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GRANT NUMBER DAMD17-97-1-7120

TITLE: New Rhenium Radiopharmaceuticals for the Selective Imaging and Therapy of Breast Cancer

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REPORT DATE: June 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	June 1999	Annual (12 May 98 - 11 May 99)

4. TITLE AND SUBTITLE
New Rhenium Radiopharmaceuticals for the Selective Imaging and Therapy of Breast Cancer

5. FUNDING NUMBERS
DAMD17-97-1-7120

6. AUTHOR(S)
Arterburn, Jeffery B., Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
New Mexico State University
Las Cruces, New Mexico 88003

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

This report describes progress achieved during year-2 of a three year project, which seeks to develop new technology to produce rhenium radiopharmaceuticals for the diagnostic imaging and therapy of breast cancer. We have carried out rhenium labeling reactions using polymer-supported estradiol hydrazine precursors under highly dilute conditions, simulating radiolabeling conditions. The labeling reactions are successful using either the rhenium(V) oxo complex $ReOCl_3(PPh_3)_2$ or perrhenate as the starting material. Labeling reactions are 50% complete after 2 hrs at 40° C. Two polymer supports have been investigated, carboxypolystyrene and the polystyrene-polyethyleneglycol conjugate Tentagel. The latter provided better yields of labeled product. The organoimidorhenium complexes **I** and **II** were stable in aqueous dimethylformamide solutions, and were not degraded by the presence of cysteine. Estrogen receptor binding affinities of the organoimidorhenium complexes **I** and **II** have been assayed and found to exhibit relative binding affinities of 4.47% and 3.39% respectively. The efficiency of the labeling chemistry, the complex stability in aqueous solvents, and the initial assessment of the receptor binding affinity of these complexes are all promising for this new class of potential rhenium radiopharmaceuticals.

14. SUBJECT TERMS
Breast Cancer

15. NUMBER OF PAGES
25

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Jeffrey Arterburn 6/2/99

PI - Signature Date

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5. INTRODUCTION:

This report describes work completed on award number DAMD17-97-1-7120 during the second year of the project (May 12, 1998- May 11, 1999). This project involves a fundamental investigation of new compounds and the development of new synthetic methodology for the imaging and radiotherapy of breast cancer with rhenium-188 labeled estradiol derivatives. Research efforts during the second year have focused on Technical Objective #2, as described in the original proposal text, and reproduced immediately below this paragraph. We have attained our goals of labeling polymer-supported estradiol precursors with rhenium, and have optimized the reaction conditions for radiolabeling conditions. We have also carried out solubility, and stability studies of the organoimidorhenium-estradiol complexes in solution. In collaboration with Dr. John Katzenellenbogen, University of Illinois have measured estrogen receptor binding affinities for two complexes.

Technical Objective #2: Investigate and Optimize the Re-Imido forming reactions.

Task 1: Months 13-18.

The reactivity of the solid supported estradiol derivatives with various rhenium complexes will be investigated for producing the target compounds. The efficiency and rates of product formation will be quantified for a series composed of different organoimido precursors with varying polymeric backbones using the stable isotope of rhenium.

Task 2: Months 19-24

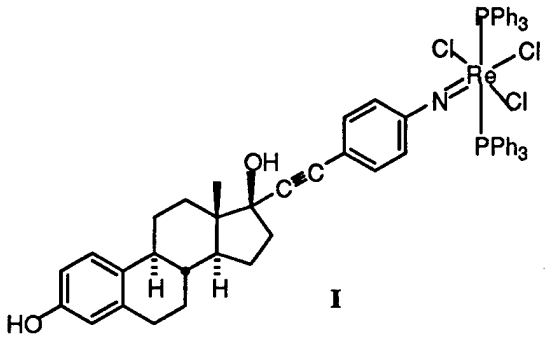
The optimal reaction conditions for ^{188}Re-radiolabeling will be determined. The effects of different solvents and concentrations of rhenium complexes will be investigated. Product formation will be monitored by HPLC and UV-Vis spectroscopy. Preparative scale reactions will be performed and compounds isolated in sufficient quantities for further study.

6. **BODY:**

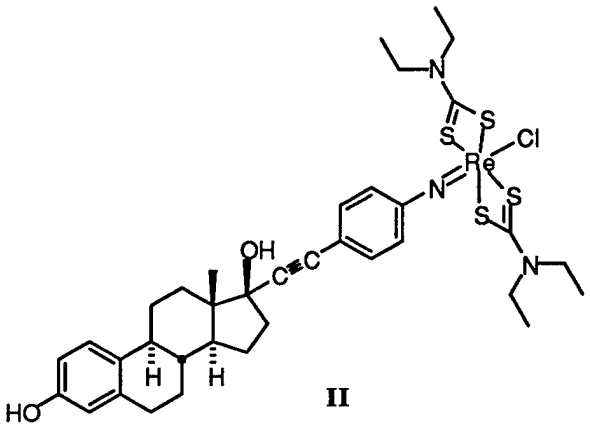
Methods. Experimental procedures were performed as described previously. UV-Vis spectra were measured using a Hewlett Packard 8452A diode array spectrophotometer.

Results/Discussion. The primary technical goals addressed during project year-2 were: 1) the optimization of the process for labeling polymer-supported estradiol precursors with various rhenium complexes; 2) the simulation of radiolabeling conditions; 3) initial studies of the solubility, and stability of the organoimidorhenium-estradiol complexes in solution. We have submitted a paper describing portions of these results for publication in the *Journal of the American Chemical Society* , a copy of which is attached to the appendice of this report.[1]. We are also currently writing a paper describing the organic syntheses of the estradiol-hydrazine precursors.[2]

The estradiol-rhenium phosphine complex (I) was synthesized as described previously. The dithiocarbamate complex (II) was also synthesized by reacting the phosphine complex (I) with tetraethylthiuram disulfide.[3,4] These compounds exhibited characteristic UV-Vis absorptions at λ = 368 nm (ε = 12,680, CH_2Cl_2) and λ = 394 nm (ε = 10,500, CH_2Cl_2) respectively. These absorptions make detection of the complexes possible under dilute conditions. This capability was used to optimize experimental conditions for the synthesis of the estradiol-rhenium complex (I) under dilute conditions to simulate future radiolabeling experiments.



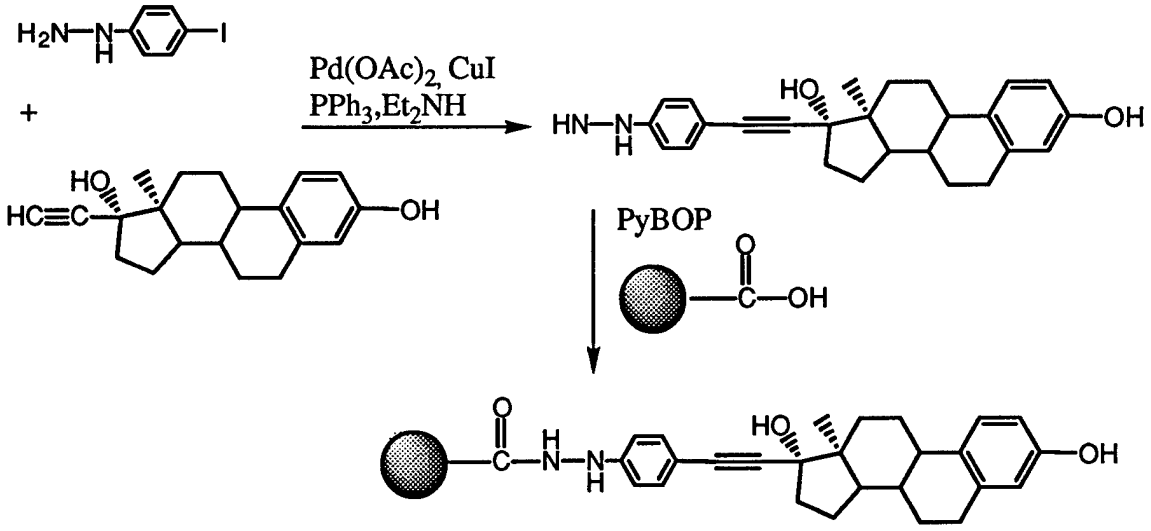
I



II

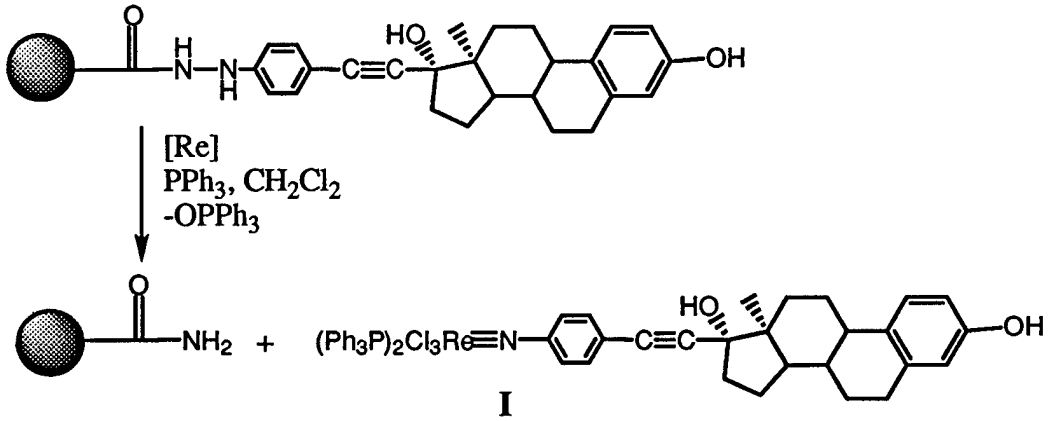
The polymer-supported estradiol precursors were synthesized by coupling the estradiol-hydrazine and carboxylated polymer supports as shown in Scheme 1. The polymer backbones consisted of polystyrene-polyetheyleneglycol conjugates (NovaSyn® Tentagel carboxy resin) and 100-200 mesh carboxy polystyrene which was1 % crosslinked with divinylbenzene. The Tentagel resin swells in a range of solvents from water to toluene, while the polystyrene only swells in organic solvents. These resins also had different loading capacities, the tentagel resing had a capacity of 0.26 mmol g^{-1}, while the carboxypolystyrene had a higher loading capacity of 1.24 mmol g^{-1}.

Scheme 1. Synthesis of Solid-Supported Ethenyl-Estradiol-Hydrazine Imido Precursors



The general reaction to produce the estradiol-rhenium complex (I) from rhenium complexes [Re] and the polymer supported hydrazine is shown in Scheme 2.

Scheme 2. Solid Supported Synthesis of Organoimido Rhenium-Estradiol Complexes



I

A series of different rhenium complexes were used as starting materials for the labeling experiments with the Tentagel-supported hydrazines, and the results are summarized in Table 1. Using the rhenium(V) oxo complex $ReOCl_3(PPh_3)_2$ as the starting complex in dichloromethane solvent at 40° C and a 100-fold excess of the polymer-bound hydrazine gave the imido complex in 72% yield after 5 hr (entry 1). Using a greater excess (1000-fold) of the polymer-bound hydrazine had no affect on the rate or yield of the reaction (entry 2). Because the starting rhenium complex obtained from generators for radiolabeling is the perrhenate anion [ReO_4^-], we sought to develop reaction conditions compatible with this material. Using conditions that have developed to convert Re-188 perrhenate to the Re-188 rhenium(V) oxo complex $ReOCl_3(PPh_3)_2$ *in situ*,[5,6] we were able to prepare the rhenium-estradiol complex with rates and yields identical to those starting from the oxo complex (entry 3). We also developed a new route starting from tetrabutylammonium perrhenate and triphenylphosphine hydrochloride in dichloromethane solvent at 40° C. The success of both of these syntheses from perrhenate holds great promise for future radiolabeling experiments with Re-188, and Tc-99m.

Table 1. Organoimido Labeling Using Solid-Supported Hydrazine

entry	concentration (x 10^{-5} M)	conditions[a]	time (hr)	yield (%)
1	2	A	2hr 5h	53 72
2	0.2	B	2hr 5h	50 70
3	9.3	C	2hr 5h	54 70
4	2	D	2hr 5h	55 65

[a] Reactions carried out in CH_2Cl_2 (10 mL), at 40°C.
A : ratio of **4c**/PPh_3/$ReOCl_3(PPh_3)_2$ = 100/100/1 ;
B: **4c**/PPh_3/$ReOCl_3(PPh_3)_2$ = 1000/1000/1;
C: **4c**/PPh_3/$KReO_4$ = 100/100/1 ;
D: **4c**/$HPPh_3Cl$/Bu_4NReO_4 = 100/100/1.

The rhenium-labeling experiments were also successful using the carboxypolystyrene-supported hydrazines. The yields of these reactions were lower than for the Tentagel-supported hydrazines, therefore we did not continue further with this support.

We have carried out some initial solubility/stability studies with compounds **I** and **II** in mixed aqueous solvents. Both the triphenylphosphine and dithiocarbamate complexes dissolve readily in dimethylformamide (1 mg complex in 1 mL DMF). These solutions were rapidly diluted with water to give 10% DMF/H_2O solutions which were stable for several hours, for example the triphenylphosphine complex **I** exhibited a UV-Vis absorption after 5 hours which was 75% of the starting value. Both classes of complex slowly degraded in neat DMF, showing 50% of the complexes remaining after 3 hours. This increased stability of the complexes in the presence of water is an intriguing, and practical observation. The stability of the triphenylphosphine complex **I** was also measured in the 10% DMF/H_2O solution containing 0.1mM cysteine, and showed 90% of the complex remaining after 5 hours. This "cysteine challenge" constitutes a preliminary test of compound stability under serum conditions, where serine can function as competitive ligand/nucleophile.

Dr. John Katzenellenbogen from the Department of Chemistry, University of Illinois, has assayed the receptor binding affinity for the organoimidorhenium complexes **I** and **II**, and found relative binding affinities of 4.47% and 3.39% respectively. These numbers represent very good binding affinity, and further measurements are currently being taken.

7. KEY RESEARCH ACCOMPLISHMENTS:

- We have labeled polymer-supported estradiol precursors with rhenium under highly dilute conditions
- We have optimized the reaction for radiolabeling conditions, using perrhenate as the starting material.
- The organoimidorhenium complexes **I** and **II** have been found to be stable in aqueous dimethylformamide solutions, and are not degraded by the presence of cysteine.
- Estrogen receptor binding affinities of the organoimidorhenium complexes **I** and **II** have been assayed and found to exhibit relative binding affinities of 4.47% and 3.39% respectively.

8. REPORTABLE OUTCOMES:

- We have submitted a paper describing portions of these results for publication in the *Journal of the American Chemical Society*, a copy of which is attached to the appendice of this report.[1]

- We presented a paper titled "Solid-Supported Instant Kits for Labeling Estradiol Ligands with Rhenium" in the Bioconjugate Chemistry in Nuclear Medicine symposium, at the 217th National Meeting of the American Chemical Society in Anaheim, California, March 21-25, 1999.

- The successful results from this project were used as part of the Preliminary Results section of a new proposal to the National Institutes of Health titled "Development of New Methods for Radiolabeling with Tc and Re."

9. CONCLUSIONS:

The results described above demonstrate that the project is proceeding on schedule according to the original plan. The efficiency of the labeling chemistry, the complex stability in aqueous solvents, and the initial assessment of the receptor binding affinity of these complexes are all promising for this new class of potential rhenium radiopharmaceuticals.

10. **REFERENCES:**

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"Solid-Supported "Instant Kits" For Labeling Estradiol Ligands with Rhenium."

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Receptor-targeted radiopharmaceuticals offer great promise for the diagnostic imaging and therapy of tumors and other disease sites. Technetium-99m is readily available in nuclear medicine clinics throughout the world for diagnostic imaging applications, and the β-emitting radioisotopes of its congener rhenium-186/188 are suitable for irradiating small to medium-size tumors.[1] Radiolabeled bioligands such as steroids, peptides, and antibodies are capable of binding to receptors expressed by cancer cells, providing the selectivity needed for diagnostic and therapeutic applications.[2-4] The estrogen and progesterone steroid hormone receptors found in approximately two thirds of breast tumors are suitable targets for steroid-based radiopharmaceuticals.[5] Radiopharmaceuticals with high specific activity are required, and the removal of all excess *unlabeled* ligand is essential to avoid competitive saturation of the receptor's binding sites. While separations using high performance liquid chromatography are frequently possible, this increases the technical complexity, waste, preparation time, and expense of the radiolabeling synthesis in a clinical environment. Herein we demonstrate a new strategy for labeling with rhenium using an organoimido-forming reaction of a polymer-supported hydrazine which simultaneously establishes the linkage and releases the labeled steroid product into solution, thereby facilitating complete removal of all unlabeled ligand by simple filtration. The approach outlined here is uniquely amenable to the specific problem of developing "instant kits" for labeling low-capacity receptor ligands, and the technology is suitable for adaptation to a wide variety of different structural classes of ligands.

The 17-α position of estradiol was selected as the site for appending the organoimido group, following the examples of organometallic steroid derivatives which exhibit high receptor binding affinities.[6-8] We have previously synthesized highly functionalized organoimido complexes from substituted acetyl phenylhydrazines using carrier free

trichlorooxobis(triphenylphosphine)rhenium(V) **1***.[9,10] Our approach required a convenient method for attaching pendant phenylhydrazine moieties to ethynylestradiol **2**. The desired hydrazines **4a-b** were obtained directly using a palladium-catalyzed coupling[11] of ethynylestradiol **2** with the 4-iodophenylhydrazine derivatives **3a-b** in diethylamine at ambient temperature Scheme 1.[12] The yields of coupled hydrazine products were very good (Table 1). The unprotected free hydrazine **4b** was attached to Tentagel® carboxy resin (loading capacity = 0.26 mmol/g) using benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP®) and diisopropylethylamine in dichloromethane to give the corresponding solid-supported acetyl hydrazine derivative **4c**. This reaction was monitored using FT-IR spectroscopy to follow the change in the carbonyl stretch from the free acid (1737 cm^{-1}) to the acetyl hydrazine (1660 cm^{-1}), and the appearance of the characteristic aryl C-H bend at 1611 cm^{-1} of the estradiol.

The organoimido-forming labeling reaction of acetyl hydrazine **4a** with **1** and triphenylphosphine occurred readily in solution to produce the air- and moisture-stable complex **5** as an olive colored solid in 87% yield Scheme 2.[13] The product exhibited a single ^{31}P NMR signal due to the coordinated triphenylphosphine ligands at δ -20.4 and displayed a characteristic UV-Vis absorption spectrum λ = 370 nm (ε = 16,200, CH_2Cl_2). A preparative scale reaction using equimolar amounts of the polymer-supported hydrazine **4c**, triphenylphosphine, and **1** (2.86 m$\underline{M}$ CH_2Cl_2) produced a green solution of the organoimido complex, which was then filtered to remove the resin. The product was precipitated with hexanes and recrystallized to afford the rhenium compound **5** in 82% isolated yield. Analysis of the crude filtrate from the reaction clearly indicated that the product organoimido complex **5** was the only detectable steroid component present in solution.

The previous example demonstrates the efficient reactivity of the polymer-supported hydrazines. The specific requirements for radiolabeling with rhenium and technetium involve highly dilute conditions, therefore a series of labeling reactions were carried out using the polymer-supported hydrazine **4c** and dilute concentrations of **1** from 10^{-5} to 10^{-6} $\underline{M}$ (Table 2). The formation of the organoimido complex **5** was followed spectroscopically by observing the

absorption at λ = 370 nm. The half lives for the labeling reactions ($t_{1/2}$ = 2hr) were unchanged using from 100- to 1000-fold excess of the resin **4c** relative to rhenium concentration. The yields of the reaction were similar when a solution of **1** prepared in situ from potassium perrhenate was used (entry 3).[10] The organoimido complex **5** was also prepared using a one-pot procedure starting with tetrabutylammonium perrhenate and triphenylphosphine hydrochloride in dichloromethane (entry 4).

These examples illustrate a new strategy for labeling estradiol ligands with rhenium using solid-supported "instant kits", and this chemistry should also be successful for preparing technetium analogs.[14] The ability to use perrhenate and pertechnetate salts for labeling is particularly advantageous, since these species are obtained directly from the radionuclide generators. The efficiency and convenience of this approach can be extrapolated to a new generation of rhenium and technetium complexes for diagnostic and therapeutic applications in nuclear medicine. Further studies that are currently in progress involve evaluation of the receptor binding affinity and *in vivo* stability of these estradiol derivatives, and the extension of this technology to other low-capacity receptor systems.

Acknowledgment: Financial support was provided by USAMRC Breast Cancer Research Program DAMD17-97-1-7120. The authors thank Dr. R. P. Hammer, and Dr. K. A. Hall for helpful discussions.

Supporting Information Available: Detailed synthetic procedures and spectroscopic data (5 pages). This material is available free of charge via the Internet at http://pubs.acs.org..

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(10) The radioactive complex **1*** $^{188}Re(O)Cl_3(PPh_3)_2$ was obtained by CH_2Cl_2 extraction of $^{188}ReO_4^-$ and $P(C_6H_5)_3$ in conc. HCl: Lisic, E. C.; Mirzadeh, S.; Knapp, F. F. Jr. *J. Labelled Compounds & Radiopharmaceuticals* **1993**, *33*, 65.

(11) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

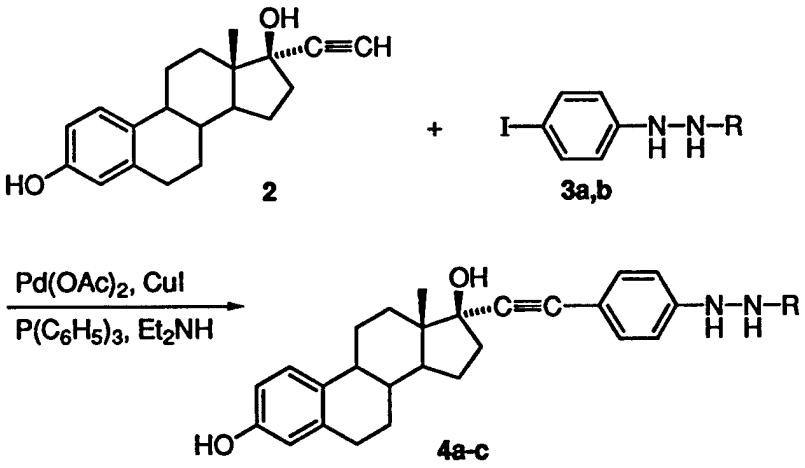
(12) Synthesis of **4a**: CuI (95 mg, 0.5 mmol) and **3a** (1.4 g, 5 mmol) were added to a solution of $Pd(OAc)_2$ (56 mg, 0.25 mmol) and $P(C_6H_5)_3$ (131 mg, 0.5 mmol) in $HN(C_2H_5)_2$ (15 mL) then stirred for 5 min. Alkyne **2** (1.5 g, 5 mmol) was added and the reaction stirred for 3 h. Volatiles were removed in vacuo, and the product purified by silica gel chromatography eluted with

5% methanol-methylene chloride to provide 4a (1.7 g, 76% yield) as a pure solid. Characterization data is given in the supporting information.

(13) Synthesis of **5**: A solution of acetyl hydrazine **4a** (444 mg, 1 mmol), oxo complex **1** (833 mg, 1 mmol), and triphenylphosphine (263 mg, 1 mmol) in CH_2Cl_2 (200 mL) was refluxed for 3 h. The product was precipitated by addition of hexanes, washed with ether, and recrystallized from CH_2Cl_2/hexanes to give **5** (1.05 g, 87% yield). Characterization data is given in the supporting information.

(14) Related technetium(V) phenylimido complexes have been synthesized directly from the reaction of TcO_4^- with $C_6H_5NHNHC(O)CH_3$ in acidic methanol. (a) Nicholson, T.; Davison, A.; Jones, A. G. *Inorg. Chim. Acta* **1991**, *187*, 51. (b) Nicholson, T.; Storm, S. L.; Davis, W. M.; Davison, A.; Jones, A. G. *Inorg. Chim. Acta* **1992**, *196*, 27. (c) Nicholson, T.; Cook, J.; Davison, A.; Jones, A. G. *Inorg. Chim. Acta* **1994**, *218*, 97. (d) Nicholson, T.; Davison, A.; Zubieta, J. A.; Chen, Q.; Jones, A. G. *Inorg. Chim. Acta* **1995**, *230*, 205. (e) Rochon, F. D.; Melanson, R.; Kong, P. C. *Inorg. Chem.* **1995**, *34*, 2273.

Scheme 1.



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Scheme 2.

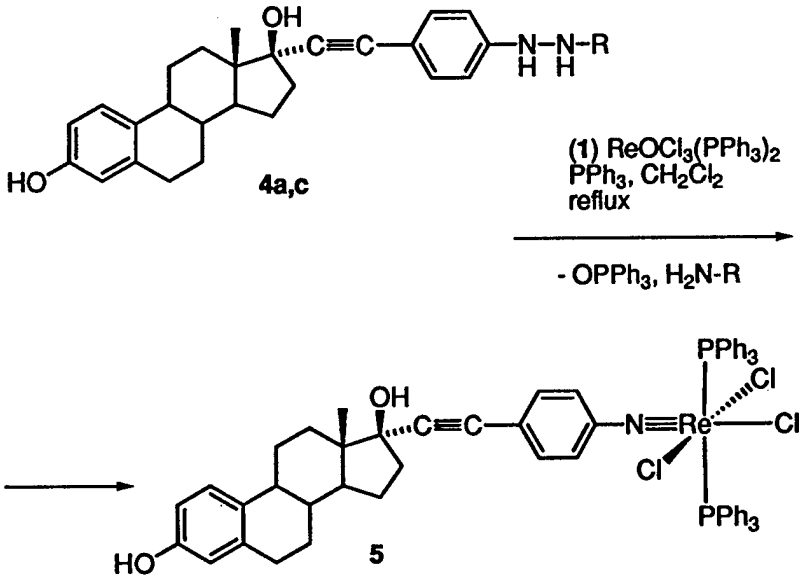

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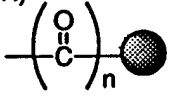
Table 1. Yields of Hydrazines **4a-c** (Scheme 1)[12]

entry	hydrazine	products	yield (%)
1	**3a** (R = $COCH_3$)	**4a** (R = $COCH_3$)	76
2	**3b** (R = H)	**4b** (R = H)	87
3		**4c** (R = 	100[a]

[a] **4b** -> **4c** using Tentagel® carboxy resin, PyBOP, DIEA, CH_2Cl_2, yield based on loading capacity = 0.26 mmol/g.

Table 2. Organoimido Labeling Using Solid-Supported Hydrazine **4c**, (Scheme 2)

entry	concentration (x 10^{-5} M)	conditions[a]	time (hr)	yield (%)
1	2	A	2hr 5h	53 72
2	0.2	B	2hr 5h	50 70
3	9.3	C	2hr 5h	54 70
4	2	D	2hr 5h	55 65

[a] Reactions carried out in CH_2Cl_2 (10 mL), at 40°C.
A : ratio of **4c**/PPh_3/$ReOCl_3(PPh_3)_2$ = 100/100/1 ;
B: **4c**/PPh_3/$ReOCl_3(PPh_3)_2$ = 1000/1000/1;
C: **4c**/PPh_3/$KReO_4$ = 100/100/1 ;
D: **4c**/$HPPh_3Cl$/Bu_4NReO_4 = 100/100/1.

Supporting Information, submitted to *J. Am. Chem. Soc.*:
"Solid-Supported "Instant Kits" for Labeling Estradiol Ligands with Rhenium."

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General Considerations. All experiments were performed in an efficient fume hood. Solvents and reagents were used without further purification. Silica gel 60, 70-230 mesh was used for column chromatography. Tentagel® carboxy resin and benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP®) were purchased from Calbiochem-Novabiochem Corp. Dichloromethane was purchased from Baker. 17-α-Ethynylestradiol was purchased from Sigma, all other chemicals were purchased from the Aldrich Chemical Company. Potassium perrhenate ($KReO_4$) was purchased from Johnson-Matthey. Deuterated solvents were purchased from Aldrich or Norell, and were used without further purification. The complex $Re(O)Cl_3(PPh_3)_2$ (**I**) was prepared according to the published procedure: Johnson, N. P.; Lock, C. J. L.; Wilkinson, G. *Inorg. Synth.* **1967**, *9*, 145).

NMR spectra were acquired at ambient temperatures (18 ± 2 °C), unless otherwise noted, using a Varian Gemini 200 Fourier transform spectrometer. The ^1H NMR spectra in $CDCl_3$ were referenced to TMS. The $^{13}C\{^1H\}$ NMR spectra were recorded at 50 MHz and referenced relative to the $^{13}C\{^1H\}$ peaks of the solvent. Spectra are reported as δ (ppm), (multiplicity, coupling constants (Hz), number of hydrogens). $^{31}P\{^1H\}$ NMR spectra were obtained at 161.9 MHz, $CDCl_3$, 22 °C, referenced to an internal capillary containing H_3PO_4 (δ = 0). Infrared spectra were recorded on a Perkin-Elmer 1720X FTIR as KBr pellets, and are reported in cm^{-1}.

Synthesis of **4a**:

A solution of palladium acetate (56 mg, 0.25 mmol) and triphenylphosphine (131 mg, 0.5 mmol) in diethylamine (15 mL) under an argon atmosphere was stirred for 10 min, then copper iodide (95 mg, 0.5 mmol) and acetyl hydrazine **3a** (1.4 g, 5 mmol) were added. After stirring for 5 min, 17-α-ethynylestradiol **2** (1.5 g, 5 mmol) was added, and the solution stirred for 3 h at 25° C. The volatiles were removed in vacuo, and the residue was chromatographed (SiO_2, 25 g) eluted with 5% methanol/dichloromethane to obtain the product **4a** (1.7 g, 76%) as a light yellow solid after removal of solvent. FT-IR (KBr, cm^{-1}) : 3290, 2930, 1684, 1609, 1254, 955, 839; ^1H NMR (Unisol) δ 9.32 (s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.6 Hz, 2H), 6.62 (d, J = 8.4 Hz, 1H), 6.55 (s, 1H), 2.90 - 1.50 (m, 18H), 2.01 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (Unisol, 50 MHz)) δ 170.36, 154.45, 148.11, 137.57, 132.33, 131.02, 125.99, 115.15, 114.29, 112.67, 112.10, 91.57, 85.29, 79.59, 49.33, 47.28, 43.35, 39.28, 38.88, 32.86, 29.36, 27.03, 26.31, 22.66, 20.48, 12.76. Compound **4a** was hydrogenated over 5% palladium/carbon in ethanol/ethyl acetate (1/9) to give the saturated analog. Analysis calculated for $C_{28}H_{36}N_2O_3$: %C 74.95, %H 8.09, %N 6.24, found %C 74.62, %H 8.40, %N 5.92.

Synthesis of **4b**:

Following the procedure described above using palladium acetate (12 mg, 0.05 mmol), triphenylphosphine (27 mg, 0.1 mmol), diethylamine (15 mL), copper iodide (19 mg, 0.1 mmol), phenyl hydrazine **3b** (234 mg, 1 mmol) and ethynylestradiol **2** (296 mg, 1 mmol) gave the product **4b** (350 mg, 87%) as a yellow solid. FT-IR (KBr, cm^{-1}) : 3420, 2930, 1676, 1608, 1255, 956, 840; ^1H NMR (Unisol) δ 7.23 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.58 (d, J = 8.2 Hz, 1H), 6.52 (s, 1H), 2.90 - 1.25 (m, 20H), 0.87 (s, 3H); ^{13}C NMR (Unisol) δ 154.03, 136.70, 131.48, 130.47, 130.12, 125.28, 114.37, 111.98, 111.46, 110.83, 90.87, 84.56, 78.45, 48.66, 46.62, 42.76, 38.69, 38.31, 32.23, 28.75, 26.44, 25.64, 21.97, 12.16.

Synthesis of **4c**:

To a suspension of TG Carboxy resin (1.0 g, 0.26 mmol) in dichloromethane (50 mL) was added benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP®) (405 mg, 0.78 mmol) followed by hydrazine **4b** and diisopropylethylamine (0.3 mL). The resulting suspension was stirred at 25° C for 20 h. The resin was filtered through a sintered glass frit (M porosity), and washed thoroughly with a sequence of dichloromethane/methanol/dichloromethane to give the shiny yellow resin **4c**. FT-IR (KBr, cm^{-1}): 3443, 2869, 1652, 1611, 1104.

Synthesis of **5** from **4a**:

A solution of the acetyl-hydrazine **4a** (444 mg, 1 mmol), rhenium complex **1** (833 mg, 1 mmol) and triphenylphosphine (263 mg, 1 mmol) in dichloromethane (200 mL) was heated at 40° C for 3 h. The solution was concentrated to ~ 5 mL, then the product was precipitated by addition of hexanes, filtered, washed with excess hexanes and ether. The product was recrystallized from dichloromethane/hexanes to obtain the pure complex **5** (1.05 g, 87%) as olive colored solid. UV-Vis (CH_2Cl_2) : λ = 234, 264, 370 nm (ε = 16,200); FT-IR (KBr, cm^{-1}) : 3420, 3058, 2927, 1610, 1436, 1093, 746, 693, 522; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.85 - 7.65 (m, 12H), 7.55 - 7.40 (m, 4H), 7.35 - 7.25 (m, 18H), 6.85 - 6.65 (m, 3H), 2.90 - 0.80 (m, 20H); $^{31}P\{^1H\}$ NMR: δ = -20.4 (s).

Synthesis of **5** from **4c**:

A suspension of resin **4c** (110 mg, 0.0286 mmol), triphenylphosphine (7.5 mg, 0.0286 mmol) and rhenium complex **1** (23.8 mg, 0.0286 mmol) in dichloromethane (10 mL) was heated at 40° C for 3 h. The reaction mixture was filtered, and washed thoroughly with dichloromethane. The combined organics were concentrated, and the product was precipitated from dichloromethane/hexanes and recrystallized to provide the pure complex **5** (28 mg, 82%) as an olive colored solid which was spectroscopically identical to **5** prepared from **4a**.

Dithiocarbamate complex of **5**:

A suspension of complex **5** (300 mg, 0.25 mmol) and tetraethylthiuramdisulfide (180 mg, 0.623 mmol) in dry acetone (30 mL) was heated to reflux under an argon atmosphere for 2 h. The volatiles were removed in vacuo, and the product was purified by repeatedly dissolving in chloroform followed by precipitation with added hexanes to give the pure dithiocarbomate complex (200 mg, 88%) as a green solid. UV-Vis (CH_2Cl_2) : λ nm = 232, 272, 326, 394 (ε = 10,500); FT-IR (KBr, cm^{-1}) : 3370, 2932, 1615, 1520, 1440, 1280, 1204; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.43 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.62 (s, 1H), 3.90 - 3.65 (m, 8H), 3.10-1.65 (m, 19H), 1.38 (t, J = 6.4 Hz, 12H), 0.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 239.27 (C=S), 156.85, 154.44, 138.41, 132.95, 132.29, 126.75, 124.28, 122.92, 115.86, 113.45, 97.04, 86.70, 81.02, 50.42, 48.22, 45.78, 44.13, 43.06, 39.95, 39.43, 33.54, 30.05, 27.72, 26.86, 23.35, 13.30, 13.00, 11.86. Analysis calculated for $C_{36}H_{49}ClN_3O_2S_4Re$: %C 47.85, %H 5.24, %N 4.65, found %C 48.45, %H 5.49, %N 4.73.

Synthesis of **5** from **1** $ReOCl_3(P(C_6H_5)_3)_2$ under dilute conditions A (Table 2):

A suspension of rhenium complex **1** (0.182 mg, 2.18×10^{-4} mmol), triphenylphosphine (6.0 mg, 0.022 mmol) and the resin **4c** (100 mg, 0.025 mmol) in dichloromethane (10 mL) was heated at 40° C. The concentration of product **5** was determined by observing the UV-Vis absorbance at λ = 370 nm. The yields of **5** at times t = 2 h, and 5 h were 53%, and 72% respectively.

Synthesis of **5** from **1** $ReOCl_3(P(C_6H_5)_3)_2$ under dilute conditions B (Table 2):

The procedure described above was repeated using rhenium complex **1** (0.0208 mg, 2.5×10^{-5} mmol), triphenylphosphine (6.5 mg, 0.025 mmol) and the resin **4c** (100 mg, 0.025 mmol) in dichloromethane (10 mL) was heated at 40° C. The concentration of product **5** was determined by observing the UV-Vis absorbance at λ = 370 nm. The yields of **5** at times t = 2 h, and 5 h were 50%, and 70% respectively.

Synthesis of **5** from $KReO_4$ under dilute conditions C (Table 2):[10]

Triphenylphosphine (25 mg, .093 mmol) was added to a solution of potassium perrhenate (0.27 mg, 9.332×10^{-4} mmol) in concentrated hydrochloric acid (10 mL) in a separatory funnel, then dichloromethane (10 mL) was added and the mixture was shaken for 5 min. The organic layer was separated, and then dried over sodium sulfate. Triphenylphosphine (25 mg, 0.093 mmol) and the resin **4c** (400 mg, 0.093 mmol) were added to the solution and heated at 40° C. The concentration of product **5** was determined by observing the UV-Vis absorbance at λ = 370 nm. The yields of **5** at times t = 2 h, and 5 h were 54%, and 70% respectively.

Synthesis of **5** using Bu_4NReO_4 under dilute conditions D (Table 2):

A suspension of tetra-butylammonium perrhenate (0.102 mg, 2.07×10^{-4} mmol), triphenylphosphine hydrochloride (6.5 mg, 0.021 mmol) and resin **4c** (100mg, 0.02mmol) in dichloromethane (10 mL) was heated at 40° C. The concentration of product **5** was determined by observing the UV-Vis absorbance at λ = 370 nm. The yields of **5** at times t = 2 h, and 5 h were 55%, and 65% respectively.