 1608 (s, C=C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.19 (s, 6H), 0.74 (s, 3H), 2.68 (d, *J* = 16.6 Hz, 1H), 2.84 (dd, *J* = 16.6, 4.9 Hz, 1H), 3.65 (t, *J* = 8.0 Hz, 1H), 4.89−4.99 (m, 2H), 5.78 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.78, −4.46, −4.38, 11.39, 18.12, 22.80, 25.37, 25.70, 25.87, 27.29, 27.64, 29.19, 30.94, 33.25, 33.84, 34.61, 37.37, 38.26, 41.94, 43.71, 46.11, 81.86, 114.25, 117.15, 120.81, 126.65, 132.52, 136.79, 139.06, 153.20. MS (EI, 70 eV): *m/z* 583 (M, 100), 526 (89), 73 (72). HRMS (EI, 70 eV) calcd for $C_{36}H_{62}O_2Si_2$: 582.4288. Found: 582.4285.

3,17β-Bis(*t*-butyldimethylsilanyloxy)-7α-(6-hydroxy-hexan-1-yl)-estra-1,3,5(10)-triene (13). A solution of 0.5 M 9-BBN in THF (12.0 mL, 6.00 mmol) was added to a solution of steroid **12** (700 mg, 1.20 mmol) in THF (40 mL). After being stirred overnight, the reaction was hydrolyzed with 3 M KOH (5 mL), followed by 30% H_2O_2 (5 mL) after 5 min. Stirring was continued for 3 h, followed by the addition of saturated $NaHCO_3$ (50 mL) and extraction with CH_2Cl_2. The organic fractions were dried over Na_2SO_4 and evaporated in vacuo, followed by purification by flash chromatography (20% EtOAc/Hex) to give **13** as a white solid (580 mg, 81%). IR (KBr): 3402 (s, OH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.19 (s, 6H), 0.74 (s, 3H), 0.89 (s, 9H), 0.98 (s, 9H), 2.68 (d, *J* = 16.6 Hz, 1H), 2.84 (dd, *J* = 16.6, 5.1 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 1H), 3.65 (t, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.61 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.79, −4.47, −4.39, 11.38, 18.11, 22.79, 25.50, 25.63, 25.68, 25.79, 25.86, 27.27, 28.17, 29.77, 30.92, 32.78, 33.28, 34.60, 37.37, 38.26, 41.94, 43.70, 46.09, 63.03, 81.83, 117.14, 120.80, 126.66, 132.54, 136.79, 153.18. MS (CI, CH_4): *m/z* 602 ($M + H^+$, 100), 586 (61), 543 (54). HRMS (EI, 70 eV) calcd for $C_{36}H_{64}O_3Si_2$: 600.4394. Found: 600.4387. Anal. Calcd for $C_{36}H_{64}O_3Si_2$·$0.5H_2O$: C, 70.88; H, 10.74. Found: C, 70.83; H, 11.02.

7α-[6-(*S*-Benzoylthio)-hexan-1-yl]-3,17β-bis(*t*-butyldimethylsilanyloxy)estra-1,3,5(10)-triene (14). DIAD (98.0 μL, 0.500 mmol) was added to a cooled solution (0 °C) of PPh_3 (131 mg, 0.500 mmol) in THF (3 mL). A white precipitate of the ylide formed, and the solution was stirred for 30 min at 0 °C. A solution of steroid **13** (150 mg, 0.250 mmol) and thiobenzoic acid (60.0 μL, 0.500 mmol) in THF (1.5 mL) was then added dropwise to the ylide. The reaction was stirred for 1 h at 0 °C and then overnight at room temperature. The clear yellow solution was concentrated and then purified by flash chromatography (10% EtOAc/Hex) to give **14** as yellow oil (181 mg, 100%). IR ($CHCl_3$): 1666 (s, C=O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.18 (s, 6H), 0.74 (s, 3H), 0.89 (s, 9H), 0.97 (s, 9H), 2.67 (d, *J* = 16.7 Hz, 1H), 2.84 (dd, *J* = 16.6, 4.9 Hz, 1H), 3.05 (t, *J* = 7.3 Hz, 1H), 3.65 (t, *J* = 8.2 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H). MS (CI, CH_4): *m/z* 720 ($M + H^+$, 23), 664 (73), 590 (100). HRMS (CI, CH_4) calcd for $C_{43}H_{68}O_3Si_2S$: 719.4350. Found: 719.4355.

7α-[6-(*S*-Benzoylthio)-hexan-1-yl]-estra-1,3,5(10)-triene-3,17β-diol (15). A solution of 40% HF (0.7 mL) was added to a solution of thiobenzoate **14** (181 mg, 0.252 mmol) in CH_3CN (1 mL) and THF (1 mL) at 60 °C. After 1 min, another 1 mL of THF was added, and heating was continued for 20 min. The reaction was quenched with $NaHCO_3$ (1 mL saturated and then solid until neutral to pH paper), extracted with CH_2Cl_2 (3 × 7 mL), and dried over Na_2SO_4. Evaporation of the organic fractions in vacuo provided **15** as a white foam (123 mg, 99%). IR (KBr): 3427 (s, OH), 1662 (s, C=O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.70 (d, *J* = 16.6 Hz, 1H), 2.87 (dd, *J* = 16.6, 5.1 Hz, 1H), 3.05 (t, *J* = 7.3 Hz, 2H), 3.75 (t, *J* = 8.5 Hz, 1H), 5.05 (bs, 1H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.96, 22.52, 25.36, 27.12, 27.87, 28.83, 28.88, 29.32, 29.41, 30.39, 33.04, 34.42, 36.72, 37.91, 41.81, 43.24, 46.29, 81.90, 112.71, 116.01, 126.93, 127.03, 128.43, 131.62, 133.13, 136.94, 137.06, 153.31, 192.18. MS (EI, 70 eV): *m/z* 492 (M, 19), 388 (100), 157 (40), 105 (79). HRMS (EI, 70 eV) calcd for $C_{31}H_{40}O_3S$: 492.2698. Found: 492.2693. Anal. Calcd for $C_{31}H_{40}O_3S$·$0.5H_2O$: C, 74.21; H, 8.24. Found: C, 74.28; H, 8.00.

7α-(6-Mercaptohexan-1-yl)-estra-1,3,5(10)-triene-3,17β-diol (16). A 1 M solution of NaOMe in MeOH (0.5 mL) was added to a solution of diol **15** (78.5 mg, 0.159 mmol) in MeOH (6 mL). The reaction was stirred at room temperature for 40 min. After the addition of 1 M HCl (5 mL), the mixture was extracted with CH_2Cl_2 (3 × 7 mL), and the organic fractions were dried over Na_2SO_4. Evaporation of the solvent and flash chromatography (50% EtOAc/Hex) provided **16** as a white foam (53.6 mg, 87%). IR (KBr): 2562 (w, SH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.50 (q, *J* = 7.3 Hz, 2H), 2.70 (d, *J* = 16.6 Hz, 1H), 2.86 (dd, *J* = 16.6, 5.1 Hz, 1H), 3.76 (t, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 2.7 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.08, 22.63, 24.61, 25.53, 27.23, 28.05, 28.42, 29.38, 30.48, 33.15, 33.98, 34.52, 36.82, 38.01, 41.90, 43.35, 46.41, 82.03, 112.81, 116.10, 127.04, 131.78, 137.05, 153.41. MS (EI, 70 eV): *m/z* 388 (M, 53), 55(100). HRMS (EI, 70 eV) calcd for $C_{24}H_{36}O_2S$: 388.2436. Found: 388.2436. Anal. Calcd for $C_{24}H_{36}O_2S$: C, 74.18; H, 9.34. Found: C, 73.93; H, 9.03.

3,17β-Bis(*t*-butyldimethylsilanyloxy)-7α-[6-(phthalimido)-hexan-1-yl]-estra-1,3,5(10)-triene (17). DIAD (327 μL, 1.66 mmol) was added dropwise to a cooled solution (0 °C) of PPh_3 (436 mg, 1.66 mmol) in THF (10 mL). A white precipitate of the ylide formed, and the reaction was stirred for 40 min at 0 °C. A solution of alcohol **13** (500 mg, 0.832 mmol) and phthalimide (244 mg, 1.66 mmol) in THF (5 mL) was then added to the ylide. The reaction was stirred for 1 h at 0 °C and then at room temperature overnight. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (5% EtOAc/Hex) to give **17** as a yellow oil (589 mg, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.19 (s, 6H), 0.74 (s, 3H), 0.90 (s, 9H), 0.97 (s, 9H), 2.67

(d, J = 16.6 Hz, 1H), 2.83 (dd, J = 16.6, 4.9 Hz, 1H), 3.66 (t, J = 7.3 Hz, 2H), 3.66 (t, J = 7.3 Hz, 1H), 6.53 (d, J = 2.6 Hz, 1H), 6.60 (dd, J = 8.5, 2.6 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.70 (dd, J = 5.4, 3.0 Hz, 2H), 7.84 (dd, J = 5.4, 3.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.79, −4.47, −4.40, 11.36, 18.10, 22.77, 25.52, 25.67, 25.86, 26.96, 27.27, 28.03, 28.59, 29.57, 30.90, 33.21, 34.53, 37.33, 38.02, 38.22, 41.91, 43.68, 46.05, 81.81, 117.12, 120.79, 123.11, 126.63, 132.14, 132.50, 133.80, 136.75, 153.17, 168.41. MS (EI, 70 eV): m/z 730 (M, 3), 673 (100). HRMS (EI, 70 eV) calcd for $C_{44}H_{67}NO_4Si_2$: 729.4609. Found: 729.4597.

7α-(6-Aminohexan-1-yl)-3,17β-bis(*t*-butyldimethylsilanyloxy)estra-1,3,5(10)-triene (18). Anhydrous hydrazine (500 μL) was added to a solution of steroid **17** (74.4 mg, 0.102 mmol) in DME (1 mL) and EtOH (1 mL). The mixture was refluxed for 2 h, during which time a white precipitate formed on the sides and the solution turned slightly green. The reaction was cooled, and 5% NaOH (1 mL) was added, dissolving the precipitate. After 30 min, water (5 mL) was added, and the solution was extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, and evaporated to give **18** as a white foam (52.2 mg, 85%). IR ($CHCl_3$): 3439 (m, NH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.19 (s, 6H), 0.74 (s, 3H), 0.89 (s, 9H), 0.98 (s, 9H), 2.68 (d, J = 17.1 Hz, 1H), 2.70 (t, J = 7.2 Hz, 2H), 2.84 (dd, J = 17.1, 4.9 Hz, 1H), 2.88 (s, 2H), 3.66 (t, J = 8.2 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 6.61 (dd, J = 8.5, 2.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.81, −4.50, −4.42, 11.34, 18.07, 22.76, 25.49, 25.66, 25.83, 26.90, 27.24, 28.15, 29.75, 30.89, 32.71, 33.23, 34.55, 37.32, 38.21, 41.71, 41.90, 43.66, 46.04, 81.79, 117.11, 120.76, 126.62, 132.48, 136.73, 153.15. MS (CI, CH_4): m/z 601 (M + H^+, 24), 585 (16), 57 (70). HRMS (EI, 70 eV) calcd for $C_{36}H_{65}NO_2Si$: 599.4554. Found: 599.4541.

[3-Thiapentane-1,5-dithiolato][7α-(6-mercaptohexan-1-yl)-estra-1,3,5(10)-triene-3,17β-diol]oxorhenium(V) (2a). A solution of thiol **16** (30.0 mg, 77.0 μmol) and Et_3N (10.0 μL) in CH_3CN (1.5 mL) was added to a solution of rhenium complex **19** (27.3 mg, 70.0 μmol) in hot CH_3CN (1.5 mL). The mixture was refluxed for 2 h, followed by evaporation of the solvent in vacuo. The residue was redissolved in $CHCl_3$ and purified by flash chromatography (5% acetone/CH_2Cl_2) to afford **2a** as a brown foam (40.0 mg, 77%). IR (KBR): 961 (s, Re═O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.65 (s, 3H), 2.21 (m, 2H), 2.60 (d, J = 16.3 Hz, 1H), 2.74 (dd, J = 16.3, 4.4 Hz, 1H), 2.99 (td, J = 14.2, 3.9 Hz, 2H), 3.53 (m, 1H), 3.76 (t, J = 7.3 Hz, 2H), 4.03 (dd, J = 10.5, 3.2 Hz, 2H), 4.26 (dd, J = 12.9, 4.4 Hz, 2H), 4.47 (d, J = 4.6 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.5, 2.7 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 8.97 (s, 1H). HRMS (FAB, 3-NBA) calcd for $C_{28}H_{44}O_3S_4Re$ (M + H): 743.1731. Found: 743.1731.

[3-Oxapentane-1,5-dithiolato][7α-(6-mercaptohexan-1-yl)-estra-1,3,5(10)-triene-3,17β-diol]oxorhenium(V) (2b). A solution of 3-oxapentane-1,5-dithiol (**20**, 10.4 μL, 87.5 μmol) and thiol **16** (34.0 mg, 87.5 μmol) in $CHCl_3$ (1 mL) was added to a cooled solution (0 °C) of $(Bu_4N)[ReOCl_4]$[39] (51.3 mg, 87.5 μmol) in EtOH (1 mL). The color of the mixture immediately turned red. Stirring was continued at 0 °C for 2 h and then overnight at room temperature. The solvent was evaporated in vacuo, and the residue was redissolved in $CHCl_3$ and purified by flash chromatography (5% acetone/CH_2Cl_2) to give **2b** as a red, glassy, solid (44.0 mg, 70%). IR (KBr): 968 (s, Re═O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.65 (s, 3H), 2.59 (d, J = 16.6 Hz, 1H), 2.74 (dd, J = 16.6, 5.1 Hz, 1H), 3.08−3.15 (m, 2H), 3.52 (m, 1H), 3.71 (bs, 2H), 3.80 (m, 2H), 4.47 (d, J = 4.4 Hz, 1H), 4.80 (bs, 2H), 6.40 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.5, 2.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 8.97 (s, 1H). HRMS (FAB, 3-NBA) calcd for $C_{28}H_{44}O_4S_3{}^{187}Re$ (M + H): 727.1959. Found: 727.1958.

[3-(*N*-Methyl)azapentane-1,5-dithiolato][7α-(6-mercaptohexan-1-yl)-estra-1,3,5(10)-triene-3,17β-diol]oxorhenium(V) (2c). Thiol **16** (53.6 mg, 138 μmol), *N*-methyl-3-azapentane-1,5-dithiol HCl[46] (**21**) (23.6 mg, 125 μmol), and $(PPh_3)_2ReOCl_3$ (104 mg, 125 μmol) were added to a solution of 1 M NaOAc/MeOH (1.5 mL) and MeOH (5 mL). The mixture was refluxed for 45 min, during which time the reaction turned a homogeneous dark green-brown color. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography (eluted first with 20% EtOAc/Hex and then with 10% MeOH/CH_2Cl_2) to give a green foam (51.4 mg, 56%). IR (KBr): 949 (s, Re═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.77 (s, 3H), 2.29 (m, 2H), 2.61 (m, 2H), 2.71 (d, J = 16.6 Hz, 1H), 2.84 (dd, J = 16.6, 5.4 Hz, 1H), 3.15 (m, 4H), 3.34 (s, 3H), 3.53 (m, 2H), 3.76 (t, J = 8.5 Hz, 1H), 5.04 (bs, 1H), 6.54 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 8.4, 2.6 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H). HRMS (FAB, 3-NBA) calcd for $C_{29}H_{47}NO_3S_3{}^{187}Re$ (M + H): 740.2276. Found: 740.2274.

3,17β-Bis(*t*-butyldimethylsilanyloxy)-7α-[6-(methanesulfonyloxy)-hexan-1-yl]-estra-1,3,5(10)-triene (22). Et_3N (66.0 μL, 0.480 mmol) was added to a cooled solution (0 °C) of alcohol **13** (130 mg, 0.220 mmol) in THF (25 mL), followed by the addition of MsCl (37.0 μL, 0.480 mmol). The reaction was stirred overnight, then diluted with saturated $NaHCO_3$ (50 mL), and extracted with $CHCl_3$. Evaporation of the solvent, followed by flash chromatography of the residue (10% EtOAc/Hex) provided **22** as a colorless oil (125 mg, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.19 (s, 6H), 0.74 (s, 3H), 0.89 (s, 9H), 0.97 (s, 9H), 2.67 (d, J = 16.6 Hz, 1H), 2.85 (dd, J = 16.6, 4.9 Hz, 1H), 2.99 (s, 3H), 3.66 (t, J = 8.0 Hz, 1H), 4.20 (t, J = 6.6 Hz, 2H), 6.53 (s, J = 2.4 Hz, 1H), 6.61 (dd, J = 8.3, 2.4 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.79, −4.47, −4.37, 11.38, 18.10, 22.79, 25.51, 25.68, 25.86, 27.28, 28.02, 29.13, 29.41, 30.92, 33.28, 34.57, 37.35, 38.26, 41.91, 43.71, 46.08, 70.11, 81.81, 117.18, 120.79, 126.69, 132.51, 136.69, 153.20. MS (CI, CH_4): m/z 680 (M + H^+, 2), 178 (54), 59 (100). HRMS (CI, CH_4) calcd for $C_{37}H_{67}O_5Si_2S$: 679.4247. Found: 679.4238.

2-(Mercaptomethyl)-ethane-1-thiol (23). A catalytic amount of DMAP was added to a solution of 2-(mercaptomethyl)-ethanol (10.0 mL, 110 mmol) in $CHCl_3$ (100 mL). The reaction was cooled to 0 °C, and then $SOCl_2$ (14.3 g, 120 mmol) was added dropwise. After the reaction was stirred for 6 h at room temperature, the solvent was removed in vacuo, and the oily residue was redissolved in 95% EtOH (50 mL). Thiourea (8.40 g, 110 mmol) was added, and the mixture was refluxed for 3 h. After the mixture cooled to room temperature, 5 M NaOH (100 mL) was added, and the mixture was refluxed again for 2 h while a slow stream of N_2 was bubbled through the solution. Following acidification with 2 M HCl, the yellow layer was separated, and the aqueous layer was extracted with $CHCl_3$. Subsequent Kugelrohr distillation provided thiol **23** as a pungent, colorless oil (5.00 g, 42%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.66−1.69 (m, 1H), 2.02 (s, 3H), 2.65−2.66 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.12, 23.99, 37.95. MS (EI, 70 eV): m/z 108 (M, 23), 75 (100), 61 (54). HRMS (EI, 70 eV) calcd for $C_3H_8S_2$: 108.0067. Found: 108.0071.

7α-(7,10-Dithia-undecan-1-yl)-estra-1,3,5(10)-triene-3,-17β-diol (24). KO*t*-Bu (53.0 mg, 0.480 mmol) was added in portions to a solution of thiol **23** (51.4 mg, 0.480 mmol) in DMF (10 mL). After 1 h, a solution of the mesylate **22** (130 mg, 0.190 mmol) in DMF (10 mL) was added dropwise to the thiolate solution. After being stirred overnight, the reaction was diluted with water (50 mL) and extracted with $CHCl_3$, and the organic fractions were evaporated in vacuo. Purification by flash chromatography (5% EtOAc/Hex) yielded 130 mg of a clear oil, which was redissolved in CH_3CN (25 mL). The solution was heated to 50 °C, and 40% HF (3 mL) was added. After being stirred for 1 h, the solution was neutralized with $NaHCO_3$, extracted with EtOAc, and purified by flash chromatography (40% EtOAc/Hex) to yield **24** as a white foam (43.0 mg, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.14 (s, 3H), 2.53 (t, J = 7.5 Hz, 2H), 2.72 (d, J = 16.4 Hz, 1H), 2.86 (dd, J = 16.4, 4.6 Hz, 1H), 3.76 (t, J = 8.3 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 8.5, 2.7 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.07, 15.54, 22.63, 25.52, 27.22, 28.02, 28.87, 29.51, 29.61, 30.50, 31.57, 32.14, 33.15, 34.15, 34.52, 36.82, 38.02, 41.90, 43.35, 46.41, 82.01, 112.82, 116.10, 127.05, 131.81, 137.05, 153.45. MS (EI, 70 eV): m/z 462 (M, 73), 157 (53), 75(100). HRMS (EI, 70 eV) calcd for $C_{27}H_{42}O_2S_2$: 462.2626. Found: 462.2630. Anal. Calcd for $C_{24}H_{36}O_2S$: C, 74.18; H, 9.34. Found: C, 73.93; H, 9.03.

Bromo-tricarbonyl-{[7α-(7,10-dithia-undecan-1-yl)-estra-1,3,5(10)-triene-3,17*β*-diol]}-rhenium(III) (3). A solution of steroid **24** (18.0 mg, 39.0 μmol) in MeOH (1 mL) was added to a solution of rhenium precursor **25**[39] (29.0 mg, 39.0 μmol) in MeOH (1 mL). After the reaction was stirred overnight at room temperature, the solvent was evaporated in vacuo. Dry THF (2 mL) was added, and the precipitate was removed by filtration. The filtrate was concentrated, and the residue was purified by flash chromatography (10% MeOH/CH_2Cl_2) to afford **3** as a white foam (25.0 mg, 79%). IR (KBr): 2034, 1938, 1903 (s, CO). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.70 (d, J = 16.8 Hz, 1H), 2.90 (dd, J = 16.8, 4.4 Hz, 1H), 3.76 (t, J = 8.4 Hz, 1H), 6.56 (dd, J = 6.3, 2.2 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H). MS (FAB, 3-NBA): *m*/*z* 812 (M, 1), 307 (47), 154 (100), 136 (89). HRMS (FAB, 3-NBA) calcd for $C_{30}H_{42}BrO_5S_2{}^{187}Re$: 812.1215. Found: 812.1217.

Tricarbonyl{[6-[3,17*β*-bis(*t*-butyldimethylsilanyloxy)-estra-1,3,5(10)-triene-7α-yl]-carbohexyloxy]cyclopentadienyl}rhenium(I) (27). A 0 °C solution of alcohol **13** (15.0 mg, 25.7 μmol), CpTR acid **26** (9.80 mg, 25.7 μmol), EDC (5.42 mg, 28.3 μmol), and a catalytic amount of DMAP in CH_2Cl_2 (1 mL) was stirred for 30 min and then for 2 h at room temperature. The volume was reduced, and the residue purified by flash chromatography (10% EtOAc/Hex) to give **27** as a colorless oil (21.0 mg, 85%). IR ($CHCl_3$): 2031, 1937 (s, C≡O), 1727 (s, C═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.19 (s, 6H), 0.74 (s, 3H), 0.89 (s, 9H), 0.98 (s, 9H), 2.67 (d, J = 16.7 Hz, 1H), 2.84 (dd, J = 16.7, 4.9 Hz, 1H), 3.66 (t, J = 8.2 Hz, 1H), 4.18 (t, J = 6.7 Hz, 2H), 5.35 (app. t, J = 2.3 Hz, 2H), 6.00 (m, 2H), 6.53 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 8.4, 2.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.78, −4.47, −4.39, 11.38, 18.13, 22.79, 25.45, 25.69, 25.86, 25.98, 27.29, 28.08, 28.55, 29.60, 30.93, 33.26, 34.57, 37.35, 38.24, 41.92, 43.70, 46.07, 65.41, 81.83, 84.79, 84.83, 88.47, 95.43, 117.15, 120.79, 126.66, 132.54, 136.77, 153.18, 163.71, 191.96. MS (FAB, 3-NBA): *m*/*z* 962 (M, 11), 437(100), 363 (74), 271 (93), 221 (77). HRMS (FAB, 3-NBA) calcd for $C_{45}H_{66}O_7Si_2{}^{187}Re$: 961.3907. Found: 961.3905.

Tricarbonyl{[6-[estra-1,3,5(10)-triene-3,17*β*-diol-7α-yl]-carbohexyloxy]cyclopentadienyl}rhenium (I) (4a). A 40% solution of HF (300 μL) was added to a solution of ester **27** (50.3 mg, 52.3 μmol) in CH_3CN (2 mL) at 50 °C. The solution became turbid, but the cloudiness disappeared after several minutes. After 20 min at 50 °C, the reaction was cooled and concentrated, and the residue was purified by flash chromatography (2.5% MeOH/CH_2Cl_2) to give **4a** as a white foam (35.5 mg, 93%). IR (KBr): 2031, 1932 (s, C≡O), 1723 (s, C═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.70 (d, J = 16.7 Hz, 1H), 2.86 (dd, J = 16.7, 5.1 Hz, 1H), 3.76 (t, J = 8.5 Hz, 1H), 5.07 (bs, 1H), 5.35 (app. t, J = 2.3 Hz, 2H), 6.00 (app. t, J = 2.2 Hz, 2H), 6.55 (d, J = 2.7 Hz, 1H), 6.63 (dd, J = 8.5, 2.7 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H). MS (FAB, 3-NBA): *m*/*z* 734 (M, 2), 307 (47), 154 (100), 136 (86). HRMS (FAB, 3-NBA) calcd for $C_{33}H_{30}O_7{}^{187}Re$: 734.2253. Found: 734.2251.

Tricarbonyl{[6-[3,17*β*-bis(*t*-butyldimethylsilanyloxy)-estra-1,3,5(10)-triene-7α-yl]-hexylamido]cyclopentadienyl}rhenium(I) (28). A solution of the amine **18** (42.8 mg, 71.4 μmol), CpTR acid **26** (27.1 mg, 71.4 μmol), and DMAP (catalytic) in CH_2Cl_2 (2 mL) was stirred at room temperature until dissolution was complete. The reaction was then cooled to 0 °C, and EDC (15.1 mg, 78.5 μmol) was added. The reaction was stirred for 1 h at 0 °C and then 1 h at room temperature. The reaction was concentrated, and the residue was purified by flash chromatography (50% EtOAc/Hex) to give **28** as a viscous yellow oil (61.0 mg, 89%). IR ($CHCl_3$): 2028, 1933 (s, C≡O), 1638 (s, C═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.19 (s, 6H), 0.74 (s, 3H), 0.89 (s, 9H), 0.98 (s, 9H), 2.67 (d, J = 16.6 Hz, 1H), 2.84 (dd, J = 16.6, 5.1 Hz, 1H), 3.31 (q, J = 6.7 Hz, 2H), 3.66 (t, J = 8.2 Hz, 1H), 5.35 (app. t, J = 2.2 Hz, 2H), 5.71 (t, J = 5.6 Hz, 1H), 5.86 (app. t, J = 2.2 Hz, 2H), 6.53 (d, J = 2.7 Hz, 1H), 6.61 (dd, J = 8.5, 2.7 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.80, −4.48, −4.40, 11.37, 18.10, 22.78, 25.53, 25.67, 25.86, 26.93, 27.27, 28.09, 29.51, 29.66, 30.91, 33.25, 34.59, 37.33, 38.23, 39.84, 41.91, 43.68, 46.05, 81.80, 84.70, 85.62, 95.31, 117.15, 120.79, 126.67, 132.55, 136.78, 153.16, 162.10, 192.44. MS (FAB, 3-NBA): *m*/*z* 961 (M, 5), 904 (100), 363 (46). HRMS (FAB, 3-NBA) calcd for $C_{45}H_{67}NO_6Si_2{}^{187}Re$: 960.4065. Found: 950.4066.

Tricarbonyl{[6-[estra-1,3,5(10)-triene-3,17*β*-diol-7α-yl]-hexylamido]cyclopentadienyl}rhenium (I) (4b). A 40% solution of HF (300 μL) was added to a solution of the amide **28** (55.8 mg, 58.1 μmol) in CH_3CN (2 mL) at 60 °C, resulting in a turbid solution which became clear after several seconds. After 15 min at 60 °C, the reaction was cooled and quenched with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and evaporated in vacuo to a yellow foam. This was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give **4b** as an off-white foam (40.9 mg, 96%). IR (KBr): 2026, 1932 (s, C≡O), 1644 (s, C═O). Normal phase HPLC [t_R = 9.4 min, 70% EtOAc/Hex, UV detection (λ_{max} = 232)] showed only one visible peak. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.69 (d, J = 16.5 Hz, 1H), 2.86 (dd, J = 16.5, 5.2 Hz, 1H), 3.30 (q, J = 6.7 Hz, 2H), 3.75 (t, J = 8.4 Hz, 1H), 5.09 (s, 1H), 5.36 (t, J = 2.2 Hz, 2H), 5.64 (t, J = 5.7 Hz, 1H), 5.86 (m, 2H), 6.55 (d, J = 2.7 Hz, 1H), 6.64 (dd, J = 8.5, 2.7 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H). MS (FAB, 3-NBA): *m*/*z* 733 (M, 3), 279 (30), 155 (100), 136 (97). HRMS (FAB, 3-NBA) calcd for $C_{33}H_{40}NO_6{}^{187}Re$: 733.2413. Found: 733.2415.

3,17*β*-Bis(*t*-butyldimethylsilanyloxy)-7α-[6-(*N*-formylamino)-hexan-1-yl]-estra-1,3,5(10)-triene (29). A solution of amine **18** (70.0 mg, 0.120 mmol) and ethylformate (10 mL) was refluxed for 8 h. Following evaporation of the ethyl formate, the residue was purified by flash chromatography (2.5% MeOH/CH_2Cl_2) to afford **29** as a white foam (52.0 mg, 71%). IR (KBr): 1667 (s, C═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.19 (s, 6H), 0.74 (s, 3H), 0.89 (s, 9H), 0.97 (s, 9H), 2.66 (d, J = 16.6 Hz, 1H), 2.85 (dd, J = 16.6, 4.6 Hz, 1H), 3.27 (q, J = 6.8 Hz, 2H), 3.67 (t, J = 8.0 Hz, 1H), 5.44 (bs, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 8.5, 2.4 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.78, −4.46, −4.39, 11.38, 18.11, 22.79, 25.42, 25.68, 25.86, 26.82, 27.27, 27.99, 29.45, 29.53, 30.92, 33.26, 34.58, 37.35, 38.15, 38.28, 41.92, 43.70, 46.08, 81.82, 117.17, 120.79, 126.70, 132.54, 136.77, 153.18, 161.06. MS (CI, CH_4): *m*/*z* 629 (M + H^+, 25), 571 (67), 497 (100). HRMS (CI, CH_4) calcd for $C_{37}H_{66}NO_3Si_2$: 628.4581. Found: 628.4566.

Tris(2-thiolatoethyl)amine-{3,17*β*-bis(*t*-butyldimethylsilanyloxy)-7α-[6-(isocyanido)-hexan-1-yl]-estra-1,3,5(10)-triene}-rhenium(III) (31). A solution of steroid **29** (32.0 mg, 51.0 μmol), $Re(NS)_3PPhMe_2$ (**30**)[48] (17.6 mg, 34 μmol), PPh_3 (16.0 mg, 61.0 μmol), Et_3N (7.00 mL, 51.0 mmol), and CCl_4 (5.00 μL, 51.0 μmol) in CH_2Cl_2 (1 mL) was refluxed for 4 h. During this time, the green color of the Re(III) precursor changed to olive-green. Two consecutive separations by flash chromatography (1. 20% EtOAc/Hex; 2. 2.5% MeOH/CH_2Cl_2) yielded the desired complex **31** as an olive-green foam (27.0 mg, 80%). IR (KBr): 2001 (s, N≡C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.19 (s, 6H), 0.73 (s, 3H), 0.89 (s, 9H), 0.97 (s, 9H), 2.68 (d, J = 16.4 Hz, 1H), 2.82 (dd, J = 17.0, 5.2 Hz, 1H), 3.02 (br, 12H), 3.65 (t, J = 8.3 Hz, 1H), 4.76 (t, J = 6.3 Hz, 2H), 6.53 (d, J = 2.3 Hz, 1H), 6.60 (dd, J = 8.4, 2.6 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H). MS (FAB, 3-NBA): *m*/*z* 991 (M, 24), 154 (100). HRMS (FAB, 3-NBA) calcd for $C_{43}H_{75}N_2O_2Si_2S_3{}^{187}Re$: 990.4087. Found: 990.4083.

Tris(2-thiolatoethyl)amine-{7α-[6-(isocyanido)-hexan-1-yl]-estra-1,3,5(10)-triene-3,17*β*-diol}-rhenium(III) (5). A 40% solution of HF (120 μL) was added to a solution of complex **31** (23.0 mg, 23.0 μmol) in CH_3CN (1 mL) at 50 °C. After 15 min the solution was loaded onto a silica column and eluted with 5% MeOH/CH_2Cl_2 to give **5** as an olive-green solid (14.0 mg, 79%). IR (KBr): 2007 (s, N≡C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.77 (s, 3H), 2.72 (d, J = 16.6 Hz), 2.85 (dd, J = 16.6, 5.1 Hz, 1H), 3.03 (br, 12H), 3.74 (t, J = 8.5 Hz, 1H), 4.55 (s, 1H), 4.76 (t, J = 6.3 Hz, 1H), 6.55 (s, 1H), 6.62 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H). MS (FAB, 3-NBA): *m*/*z* 762 (M, 22), 307 (64), 289 (31), 154 (100), 136 (92). HRMS (FAB, 3-NBA) calcd for $C_{31}H_{47}N_2O_2S_3{}^{187}Re$: 762.2357. Found: 762.2355.

17β-(*t*-Butyldimethylsilanyloxy)-7α-(5-hexen-1-yl)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene (32). A 1 M solution of TBAF in THF (2.00 mL, 2.04 mmol) was added to a cooled solution (0 °C) of alkene **12** (946 mg, 1.62 mmol) in THF (10 mL). The reaction was stirred at 0 °C for 5 min and then room temperature for 15 min. A few drops of water were added, followed by evaporation of the solvent in vacuo. Purification of the residue by flash chromatography (30% EtOAc/Hex) yielded the deprotected product as a white foam (797 mg, >100%). A portion of this (582 mg, 1.24 mmol) was redissolved in THF (5 mL) and cooled to 0 °C. NaH (95.6 mg, 2.40 mmol) was added, and the reaction was stirred for 25 min at 0 °C. MEMCl (274 μL, 2.40 mmol) was then added to the solution, resulting in a white precipitate of NaCl. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with water, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (1.25% MeOH/CH_2Cl_2) to yield **32** as an oil (697 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.77 (s, 3H), 0.92 (s, 9H), 2.05 (q, *J* = 6.9 Hz, 2H), 2.76 (d, *J* = 16.8 Hz, 1H), 2.90 (dd, *J* = 16.8, 5.0 Hz), 3.40 (s, 3H), 3.58 (m, 2H), 3.69 (t, *J* = 8.2 Hz, 1H), 3.79 (m, 2H), 4.97 (m, 2H), 5.25 (s, 2H), 5.80 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 6.79 (d, *J* = 2.6 Hz, 1H), 6.87 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.84, −4.53, 11.30, 18.03, 22.73, 25.34, 25.81, 27.27, 27.59, 29.11, 30.87, 33.14, 33.79, 34.64, 37.29, 38.13, 41.86, 43.62, 46.03, 58.92, 67.41, 71.58, 81.79, 93.49, 113.71, 114.17, 117.00, 126.78, 133.28, 136.88, 138.89, 155.10. MS (EI, 70 eV): *m*/*z* 557 (M, 67), 499 (57), 89(100). HRMS (EI, 70 eV) calcd for $C_{34}H_{56}O_4Si$: 556.3948. Found: 556.3942.

17β-(*t*-Butyldimethylsilanyloxy)-7α-(6-hydroxyhexan-1-yl)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene (33). A solution of 0.5 M 9-BBN in THF (4.00 mL, 2.00 mmol) was added to a solution of steroid **32** (226 mg, 0.406 mmol) in THF (5 mL). After being stirred for 24 h, the reaction was cooled to 0 °C, and to it was added 3 M KOH (1.5 mL), followed 5 min later by 30% H_2O_2 (1.5 mL). The mixture was stirred for 3 h, at which time saturated $NaHCO_3$ (7 mL) was added, and the solution was stirred 30 min longer. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried over Na_2SO_4, and concentrated to a cloudy oil. This was purified by flash chromatography (40% EtOAc/Hex) to provide **33** as a colorless, viscous oil (191 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.74 (s, 3H), 0.89 (s, 9H), 2.73 (d, *J* = 16.8 Hz, 1H), 2.87 (dd, *J* = 16.8, 5.1 Hz, 1H), 3.38 (s, 3H), 3.56 (m, 2H), 3.60 (t, *J* = 6.7 Hz, 2H), 3.66 (t, *J* = 8.2 Hz, 1H), 3.82 (m, 2H), 5.23 (s, 2H), 3.76 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.85, −4.53, 18.04, 22.71, 25.48, 25.75, 25.80, 27.24, 28.12, 29.71, 30.85, 32.71, 33.15, 34.62, 37.25, 38.11, 41.83, 43.61, 45.99, 58.94, 62.85, 67.41, 71.55, 81.76, 93.49, 113.69, 116.99, 126.80, 133.35, 136.93, 155.04. MS (EI, 70 eV): *m*/*z* 575 (M, 8), 498 (40), 441 (53), 133 (46), 89 (78). HRMS (EI, 70 eV) calcd for $C_{34}H_{58}O_5Si$: 574.4054. Found: 574.4045.

7α-(15-Benzyloxy-7,10,13-trioxa-pentadecan-1-yl)-17β-(*t*-butyldimethylsilanyloxy)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene (35). To a cooled solution (0 °C) of alcohol **33** (63.2 mg, 0.110 mmol) in CH_2Cl_2 (1 mL) was added 2,6-lutidine (17.0 μL, 0.143 mmol), followed by triflic anhydride (22.0 μL, 0.132 mmol). After 15 min, the reaction was diluted with CH_2Cl_2 (5 mL), and the reaction was poured into brine (5 mL). The organic layer was removed and dried over Na_2SO_4. After careful removal of the solvent, the triflate was placed under high vacuum for 10 min. The triflate was dissolved in CH_2Cl_2 (2 mL) and added to a flask containing 10-phenyl-3,6,9-trioxa-decan-1-ol (**34**)[50] (53.1 mg, 0.220 mmol) at 0 °C. NaH (11.0 mg, 0.275 mmol) was then added, and the reaction bubbled vigorously. After several minutes, 15-crown-5 (1 drop) was added. The ice bath was removed, and the reaction was stirred for another 30 min, turning to an orange color. The reaction was quenched with water, concentrated, and purified by flash chromatography (40% EtOAc/Hex) to afford **35** as a yellow oil (51.5 mg, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.74 (s, 3H), 0.90 (s, 9H), 2.73 (d, *J* = 16.6 Hz, 1H), 2.87 (dd, *J* = 16.6, 5.0 Hz, 1H), 3.39 (s, 3H), 3.43 (t, *J* = 6.8 Hz, 2H), 3.57 (m, 4H), 3.66 (m, 11H), 3.83 (m, 2H), 4.57 (s, 2H), 5.24 (s, 2H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.82, −4.50, 11.31, 18.08, 22.74, 25.58, 25.83, 26.16, 27.27, 28.17, 29.61, 29.85, 30.88, 33.16, 34.64, 37.27, 38.10, 41.84, 43.63, 46.00, 58.99, 67.44, 69.36, 69.98, 70.58, 70.61, 71.45, 71.58, 73.18, 81.78, 93.52, 113.67, 117.02, 126.83, 127.53, 127.69, 128.30, 133.39, 137.00, 155.08. MS (FAB, 3-NBA): *m*/*z* 796 (M − H, 2), 154 (94), 136 (100). HRMS (FAB, 3-NBA) calcd for $C_{47}H_{75}O_8Si$: 795.5231. Found: 795.5223.

17β-(*t*-Butyldimethylsilanyloxy)-7α-(15-hydroxy-7,10,13-trioxa-pentadecan-1-yl)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene (36). To a solution of steroid **35** (48.4 mg, 60.6 μmol) in EtOH (1 mL) was added 10% Pd/C (10.0 mg, 9.10 μmol). The reaction flask was evacuated of air and filled to a pressure of 1 atm with H_2. The reaction was stirred under H_2 for 5 h, at which time the EtOH was evaporated in vacuo, and the residue was purified by flash chromatography (2.5% to 5% MeOH/CH_2Cl_2) to yield **36** as a slightly turbid oil (47.6 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 2.53 (bs, 1H), 2.72 (d, *J* = 16.8 Hz, 1H), 2.86 (dd, *J* = 16.8, 4.6 Hz, 1H), 3.38 (s, 3H), 3.43 (t, *J* = 6.8 Hz, 2H), 3.55−3.72 (m, 15H), 3.82 (m, 2H), 5.23 (s, 2H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.84 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.83, −4.51, 11.29, 18.06, 22.73, 25.57, 25.82, 26.13, 27.26, 28.15, 29.53, 29.82, 30.86, 33.15, 34.62, 37.26, 38.09, 41.83, 43.61, 45.99, 58.97, 61.68, 67.43, 69.92, 70.29, 70.56, 71.46, 71.57, 72.42, 81.77, 93.51, 113.66, 117.00, 126.80, 133.36, 136.98, 155.05. MS (EI, 70 eV): *m*/*z* 707 (M, 1), 630 (76), 89 (72), 59 (100). HRMS (EI, 70 eV) calcd for $C_{40}H_{70}O_8Si$: 706.4840. Found: 706.4847.

7α-(15-Amino-7,10,13-trioxa-pentadecan-1-yl)-17β-(*t*-butyldimethylsilanyloxy)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene (37). DIAD (25.0 μL, 125 μmol) was added dropwise to a cooled solution (0 °C) of PPh_3 (32.8 mg, 125 μmol) in THF (0.75 mL). After a precipitate of the ylide formed, the reaction was stirred for 30 min at 0 °C. A solution of alcohol **36** (44.2 mg, 62.4 μmol) in THF (0.5 mL) was then added to the ylide, followed by diphenylphosphoryl azide (27.0 μL, 125 μmol). The reaction was stirred for 30 min at 0 °C and then and then 3.5 h at room temperature. The reaction was concentrated and purified by flash chromatography (20% EtOAc/PhH) to give the azide as a yellow oil contaminated with a PPh_3-like impurity (73.1 mg). This oil was redissolved in EtOH (1 mL), and to it was added 10% Pd/C (10.0 mg, 9.36 μmol). The flask was evacuated of air and filled to an pressure of 1 atm with H_2. The reaction was stirred under H_2 for 8.5 h. The EtOH was evaporated in vacuo, and the residue was purified by flash chromatography (eluted first with 40% EtOAc/Hex and then 20% MeOH/CH_2Cl_2 with 0.5% Et_3N) to give **37** as a yellow oil (26.1 mg, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.01 (s, 3H), 0.02 (s, 3H), 0.72 (s, 3H), 0.89 (s, 9H), 2.71 (d, *J* = 16.8 Hz, 1H), 2.86 (dd, *J* = 16.8, 4.6 Hz, 1H), 2.96 (t, *J* = 7.3 Hz, 2H), 3.37 (s, 3H), 3.43 (t, *J* = 7.0 Hz, 2H), 3.54−3.66 (m, 13H), 3.81 (m, 2H), 5.22 (s, 2H), 5.39 (bs, 2H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.82, −4.50, 11.29, 18.06, 22.73, 25.57, 25.82, 26.13, 27.25, 28.18, 29.53, 29.84, 30.86, 33.15, 34.62, 37.25, 38.08, 41.82, 43.61, 45.72, 45.99, 58.98, 67.43, 69.82, 70.14, 70.40, 70.46, 71.43, 71.57, 81.76, 93.51, 113.66, 117.02, 126.81, 133.38, 136.98, 155.05. MS (CI, CH_4): *m*/*z* 707 ($M + H^+$, 100). HRMS (EI, 70 eV) calcd for $C_{40}H_{71}NO_7Si$: 705.5000. Found: 705.5008.

Tricarbonyl{[15-[17β-(*t*-butyldimethylsilanyloxy)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene-7α-yl]-3,6,9-trioxa-pentadecylamido]cyclopentadienyl}rhenium-(I) (38). A solution of amine **37** (13.6 mg, 19.3 μmol), CpTR acid **26** (12.3 mg, 32.4 μmol), and DMAP (catalytic) in CH_2Cl_2 (2 mL) was stirred at room temperature until just dissolved. To the solution was added EDC (6.00 mg, 33.8 μmol), and the reaction was stirred for 45 min at room temperature. The reaction was concentrated and purified by flash chromatog-

raphy (EtOAc) to give **38** as a viscous colorless oil (17.3 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 2.72 (d, J = 16.8 Hz, 1H), 2.87 (dd, J = 16.8, 4.6 Hz, 1H), 3.38 (s, 3H), 3.43 (t, J = 6.8 Hz, 2H), 3.51−3.68 (m, 15H), 3.82 (m, 2H), 5.23 (s, 2H), 5.33 (t, J = 2.2 Hz, 2H), 5.97 (t, J = 2.2 Hz, 2H), 6.58 (m, 1H), 6.76 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 8.5, 2.6 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.82, −4.49, 11.31, 18.09, 22.75, 25.60, 25.83, 26.16, 27.27, 28.20, 29.57, 29.85, 30.89, 33.18, 36.64, 37.28, 38.11, 39.73, 41.84, 43.64, 46.01, 59.01, 67.46, 69.61, 69.91, 70.36, 70.47, 70.51, 71.50, 71.58, 81.79, 84.62, 85.99, 93.55, 95.24, 113.70, 117.03, 126.86, 133.40, 136.99, 155.08, 162.05, 192.57. MS (FAB, 3-NBA): m/z 1068 (M, 1), 406 (61), 136 (100). HRMS (FAB, 3-NBA) calcd for $C_{49}H_{75}NO_{11}Si^{187}Re$: 1068.4667. Found: 1068.4670.

Tricarbonyl{[15-(estra-1,3,5(10)-triene-3,17β-diol-7α-yl)-3,6,9-trioxa-pentadecylamido]cyclopentadienyl}-rhenium(I) (6). A 40% solution of HF (150 μL) was added to a solution of the amide **38** (12.3 mg, 11.5 μmol) in CH_3CN (1 mL) and THF (250 μL) at 60 °C, resulting in a turbid solution which became clear after several seconds. After 15 min at 60 °C, the reaction was cooled and quenched with $NaHCO_3$ (1 mL saturated and then solid $NaHCO_3$ until neutral). The mixture was extracted with CH_2Cl_2 (3 × 3 mL) and evaporated in vacuo. The residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give a clear residue (7.40 mg, 74%). A foam was obtained by rapid evaporation from an acetone solution. IR (KBr): 2025, 1926 (s, C≡O), 1647 (C═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.70 (d, J = 16.6 Hz, 1H), 2.84 (dd, J = 16.6, 4.6 Hz, 1H), 3.30−3.71 (m, 14H), 3.74 (t, J = 8.4 Hz, 1H), 5.32 (t, J = 2.3 Hz, 2H), 5.99 (m, 2H), 6.37 (bs, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 8.4, 2.4 Hz, 1H), 6.85 (m, 1H), 7.14 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.12, 22.62, 24.78, 25.35, 27.21, 27.36, 29.08, 29.15, 30.51, 33.30, 34.73, 36.89, 38.30, 39.80, 42.02, 43.38, 46.48, 69.70, 69.76, 70.15, 70.47, 70.52, 71.53, 81.98, 84.66, 84.75, 85.99, 86.20, 95.04, 113.03, 116.22, 127.04, 131.41, 136.93, 153.72, 162.36, 192.60. MS (FAB, 3-NBA): m/z 866 (M + H, 0.5), 154 (100), 136 (87). HRMS (FAB, 3-NBA) calcd for $C_{39}H_{53}NO_9{}^{187}$Re: 866.3278. Found: 866.3280.

3,17β-Bis(2-tetrahydropyranyloxy)-7α-(2-propen-1-yl)-estra-1,3,5(10)-triene-6-one (39). A 1 M solution of KO*t*-Bu in THF (3.10 mL, 3.07 mmol) was added to a cooled solution (0 °C) of ketone **8** (1.27 g, 2.79 mmol) in THF (50 mL). The reaction was stirred at 0 °C for 40 min and then cooled to −78 °C. Allyl iodide (255 μL, 2.79 mmol) was then added dropwise to the solution. After 10 min, the reaction was quenched with water and warmed to room temperature. The solvents were removed in vacuo, redissolved in ether, and then passed through a plug of silica. After the solvent was evaporated in vacuo, the residue was dissolved in MeOH (50 mL), and to this was added several small pieces of sodium. The mixture was stirred for 4 h at room temperature. After the reaction was quenched with water, the MeOH was evaporated, and the product was extracted from water with ether. The solvents were evaporated in vacuo, and the residue was purified by flash chromatography (10% EtOAc/Hex with 1% Et_3N) to give **39** as a white foam (230 mg, **8** = 1.00 g, 77% corrected yield). This process can be repeated several times to provide 1.70 g of **39** for subsequent reactions. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.77, 0.79 (2s, 3H), 2.30−2.42 (m, 2H), 2.50−2.55 (m, 1H), 2.65−2.72 (m, 1H), 3.43−3.48 (m, 1H), 3.55−3.58 (m, 1H), 3.71, 3.74 (2t, J = 8.2 Hz, 1H), 3.82−3.90 (m, 2H), 4.60−4.66 (m, 1H), 4.88−4.96 (m, 2H), 5.41−5.44 (m, 1H), 5.70−5.81 (m, 1H), 7.18, 7.19 (2dd, J = 8.5, 2.7 Hz, 1H), 7.28, 7.30 (2d, J = 8.5 Hz, 1H), 7.66 (2d, J = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.32, 11.35; 18.63, 18.68; 19.20, 19.57; 22.04, 22.15; 25.00; 25.36, 25.45; 26.45, 26.84; 28.44, 28.67, 28.75; 30.07, 30.12; 30.83, 30.90; 36.74, 37.26; 37.16, 37.23; 41.89, 41.94; 41.98, 42.02; 42.66, 43.14; 45.12, 45.23; 48.77, 48.84, 48.92; 61.73, 61.96; 62.04, 62.40; 83.63, 86.09; 96.04, 96.27; 96.47, 99.15; 114.41, 114.52; 116.24; 122.19, 122.30; 126.83, 126.88, 126.92; 132.12, 132.15; 135.57, 135.60; 139.05, 139.18; 155.33, 155.36, 155.42, 155.44; 199.53, 199.60, 199.64. MS (CI, CH_4): m/z 495 (M + H^+, 33), 411 (100), 85 (86). HRMS (CI, CH_4) calcd for $C_{31}H_{43}O_5$: 495.3110. Found: 495.3103.

7α-(2-Propen-1-yl)-estra-1,3,5(10)-triene-3,17β-diol (40). Acetyl chloride (20 drops) was added to a solution of ketone **39** (1.70 g, 3.43 mmol) in a minimum amount of MeOH. After 1 h, saturated $NaHCO_3$ was added until neutral, and the MeOH was evaporated in vacuo. The residue was diluted with CH_2Cl_2 and EtOAc and then was passed through a plug of silica and Na_2SO_4. The filtrate was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (100 mL). To this solution was added Et_3SiH (15 mL), followed by $BF_3{\cdot}OEt_2$ (60 mL) dropwise. After 1 h, a white precipitate was evident. The reaction was stirred for 2 days, cooled to 0 °C, and quenched with 10% K_2CO_3 (100 mL). The heterogeneous solution was filtered through a short silica plug, and the organic layer separated. The aqueous layer was extracted two more times with CH_2Cl_2 (50 mL each). The organic fractions were combined, dried over Na_2SO_4, and evaporated in vacuo to a yellow solid. Purification by flash chromatography (40% EtOAc/Hex) provided **40** as a white foam (587 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.79 (s, 3H), 2.72 (d, J = 16.5 Hz, 1H), 2.83 (dd, J = 16.5, 5.1 Hz, 1H), 3.76 (t, J = 8.5 Hz, 1H), 4.93 (dd, J = 16.5, 1.2 Hz, 1H), 4.97 (d, J = 10.1 Hz, 1H), 5.43 (bs, 1H), 5.78 (dddd, J = 16.9, 10.1, 8.0, 5.8 Hz, 1H), 6.54 (d, J = 2.7 Hz, 1H), 6.64 (dd, J = 8.5, 2.7 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.09, 22.50, 27.18, 30.32, 30.51, 32.94, 33.87, 36.77, 38.01, 41.51, 43.36, 46.41, 82.01, 112.93, 115.84, 116.13, 126.95, 131.29, 136.65, 137.99, 153.66. MS (CI, CH_4): m/z 313 (M + H^+, 100), 295 (69). HRMS (EI, 70 eV) calcd for $C_{21}H_{28}O_2$: 312.2089. Found: 312.2094. Anal. Calcd for $C_{21}H_{28}O_2{\cdot}0.3H_2O$: C, 79.35; H, 9.07. Found: C, 79.39; H, 9.22.

3,17β-Bis(*t*-butyldimethylsilanyloxy)-7α-(2-propen-1-yl)-estra-1,3,5(10)-triene (41). A solution of TBSCl (1.27 g, 8.45 mmol) in DMF (5 mL) was added to a cooled solution (0 °C) of imidazole (1.28 g, 18.8 mmol) in DMF (10 mL). The reaction was warmed to room temperature for 30 min. A solution of diol **40** (587 mg, 1.88 mmol) was then added to the TBSCl mixture, and the reaction was stirred overnight. The DMF was removed in vacuo, and the residue was diluted with 0.1% K_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were passed through a silica plug and then evaporated in vacuo to yield **41** as a yellow oil (917 mg, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.18 (s, 6H), 0.75 (s, 3H), 0.89 (s, 9H), 0.97 (s, 9H), 2.70 (d, J = 16.5 Hz, 1H), 2.81 (dd, J = 16.5, 5.2 Hz, 1H), 3.65 (t, J = 8.3 Hz, 1H), 4.91 (d, J = 17.0 Hz, 1H), 4.97 (d, J = 10.1 Hz, 1H), 5.78 (dddd, J = 17.0, 10.1, 8.1, 5.8 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 8.4, 2.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ −4.85, −4.54, −4.48, 11.34, 18.05, 18.10, 22.66, 25.61, 25.64, 25.81, 27.23, 30.48, 30.87, 33.02, 33.93, 37.31, 38.29, 41.55, 43.72, 46.12, 81.78, 115.65, 117.27, 120.84, 126.64, 132.30, 136.43, 138.18, 153.28. MS (EI, 70 eV): m/z 541 (M, 100), 483 (72), 407 (78). HRMS (EI, 70 eV) calcd for $C_{33}H_{56}O_2Si_2$: 540.3818. Found: 540.3814.

3,17β-Bis(*t*-butyldimethylsilanyloxy)-7α-(3-hydroxypropan-1-yl)-estra-1,3,5(10)-triene (42). A 0.5 M solution of 9-BBN in THF (17.0 mL, 8.50 mmol) was added to a solution of steroid **41** (917 mg, 1.70 mmol) in THF (20 mL). After 3 days, the reaction was cooled to 0 °C and quenched with 3 M KOH (10 mL), followed by 30% H_2O_2 (10 mL) after 5 min. After the reaction was stirred for 3 h, saturated $NaHCO_3$ (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The organic fractions were dried over Na_2SO_4 and evaporated in vacuo, and the residue was purified by flash chromatography (20% to 60% EtOAc/Hex) to provide **42** as a viscous oil (625 mg, 67%). The 3-deprotected compound was also isolated (169 mg, 0.380 mmol). Corrected yield of **42** is 86%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.20 (s, 6H), 0.76 (s, 3H), 0.90 (s, 9H), 0.99 (s, 9H), 2.69 (d, J = 16.6 Hz, 1H), 2.89 (dd, J = 16.6, 5.2 Hz, 1H), 3.59 (t, J = 6.6 Hz, 2H), 3.66 (t, J = 8.3 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.3, 2.4 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.80, −4.48, −4.39, 11.37, 18.10, 18.12, 21.73, 22.77, 25.64, 25.68, 25.86, 27.29, 30.91, 31.36,

33.22, 34.58, 37.36, 38.26, 41.95, 43.72, 46.08, 63.22, 81.81, 117.27, 120.79, 126.71, 132.39, 136.44, 153.26. MS (EI, 70 eV): *m*/*z* 558 (M, 15), 91 (58), 75 (100). HRMS (EI, 70 eV) calcd for $C_{33}H_{58}O_3Si_2$: 558.3924. Found: 558.3923.

3-(Benzyloxy)-17*β*-(*t*-butyldimethylsilanyloxy)-7α-(3-hydroxypropan-1-yl)-estra-1,3,5(10)-triene (43). A 1 M solution of TBAF in THF (0.910 mL, 0.910 mmol) was added to a cooled solution (0 °C) of steroid **42** (391 mg, 0.699 mmol) in THF (10 mL). The yellow solution was stirred for 5 min at 0 °C and then 15 min at room temperature. The THF was removed in vacuo, and the residue was passed through a silica plug with 5% MeOH/CH_2Cl_2. The filtrate was then evaporated to a yellow foam. The foam was dissolved in acetone (28 mL), and to it were added BnBr (106 μL, 0.893 mmol), K_2CO_3 (823 mg, 5.95 mmol), and 18-crown-6 (59.0 mg, 0.223 mmol). The mixture was refluxed for 16 h, then cooled, and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (20% EtOAc/Hex) to give **43** as a colorless oil (417 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.78 (s, 3H), 0.92 (s, 9H), 2.76 (d, J = 16.6 Hz, 1H), 2.95 (dd, J = 16.6, 5.1 Hz, 1H), 3.61 (t, J = 6.5 Hz, 2H), 3.68 (t, J = 8.3 Hz, 1H), 5.04 (s, 2H), 6.73 (d, J = 2.6 Hz, 1H), 6.81 (dd, J = 8.7, 2.6 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.32−7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.83, −4.51, 11.31, 18.06, 21.71, 22.72, 28.83, 27.30, 30.85, 31.29, 33.14, 34.68, 37.25, 38.10, 41.89, 43.66, 45.98, 63.13, 69.83, 81.75, 113.34, 115.55, 126.89, 127.44, 127.80, 128.47, 132.22, 136.59, 137.23, 156.68. MS (CI, CH_4): *m*/*z* 534 (M, 46), 91 (100). HRMS (EI, 70 eV) calcd for $C_{34}H_{50}O_3Si$: 534.3529. Found: 534.3519. Anal. Calcd for $C_{34}H_{50}O_3Si\cdot 0.7H_2O$: C, 74.59; H, 9.46. Found: C, 74.66; H, 9.61.

3-(Benzyloxy)-7α-(6-benzyloxy-4-oxa-hexan-1-yl)-17*β*-(*t*-butyldimethylsilanyloxy)-estra-1,3,5(10)-triene (45). To a cooled solution (0 °C) of alcohol **43** (100 mg, 0.189 mmol) in CH_2Cl_2 (2 mL) was added 2,6-lutidine (28.6 μL, 0.246 mmol), followed by triflic anhydride (38.0 μL, 0.227 mmol). Another reaction flask using the exact same quantities of reagents was also run at the same time. After 15 min each reaction was diluted with CH_2Cl_2 (5 mL) and poured separately into brine (5 mL). The organic layer was dried over Na_2SO_4; the solution was kept at 0 °C. The CH_2Cl_2 was carefully evaporated, followed by drying of both sets of triflates under high vacuum for 10 min. Each triflate residue was dissolved in CH_2Cl_2 (1 mL) and added to a flask containing 2-benzyloxyethanol (**44**)[50] (115 mg, 0.756 mmol) at 0 °C. To this solution was added NaH (45.2 mg, 1.13 mmol), followed by 15-crown-5 (several drops). The reaction was stirred for 2 h, then quenched with water, concentrated, and purified by flash chromatography (10% EtOAc/Hex) to give **45** as a colorless oil (148 mg, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.77 (s, 3H), 0.92 (s, 9H), 2.77 (d, J = 16.8 Hz, 1H), 2.94 (dd, J = 16.8, 5.0 Hz, 1H), 3.45 (m, 2H), 3.61 (m, 4H), 3.66 (t, J = 8.3 Hz, 1H), 4.58 (s, 2H), 5.04 (s, 2H), 6.72 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 8.6, 2.4 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.27−7.46 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.82, −4.50, 11.32, 18.08, 21.93, 22.70, 25.83, 27.32, 28.12, 30.89, 33.05, 34.67, 37.26, 38.09, 41.90, 43.68, 46.00, 69.27, 69.85, 70.15, 71.57, 73.15, 81.76, 112.36, 115.51, 126.88, 127.46, 127.52, 127.66, 127.80, 128.30, 128.49, 132.26, 136.71, 137.26, 138.24, 156.68. MS (EI, 70 eV): *m*/*z* 669 (M, 3), 577 (36), 91 (100). HRMS (EI, 70 eV) calcd for $C_{43}H_{60}O_4Si$: 668.4247. Found: 668.4254.

17*β*-(*t*-Butyldimethylsilanyloxy)-7α-(6-hydroxy-4-oxa-hexan-1-yl)-estra-1,3,5(10)-triene-3-ol (46). To a solution of steroid **45** (147 mg, 0.220 mmol) in EtOAc (2 mL) and EtOH (1.5 mL) was added 10% Pd/C (35.0 mg, 33.0 μmol). The flask was evacuated of air and filled to a pressure of 1 atm with H_2. The reaction was stirred under H_2 for 6 h. The solvents were removed in vacuo, and the residue was purified by flash chromatography (40% EtOAc/Hex) to give **46** as a white solid (78.3 mg, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.74 (s, 3H), 0.89 (s, 9H), 2.69 (d, J = 16.6 Hz, 1H), 2.87 (dd, J = 16.6, 4.9 Hz, 1H), 3.43 (m, 2H), 3.51 (t, J = 4.5 Hz, 2H), 3.65 (t, J = 8.2 Hz, 1H), 3.71 (t, J = 4.5 Hz, 2H), 6.11 (bs, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 8.4, 2.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.82, −4.50, 11.33, 18.06, 21.87, 22.72, 25.82, 27.33, 28.07, 30.86, 33.08, 34.49, 37.24, 38.11, 41.91, 43.68, 46.01, 61.70, 71.52, 71.68, 81.75, 112.94, 116.08, 127.03, 131.57, 136.69, 153.68. MS (CI, CH_4): *m*/*z* 489 (M + H^+, 29), 427 (74), 295 (100). HRMS (EI, 70 eV) calcd for $C_{29}H_{49}O_4Si$: 488.3322. Found: 488.3316. Anal. Calcd for $C_{29}H_{48}O_4Si\cdot H_2O$: C, 68.73; H, 9.94. Found: C, 68.82; H, 9.89.

7α-(6-Azido-4-oxa-hexan-1-yl)-17*β*-(*t*-butyldimethylsilanyloxy)-estra-1,3,5(10)-triene-3-ol (47). DIAD (78.0 μL, 0.395 mmol) was added to a cooled solution (0 °C) of PPh_3 (104 mg, 0.395 mmol) in THF (1 mL). After the reaction was stirred for 30 min at 0 °C, a solution of alcohol **46** (77.3 mg, 0.158 mmol) and diphenylphosphoryl azide (85.0 μL, 0.395 mmol) in THF (1 mL) was added to the ylide. The reaction was stirred for 1 h at 0 °C and then overnight at room temperature. The mixture was then concentrated, and the residue was purified by flash chromatography (2.5% EtOAc/PhH) to yield **47** as a yellow oil (60.2 mg, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.74 (s, 3H), 0.90 (s, 9H), 2.70 (d, J = 16.8 Hz, 1H), 2.88 (dd, J = 16.8, 4.9 Hz, 1H), 3.35 (t, J = 4.9 Hz, 2H), 3.44 (t, J = 6.6 Hz, 2H), 3.58 (t, J = 4.9 Hz, 2H), 3.65 (t, J = 8.2 Hz, 1H), 4.97 (bs, 1H), 6.54 (d, J = 1.7 Hz, 1H), 6.63 (dd, J = 8.3, 1.7 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.82, −4.50, 11.32, 18.08, 21.84, 22.71, 25.83, 27.33, 28.09, 30.87, 32.98, 34.44, 37.24, 38.06, 41.90, 43.65, 45.94, 50.70, 69.50, 71.52, 81.77, 112.81, 116.05, 127.08, 132.02, 136.88, 153.28. MS (CI, CH_4): *m*/*z* 514 (M + H^+, 22), 498 (41), 486 (80), 456 (100). HRMS (EI, 70 eV) calcd for $C_{29}H_{47}N_3O_3Si$: 513.3387. Found: 513.3391.

7α-(6-Azido-4-oxa-hexan-1-yl)-17*β*-(*t*-butyldimethylsilanyloxy)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene (48). NaH (5.07 mg, 127 μmol) was added to a cooled solution (0 °C) of azide **47** (21.7 mg, 42.2 μmol) in THF (0.8 mL). After the reaction was stirred for 20 min at 0 °C, MEMCl (10.0 μL, 84.4 μmol) was added to the yellow solution, and the reaction was gradually warmed to room temperature over the course of 2.5 h. The yellow color gradually dissipated, and a white precipitate of NaCl formed. One drop of water was added to quench excess NaH, then the reaction was concentrated, and the residue was purified by flash chromatography (1.25% MeOH/CH_2Cl_2) to give **48** as a colorless oil (24.4 mg, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.74 (s, 3H), 0.89 (s, 9H), 2.74 (d, J = 16.8 Hz, 1H), 2.91 (dd, J = 16.8, 4.9 Hz, 1H), 3.35 (m, 2H), 3.39 (s, 3H), 3.43 (m, 2H), 3.57 (m, 4H), 3.65 (t, J = 8.2 Hz, 1H), 3.83 (m, 2H), 5.24 (s, 2H), 6.77 (d, J = 2.3 Hz, 1H), 6.85 (dd, J = 8.5, 2.3 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.83, −4.50, 11.30, 18.07, 21.84, 22.70, 25.83, 27.27, 28.12, 30.86, 32.99, 34.54, 37.24, 38.08, 41.83, 43.64, 45.94, 50.72, 59.00, 67.45, 69.51, 71.47, 71.58, 81.76, 93.52, 113.78, 117.01, 126.88, 131.30, 136.72, 155.10. MS (CI, CH_4): *m*/*z* 601 (M, 46), 574 (45), 498 (100). HRMS (EI, 70 eV) calcd for $C_{33}H_{55}N_3O_5Si$: 601.3911. Found: 601.3917.

7α-(6-Amino-4-oxa-hexan-1-yl)-17*β*-(*t*-butyldimethylsilanyloxy)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene (49). To a solution of azide **48** (59.5 mg, 98.9 μmol) in EtOAc (0.5 mL) and EtOH (1 mL) was added 10% Pd/C (15.8 mg, 14.8 μmol). The flask was evacuated of air and filled to a pressure of 1 atm with H_2. After the reaction was stirred under H_2 overnight, the solvent was evaporated in vacuo, and the residue was purified by flash chromatography (10% MeOH/CH_2Cl_2) to provide **49** as a yellow oil (54.7 mg, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.01 (s, 3H), 0.02 (s, 3H), 0.72 (s, 3H), 0.88 (s, 9H), 2.71 (d, J = 16.6 Hz, 1H), 2.85 (t, J = 7.0 Hz, 2H), 2.89 (dd, J = 16.6, 4.9 Hz, 1H), 3.37 (s, 3H), 3.39 (m, 4H), 3.55 (m, 2H), 3.64 (t, J = 8.2 Hz, 1H), 5.22 (s, 2H), 6.75 (s, 1H), 6.83 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.83, −4.55, 11.26, 18.01, 21.87, 22.65, 25.77, 27.22, 28.06, 30.82, 32.99, 34.50, 37.19, 38.05, 41.55, 41.77, 43.60, 49.95, 58.92, 67.39, 71.21, 71.51, 72.24, 81.69, 93.44, 113.74, 116.95, 126.83, 133.18, 136.64, 155.05. MS (CI, CH_4): *m*/*z* 576 (M + H^+, 100), 560 (26), 500 (27). HRMS (EI, 70 eV) calcd for $C_{33}H_{57}NO_5Si$: 575.4006. Found: 575.3999.

Tricarbonyl{[6-[17β-(*t*-butyldimethylsilanyloxy)-3-(methoxyethoxymethoxy)-estra-1,3,5(10)-triene-7α-yl]-3-oxa-hexylamido]cyclopentadienyl}rhenium(I) (50). A solution of the amine **49** (24.6 mg, 42.7 μmol), CpTR acid **26** (16.2 mg, 42.7 μmol), and DMAP (catalytic) in CH_2Cl_2 (2 mL) was stirred at room temperature until just dissolved. To the solution was added EDC (10.6 mg, 55.5 μmol), and the reaction was stirred overnight at room temperature. The reaction was concentrated and purified by flash chromatography (50% EtOAc/Hex) to give **50** as a viscous colorless oil (32.0 mg, 80%). IR (NaCl, CH_2Cl_2): 2027, 1941 (s, C≡O), 1662 (s, C═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 2.73 (d, J = 16.8 Hz, 1H), 2.91 (dd, J = 16.8, 4.9 Hz, 1H), 3.38 (s, 3H), 3.41 (m, 6H), 3.56 (m, 2H), 3.65 (t, J = 8.1 Hz, 1H), 3.82 (m, 2H), 5.23 (s, 2H), 5.34 (m, 2H), 5.82 (m, 2H), 6.08 (bs, 1H), 6.71 (s, 1H), 6.85 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.47, 11.34, 18.09, 22.11, 22.75, 25.84, 27.30, 28.21, 30.90, 33.19, 34.63, 37.26, 38.14, 39.44, 41.82, 43.70, 46.05, 59.01, 67.51, 68.99, 71.54, 71.58, 81.76, 84.59, 84.86, 85.68, 85.94, 93.55, 94.87, 113.88, 117.05, 126.93, 133.28, 136.72, 155.12, 162.08, 192.39. MS (FAB, 3-NBA): *m*/*z* 936 (M + H, 10), 862 (74), 406 (100), 363 (80), 135 (53). HRMS (FAB, 3-NBA) calcd for $C_{42}H_{59}NO_9Si^{185}Re$: 934.3489. Found: 934.3477.

Tricarbonyl{[6-(estra-1,3,5(10)-triene-3,17β-diol-7α-yl)-3-oxa-hexylamido]cyclopentadienyl}rhenium(I) (7). The reaction was performed and purified in the same manner as that for **6**, using 13.2 mg (14.1 μmol) of amide **50**. The final product **7** was isolated as a yellow oil (7.60 mg, 73%), which could be converted into a foam by quickly evaporating a solution of it in acetone. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H), 2.71 (d, J = 16.8 Hz, 1H), 2.90 (dd, J = 16.8, 4.9 Hz, 1H), 3.40 (m, 6H), 3.73 (t, J = 8.2 Hz, 1H), 5.35 (s, 2H), 5.59 (bs, 1H), 5.82 (m, 2H), 6.17 (bs, 1H), 6.55 (d, J = 2.2 Hz, 1H), 6.64 (dd, J = 8.5, 2.2 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.09, 22.16, 22.61, 27.24, 28.16, 30.45, 33.21, 34.53, 36.82, 38.02, 39.44, 41.88, 43.37, 46.41, 69.05, 71.56, 81.92, 84.70, 84.90, 85.78, 85.96, 94.65, 112.97, 116.11, 127.11, 131.54, 136.76, 153.58, 162.26, 192.41. MS (FAB, 3-NBA): *m*/*z* 736 (M + H, 11), 503 (406), 154 (100), 137 (92). HRMS (FAB, 3-NBA) calcd for $C_{32}H_{39}NO_7{}^{187}Re$: 736.2284. Found: 736.2280.

Measurement of the Octanol/Water Partition Coefficient. The log $P_{o/w}$ values were estimated from log k'_w values determined by reverse-phase HPLC following the method outlined by Minick.[54] A Chromegabond C8 (5 mm, 60 Å, ES Industries) 15 cm × 4.6 mm column served as the stationary phase. The organic mobile phase was methanol containing 0.25% (v/v) 1-octanol, and the aqueous phase consisted of octanol-saturated water containing 0.25% (v/v) M MOPS (3-morpholinopropanesulfonic acid, Sigma) buffer and 0.15% (v/v) *n*-decylamine, adjusted to pH 7.4. The flow rate was 1 mL/min.

Estrogen Receptor Binding Affinity. Receptor binding affinity (RBA) values were determined by a competitive radiometric binding assay, using tritiated estradiol as the tracer and lamb uterus cytosol as the source of receptor, according to a previously established method.[55]

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