Heterodimeric Bis(amino thiol) Complexes of Oxorhenium(V) That Mimic the Structure of Steroid Hormones. Synthesis and Stereochemical Issues

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We have prepared a series of bis-bidentate complexes of rhenium that mimic the size, shape, and peripheral functionality of steroidal androgens. In a model system, we used 2D NMR and X-ray crystallographic analysis to show that adjacent *N*-methyl and oxo substitutents adopt an *anti* configuration during the coordination reaction. We have synthesized a bis-bidentate oxorhenium(V) complex whose structure and peripheral functionality mimic 5α-dihydrotestosterone. 2D-NMR analysis indicates that the *N*-methyl and oxo substituents are driven into the steroidal *anti* configuration (*β*-*N*-methyl, α-oxo) by the *β*-orientation of the methyl group equivalent to C-18. Thus, this metal complex provides a remarkable structural and stereochemical mimic of a steroid. Its in vivo stability, however, appears to be limited.

Introduction

Technetium-99m radiopharmaceuticals have played a vital role in diagnostic medical imaging. Largely due to its availability via the molybdenum-99/technetium-99m generator,[1] this radionuclide is used in the vast majority of routine imaging procedures. There has also been interest in developing rhenium-containing compounds, not only because they are structurally related to their technetium-99m analogues, but because the radioactive rhenium-188 is similarly attainable from a tungsten-188/rhenium-188 generator, which may make this radionuclide available for therapeutic applications.[2] As a result, a class of these agents, the N_2S_2 or bisamine−bisthiol complexes, have been the subject of a great deal of recent research.[3]

While most technetium and rhenium N_2S_2 complexes are used to measure blood flow or metabolic activities in vivo, there is a growing interest in developing radiopharmaceuticals labeled with these metals that act as ligands for receptors. Two general strategies have been used in the design of such receptor-binding radiopharmaceuticals, the conjugate or pendant design and the integrated design. In the pendant design, a conjugate is prepared by attaching a metal chelate system via a tether to a sterically tolerant site on a compound of known receptor binding affinity.[4] We have prepared technetium- and rhenium-containing components of this conjugate design as ligands for the progesterone receptor. Although the in vitro binding of these compounds was quite high (up to three times that of progesterone itself),[4a] in vivo, these compounds exhibited high nonspecific binding.[4b] Even when their surprisingly high lipophilicity was moderated, the compounds did not provide a satisfactory target to nontarget tissue biodistribution,[4c] likely due to the large overall bulk and mass of these systems.

The relatively low polarity of the metal complex in these conjugate systems suggested an alternative approach, that of integrating the metal complex within the structure of the steroid itself. There are many ways in which this integration might be done; the one that we have investigated first results in the replacement of the B and C rings of a steroid by the metal−chelate system (see below).[5] In this fashion, the steric contour of the steroid is mimicked well, and the functionalities necessary for receptor binding are preserved. The desired consequence of the integrated design is that both the size and the lipophilicity of the integrated complexes would be lower than those of the conjugated series, which may facilitate their delivery to the desired target tissue.

Our continuing interest in developing technetium- and rhenium-containing compounds as ligands for steroid receptors has led us to the synthesize and evaluate such integrated complexes as potential diagnostic imaging agents for steroid hormone-responsive cancers. In previous work, we have described the selective formation of prototypical hetero-bisbidentate integrated systems, and we have made a preliminary evaluation of their in vivo stability.[5] In the present study, we describe the synthesis of a series of oxorhenium(V) complexes including the first hetero-bisbidentate complex to mimic the steric structure

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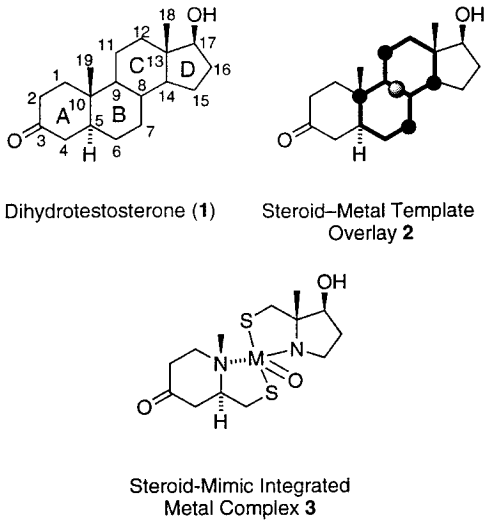

Figure 1. Template design of steroid−mimic integrated metal complexes.

of an androgen. In particular, our investigation has focused on critical stereochemical issues which arise upon formation of these complexes and determine the degree to which they mimic the configuration of a steroid. We have examined this issue both in a set of model complexes, as well as in a complex that is the mimic of 5α-dihydrotestosterone. The preferred stereochemistries that we find can be rationalized on the basis of the minimization of steric interaction during formation of the hetero-bisbidentate N_2S_2 oxometal complex, with the result that the steroid mimic adopts the desired stereochemistry, the one that most corresponds to that of the steroid, while for the same reason, the model system adopts an alternate stereochemistry.

Results and Discussion

Design of Oxometal(V) Complexes That Mimic the Structure of Androgens. Our approach to the design of oxometal(V) compounds that mimic the structure of steroids has been previously described and is illustrated in Figure 1.[5] Because the metal−heteroatom bonds in N_2S_2 oxometal complexes are significantly longer than the C−C bonds in a steroidal skeleton (**1**), one can envision the replacement of the B and C ring decalin system with the metal−N_2S_2 complex, the metal atom being centered on the C_8−C_9 bond. The steroid−metal complex overlay **2**, thus, suggests the design of a complex **3** whose structure closely mimics that of the androgen receptor ligand 5α-dihydrotestosterone (DHT) (**1**).

The accuracy of this rather simple template overlay approach may be verified by more quantitative modeling of the proposed complex (Figure 2). In a space filling model generated from Syby, one can see that the overall bulk of the proposed complex is very similar to that of the steroid (in fact, the calculated volume of complex **3** is within 3% of that determined for dihydrotestosterone). Furthermore, from the stereo overlay view, it is evident that the relative positions of the keto, alcohol, and methyl groups critical to high affinity binding of DHT to the androgen receptor are very well preserved in complex **3**.

Synthesis of a Model Complex 4. While complex **3** appears to be an excellent steric mimic of a steroid, a critical stereochemical question needed to be addressed regarding its formation: While appropriate synthetic methods can be used to obtain steroid-like configurations at the stereocenters that correspond to the 5α and 13β centers in DHT, it was difficult to predict the configurations of the metal oxo and quaternary amine centers in **3**, since these stereocenters are only formed upon complex formation. In order to address this issue, we first synthesized a simpler model complex **4** (Figure 3).

The synthesis of the amino thiol ligands necessary to form model system **4** is illustrated in Scheme 1. The steroid A-ring mimic, *N*-methyl-2-(mercaptomethyl)-piperidine (**6**), was prepared by Mitsunobu thiolation of the commercially available racemic amino alcohol **5** followed by cleavage of the acetate in base.[6] We have already described the synthesis of the D-ring mimic (*S*)-2-(mercaptomethyl)pyrrolidine hydroiodide (**8**·HI) from L-prolinol (**7**).[5b]

Complex **4** was prepared by subjecting a 1:1:1 mixture of bidentate ligands **6** and **8**·HI with trichlorobis(triphenylphosphine)oxorhenium(V) under weak alkaline conditions (Figure 4). A 1:1 diastereomeric mixture of the hetero-bisbidentate complexes **4a** and **4b**, isolated in 16% unoptimized yield, was separated by flash chromatography.

The structures of both diastereomers **4a** and **4b** were elucidated by ^{1}H, ^{13}C, and 2D (^{1}H−^{1}H and ^{1}H−^{13}C correlated) NMR spectrometry. The most prominent features in the ^{1}H NMR spectrum of each of these compounds, the methyl resonances, were also the most informative regarding the relative configurations of the metal and quaternary nitrogen. The methyl protons in **4a** (δ 2.23 ppm) and **4b** (δ 2.29) appear at about the same chemical shift as does the methyl group resonance in the free ligand **6** (δ 2.32). If the NCH_3 and Re═O substituents were *syn*, one would expect a large downfield shift of the methyl protons due to the pronounced deshielding effect that is experienced at the periphery of the Re═O bond. This effect has been previously noted in syn vs anti *N*-benzyl oxorhenium complexes,[7] and also in syn vs anti *N*-substituted oxotechnetium(V) species.[8] Since the effect is not observed, an *anti* disposition of the *N*-methyl and oxo substituents can be deduced.

The O═Re deshielding effect was also vital in identifying each diastereomer. The *anti* C-5 methine proton in **4a** (δ 2.35−2.49) was significantly farther upfield compared to the deshielded *syn* methine proton in **4b** (δ 3.72−3.80). Because the axial proton on the pyrrolidine ligand was known, from X-ray structures of similar compounds, to form in a *syn* disposition with the oxo substituent,[5] the absolute configurations of **4a** and **4b** were determined to be as shown in Figure 4.

X-ray crystallographic data[20] collected on each of the diastereomers confirmed the absolute configuration assigned by ^{1}H NMR analysis (Figure 5). Additionally, the ORTEP diagrams show both diastereomers to be of distorted square pyramidal geometry, similar to other five-coordinate oxorhenium(V) and oxotechnetium(V) compounds previously studied.[9]

Although the quaternary nitrogen in the model complexes **4a** and **4b** was of the opposite configuration desired for mimicry of DHT, these results indicated that the steric forces that govern the complexation might, in fact, aid in the formation of the desired, steroid-like

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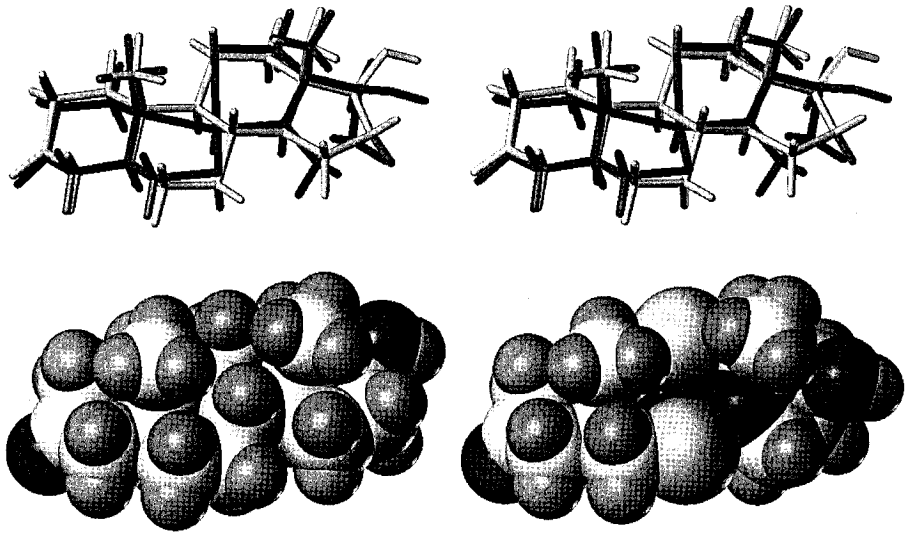


Figure 2. Top: Crossed stereoview of superposition of dihydrotestosterone (**1**) (light shading) and proposed mimic **3** (dark shading). Bottom: Space filling models of **1** (left) and **3** (right).

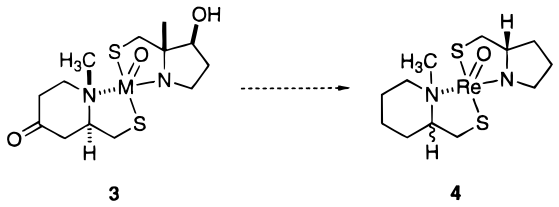


Figure 3. Rationale for the choice of model complex.

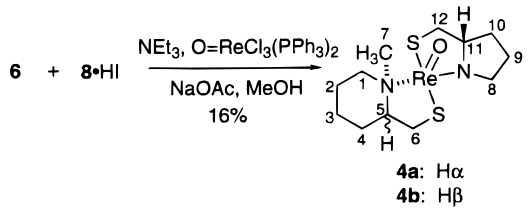


Figure 4. Coordination reaction of model complex.

configuration in the real complex **3**: The exclusive *anti* relative configuration of the *N*-methyl and oxo substituents in the model systems **4a** and **4b**, which we could rationalize on the basis of minimizing steric repulsion, clearly led us to expect that these two groups will be *anti* in **3**. However, in the model complexes **4a** and **4b** the metal oxo center formed exclusively *syn* to the methine proton of the pyrrolidine ligand. We thought that this preference might be reversed in the real complex **3**, where this methine proton would be replaced with a sterically more demanding axial methyl substituent. Thus, minimization of steric repulsion led us to expect that complex **3** would have the *anti*,*anti* disposition of the *N*-methyl, oxometal, and axial methyl moieties, as required for mimicry of the 19β-methyl group in DHT.

Synthesis of Ligands 9 and 19 for the Oxometal Dihydrotestosterone Structural Mimic. The A-ring mimic, *N*-methyl-2-(mercaptomethyl)-4-pyridone hydrochloride (**9**·HCl), was prepared according to the route shown in Scheme 2. From commercially available 2-picoline *N*-oxide (**10**), nitration provided **11** in good yield. Nucleophilic displacement of the nitro group with benzyl oxide generated 4-(benzyloxy)-2-picoline *N*-oxide (**12**), which then could be treated with acetic anhydride to undergo a novel rearrangement to provide pyridine acetate **13**.[10] Saponification gave alcohol **14** and Mit-

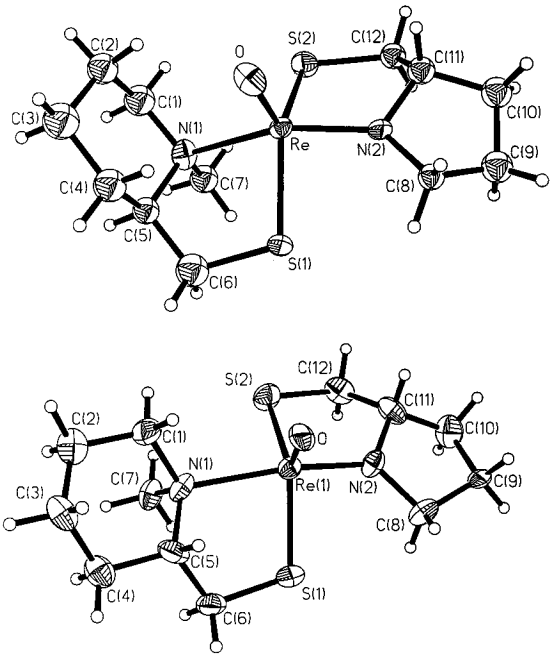
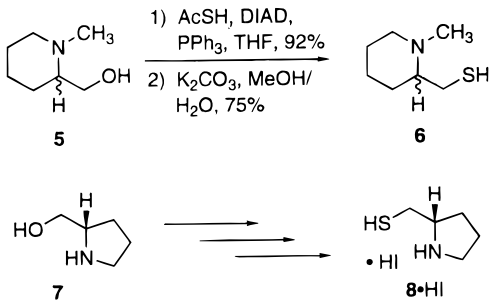


Figure 5. ORTEP diagrams of **4a** (top) and **4b** (bottom).

Scheme 1



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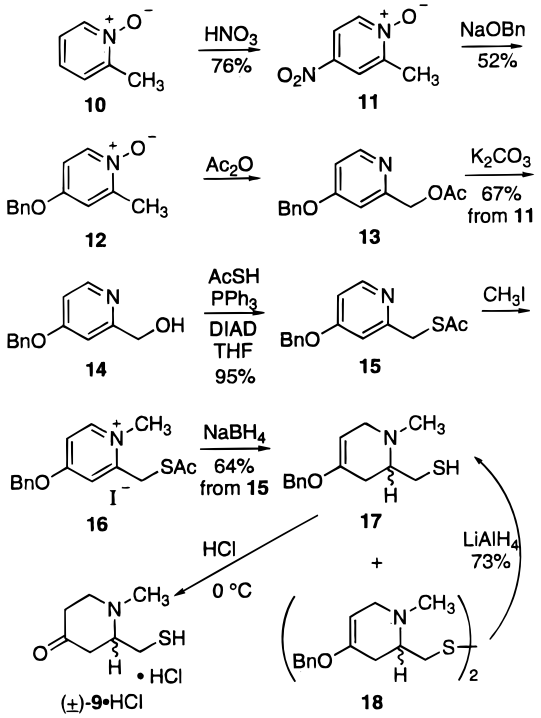
Scheme 2

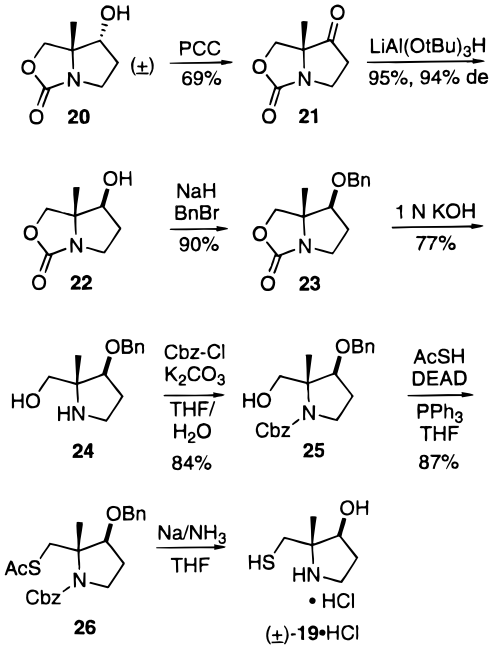


sunobu thiolation provided protected pyridine thioacetate **15** in excellent yield.[6] The *N*-methylpyridinium iodide **16** was reduced with sodium borohydride to give a mixture of thiol **17** and disulfide **18**, which was treated with lithium aluminum hydride to afford only amino thiol **17**. Direct reduction of the pyridinium ring with lithium aluminum hydride also gave **17**, but in lower yield (18%). Thiol **17** was treated with HCl to provide A-ring mimic as the crystalline hydrochloride salt **9**·HCl.

The D-ring mimic, *trans*-2-methyl-2-(mercaptomethyl)-3-pyrrolidinol hydrochloride (**19**·HCl), was prepared according to the route outlined in Scheme 3. From *trans*-6-hydroxy-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-3-one (**20**),[11] pyridinium chlorochromate (PCC) oxidation to gave ketone **21**. Reduction of the ketone allowed for inversion of the secondary alcohol relative configuration. Mitsunobu inversion of alcohol **20** using benzoic acid[12] or 3-nitrobenzoic acid[13] resulted in low yields and incomplete stereochemical inversion. Secondary alcohol **22** was then benzyl protected, the amine and primary alcohol functionalities deprotected, and the amine reprotected to provide neopentyl alcohol **25**. Mitsunobu thiolation on this highly hindered alcohol yielded tris-protected pyrrolidine derivative **26** in good yield. Treatment with sodium in ammonia allowed for simultaneous deprotection of all groups, and acidification afforded D-ring mimic **19**·HCl.

Formation of Oxometal Dihydrotestosterone Mimic 3. As with model complexes **4a** and **4b**, oxorhenium species **3a** and **3b** were formed by coordination under typical conditions, with a 1 : 1 ratio of bidentate ligands **9**·HCl and **19**·HCl (Figure 6). Trichlorobis(triphenylphosphine)oxorhenium(V) was found to be the

Scheme 3



best metal precursor for this complexation, since the ratio of **3a** (desired DHT mimic) to **3b** (undesired diastereomer) was as high as 1:3, while with other rhenium reagents ([$BnEt_3N$][$OReCl_4$],[9d] [*n*-Bu_4N][$OReBr_4$],[14] or $NH_4ReO_4/SnCl_2$) either a lower yield or a lower ratio of **3a** to **3b** was obtained. The modest yield and the fact that the undesired diasteromer **3b** is isolated in a higher proportion may be explained by the stability of these complexes (*vide infra*).

Oxotechnetium(V) complexes **27a** and **27b** were also formed by ligand exchange with tetrabutylammonium tetrachlorooxotechnetate(V). The technetium (V) complexes formed in similar yield and under much milder conditions compared with those used for the rhenium complexes **3a** and **3b** (0 °C vs 80 °C), as consistent with previous observations on similar systems.[5,7] Compounds **27a** and **27b**, however, were not characterized owing to their low stability (*vide infra*).

^{1}H NMR analysis once again proved vital to the assignment of the relative stereochemistry of complexes **3a** and **3b**. In the 1D spectra of **3a** and **3b**, the prominent *N*-methyl and axial methyl protons were clearly not shifted downfield compared to the free ligand methyl resonances. As described earlier, this indicated that both diastereomers had the *anti*,*anti* relationship of the *N*-methyl, oxo, and axial methyl substituents predicted by the consideration of steric repulsion. 2D COSY analysis of each isomer allowed for identification of the diastereomers, using the chemical shift data of the C-5 methine proton, in a similar process to that used for model complexes **4a** and **4b**. The *cis*-fused compound **3b** exhibited an upfield resonance (δ 2.87−3.00) for the C-5 methine proton, while *trans*-fused **3a** showed a C-5 methine resonance dramatically deshielded (δ 3.95−4.02) by the adjacent O═Re moiety. In contrast to model compounds **4a** and **4b**, attempts at obtaining crystals of compound **3a** suitable for X-ray diffraction proved impractical, owing to the small amount of pure material which was available.

Determination of Complex Lipophilicity. In order to determine lipophilicity of **3a** and **3b**, the log $P_{o/w}$ values

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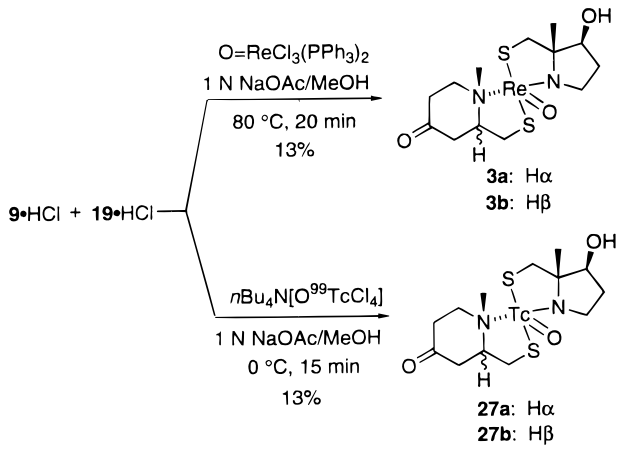

Figure 6. Coordination reaction to form steroidal mimics **3a** and **3b**.

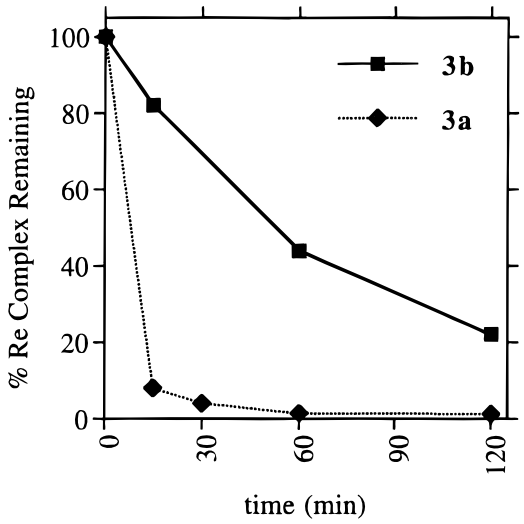

Figure 7. In vitro stability of rhenium complexes **3a** and **3b** in buffer solution.

were estimated by the reversed-phase HPLC method of Minick.[15] The log $P_{o/w}$ values were the following: for **3a**, 1.47; for **3b**, 1.69. Compared to dihydrotestosterone (log $P_{o/w} = 3.90$), oxorhenium(V) mimic **3a** was 250 times less lipophilic. Thus, integration of the metal complex within the periphery of the steroid, which was done in part to reduce the lipophilicity of the metal-containing system, has resulted in compounds which may be too polar.

Stability of Oxometal(V) Complexes and Androgen Receptor Binding Affinity. Studies of the in vitro stability of **3a** and **3b** in androgen receptor buffer indicated significant decomposition (Figure 7).[16] After only 1 h in buffer solution, complex **3a** has nearly completely disappeared, and after 2 h only 22% of **3b** remained. Further investigations determined that competitive ligand exchange from water and not solutes in the buffer contributed to the destruction of the bisbidentate complexes. The relative stability of **3b** over **3a** was likely due to the *cis*-fused piperidone ring of **3b**, which hindered the nucleophilic *anti* attack of water at the metal center; **3a**, lacking this steric protection, decomposed much faster.

As a result of the hydrophilicity and low stability of the rhenium species, both complexes **3a** and **3b** exhibited very low binding affinity for the androgen receptor (<0.02%; R1881, 100%). To our knowledge, no compound of such low lipophilicity has exhibited significant binding for the androgen receptor.

The technetium-99 complexes were very unstable under aqueous conditions; attempted reversed-phase HPLC analysis of the compounds resulted in total decomposition. Owing to the lack of promise for further development as imaging agents, the technetium complexes were not investigated further.

Conclusion

We have shown it is possible to synthesize an oxometal(V) N_2S_2 hetero-bisbidentate complex which is a close structural and stereochemical mimic of the androgen 5α-dihydrotestosterone. The minimization of steric repulsion during complex formation assists in the generation of the desired steroid-like stereochemistry. This oxometal mimic, however, exhibited low stability and low lipophilicity, which precluded its use in vivo.

Experimental Section

Molecular Modeling. Molecular modeling calculations were performed on a Silicon Graphics Indigo Elan computer. Compound **3a** was built using the SYBYL Molecular Modeling Package (Version 6.1, Tripos Associates, St. Louis, MO) around the X-ray crystal parameters for rhenium and the five surrounding heteroatoms from **4a**. The compound was energy minimized to a gradient of <0.05 kcal/mol Å with the Tripos force field. Molecular volumes were determined by reading these minimized structures into Macromodel[17] v.4.5 and calculating the total van der Waals volume occupied by the sum of the atoms.

General. All reagents and solvents were obtained from Aldrich, Eastman, Fisher, or Mallinckrodt. All reactions were performed under a nitrogen atmosphere unless otherwise indicated. The synthesis of (*S*)-2-(mercaptomethyl)pyrrolidine hydroiodide has been previously described.[5] Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use in reactions unless specified otherwise. Dimethylformamide (DMF) was distilled from and stored over 4 Å molecular sieves. Hexanes were distilled from calcium sulfate (Drierite) before use in column chromatography.

Reaction progress was monitored with analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved using phosphomolybdic acid (PMA), $KMnO_4$, or ninhydrin spray reagents, or UV illumination. Flash chromatography was performed according to the method of Still[18] with Woelm silica gel (0.040−0.063 mm) packing. High performance liquid chromatography (HPLC) was performed isocratically on a Spectra-Physics Model 8700 with an analytical 5-mm SiO_2 cyanopropyl column (4.6 mm × 30 cm, Supelco LC−CN) or a semipreparative SiO_2 cyanopropyl column (10 mm × 50 cm, Phenomenex IB-SIL). The UV/visible absorbance of the eluent was monitored at 254 or 410 nm. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. Crystallographic measurements were made on an Enraf-Nonius CAD4 automated κ-axis diffractometer equipped with graphite monochromated Mo radiation, $\lambda(K\bar{\alpha}) = 0.71073$ Å.

^1H and ^{13}C NMR spectra were obtained on a General Electric QE-300 (300 MHz) or a Varian Unity (400 MHz) spectrometer and are reported in parts per million downfield from internal tetramethylsilane or from proton resonances resulting from incomplete deuteration of the NMR solvent (δ scale). COSY and HETCOR spectra were obtained on a Varian Unity (400

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MHz) spectrometer. Low resolution electron impact (EI), chemical impact (CI), and fast atom bombardment (FAB) mass spectra were obtained on Finnigan MAT CH5, VG 70-VSE, and VG ZAB-SE spectrometers, respectively. High resolution EI, CI, and FAB mass spectra were obtained on Finnigan MAT 731, VG 70-VSE, and VG 70-SE-4F spectrometers, respectively. Elemental analyses were performed by the Microanalytical Service of the University of Illinois.

***N*-Methyl-2-(mercaptomethyl)piperidine (6).** Triphenylphosphine (12.18 g, 46.5 mmol) was dissolved in THF (100 mL), and diisopropyl azodicarboxylate (9.1 mL, 46 mmol) was added at rt. The solution was cooled to 0 °C, and additional THF (50 mL) was added via syringe into the flask. *N*-Methyl-2-piperidinemethanol (**5**, 4.96 g, 39 mmol) in THF (25 mL) was added after 20 min, and thiolacetic acid (3.5 mL, 46.5 mmol) was added dropwise immediately thereafter with stirring. The reaction was allowed to stir at 0 °C for 1 h and then at room temperature for 16 h. The mixture was concentrated, and flash chromatography (5% MeOH/CH_2Cl_2, R_f 0.24 in 10% MeOH/CH_2Cl_2; $KMnO_4$) yielded slightly yellow liquid as *N*-methyl-2-(thioacetyl)methylpiperidine (6.04 g, 92%).

To a solution of *N*-methyl-2-[(acetylthio)]methylpiperidine (2.13 g, 12.1 mmol) in 5:1 MeOH:H_2O (60 mL) was added potassium carbonate (5.13 g, 37.1 mmol) in one portion. After 15 min, additional MeOH/H_2O (50 mL/15 mL) was added to help solubilize any remaining solid. TLC showed one spot near the base line (20% MeOH/CH_2Cl_2 ; $KMnO_4$) after 15 additional min. The solution was concentrated to 30 mL and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and concentrated to afford the title compound (1.32 g, 75%). A small amount of the slightly yellow oil was purified by Kugelrohr distillation (130 °C, 0.7 torr) to yield an analytically pure sample: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.34 (m, 1), 1.42−1.51 (m, 1), 1.51−1.63 (m, 2), 1.68−1.76 (m, 1), 1.76−1.83 (m, 1), 2.04−2.14 (m, 1), 2.14−2.21 (m, 1), 2.32 (s, NCH_3, 3), 2.85 (dt, J = 11.5, 3.9 Hz, 1), 2.92 (dd, B of AB q, J = 12.8, 7.2 Hz, CH_2OH, 1), 3.00 (ddd, A of AB q, J = 12.9, 4.2, 3.2 Hz, CH_2OH, 1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 25.5, 30.6, 43.11, 43.14, 56.6 (NCH_3), 62.9 (C_2); MS (CI, CH_4) (*m*/*z*) 290 (10), 289 (M + H^+ of dithiol, 58), 287 (14), 146 (M + H^+, 59), 145 (24), 144 (100), 142 (28), 112 (50), 98 (81); HRMS calcd for $C_7H_{16}NS^+$ 146.1003, found 146.0992. Anal. Calcd for $C_7H_{15}NS$: C, 57.89; H, 10.42; N, 9.65. Found: C, 58.29; H, 10.55; N, 10.03.

[(1*R*,2*R*)-*N*-Methyl-2-(mercaptomethyl)piperidinato]-[(*S*)-2-(mercaptomethyl)pyrrolidinato]oxorhenium(V) (4a) and [(1*R*,2*S*)-*N*-Methyl-2-(mercaptomethyl)piperidinato]-[(*S*)-2-(mercaptomethyl)pyrrolidinato]oxorhenium(V) (4b). A sample vial (5 mL) was charged with amino thiol **6** (30.6 mg, 0.2 mmol), a stir bar, and 1 N methanolic NaOAc solution (2 mL, 2.0 mmol). To it was added the oxotrichlorobis(triphenylphosphine)rhenium(V) (166 mg, 0.2 mmol), and then, in succession, amino thiol **8**·HCl (49.0 mg, 0.2 mmol) and triethylamine (28 μL, 0.2 mmol). The vial was sealed and heated to 75 °C for 20 min. From the dark burgundy red reaction mixture, rhenium starting material (4 mg) was isolated by filtration. The filtrate was then concentrated, and flash chromatography (10-30% EtOAc/hexanes) yielded an orange complex **4a** (R_f 0.10 in 10% EtOAc/hexanes) and a red complex **4b** (R_f 0.056 in 10% EtOAc/hexanes) as solid products (14.4 mg, 16% of a 1:1 ratio of isomers). Recrystallization of each diastereomer by vapor diffusion from EtOAc/pentane at −20 °C afforded crystals suitable for X-ray analysis.

(1*R*,2*R*)-4a: IR (cm^{-1}, KBr pellet) 944; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40−1.49 (m, 3α, 1), 1.63−1.73 (m, 2α, 10α, 2), 1.78−1.85 (m, 3β, 1), 1.96−2.08 (m, 9α, 1), 2.08−2.19 (m, 9β, 1), 2.19−2.35 (m, 4α, 4β, 2), 2.23 (s, 7-CH_3, 3), 2.35−2.49 (m, 5α, 10β, 2), 2.45 (t, J = 11.0 Hz, 12α, 1), 2.88 (dd, A of ABC, J = 12.9, 5.4 Hz, 6α, 1), 2.93−3.04 (m, 6β, 1α, 2), 3.27 (dd, J = 10.7, 5.6 Hz, 12β, 1), 3.90−4.02 (m, 11β, 1), 4.16 (ddt, J = 12.6, 4.0, 1.7 Hz, 1β, 1), 4.24 (ddddd, J = 12.7, 8.5, 3.9, 1.3, 0.7 Hz, 8α, 1), 4.62 (ddddd, J = 13.1, 8.8, 7.2, 1.7, 0.5 Hz, 8β, 1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.12, 23.16, 27.8 (C_9), 29.0 (C_3), 32.0 (C_{10}), 45.1, 45.2, 53.2 (C_7), 63.1 (C_1), 65.9 (C_8), 74.7 (C_5), 86.1 (C_{11}); MS (EI, 10 eV) (*m*/*z*) 464 (11), 463 (16), 462 (M^+ for ^{187}Re, 100), 461 (13), 460 (M^+ for ^{185}Re, 59), 395 (11), 394 (10), 393 (88), 391 (49), 112 (62), 111 (51), 99 (10), 98 (84); HRMS calcd for $C_{12}H_{23}N_2OS_2{}^{185}$Re 460.0782, found 460.0778. Anal. Calcd for $C_{12}H_{22}N_2OS_2Re$: C, 31.22; H, 5.02; N, 6.07. Found: C, 31.31; H, 5.13; N, 5.89.

(1*R*,2*S*)-4b: IR (cm^{-1}, KBr pellet) 930; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47−1.55 (m, 2α, 1), 1.67−1.77 (m, 4α, 10α, 2), 1.82−1.95 (m, 3α, 3β, 2), 1.95−2.06 (m, 2β, 4β, 9α, 3), 2.06−2.15 (m, 9β, 1), 2.29 (s, 7-CH_3, 3), 2.40−2.48 (m, 10β, 1), 2.58 (t, J = 11.1 Hz, 12α, 1), 2.66 (dd, J = 13.0, 12.0 Hz, 6α, 1), 3.11 (dd, J = 12.9, 4.9 Hz, 6β, 1), 3.39 (dd, J = 11.0, 5.6 Hz, 12β, 1), 3.72−3.80 (m, 5β, 1) 3.85−3.95 (m, 11β, 1), 4.02 (dtq, J = 13.4, 3.5, 0.6 Hz, 1α, 1), 4.10 (ddddd, J = 13.1, 7.9, 4.2, 1.5, 0.5 Hz, 8α, 1), 4.27 (dddt, J = 13.9, 3.5, 2.0, 0.6 Hz, 1β, 1), 4.50 (ddddd, J = 13.2, 8.5, 6.9, 2.1, 0.5 Hz, 8β, 1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 22.9, 24.3 (C_4), 27.6 (C_9), 32.0 (C_{10}), 37.6 (C_7), 43.2 (C_6), 48.3 (C_{12}), 66.0 (C_1), 66.4 (C_8), 77.3 (C_5), 86.5 (C_{11}); MS (EI, 10 eV) (*m*/*z*) 463 (20), 462 (M^+ for ^{187}Re, 100), 461 (11), 460 (M^+ for ^{185}Re, 56), 393 (84), 391 (52), 278 (17), 277 (23), 113 (13), 112 (63), 111 (48), 98 (83); HRMS calcd for $C_{12}H_{23}N_2OS_2{}^{185}$Re 460.0782, found 460.0782. Anal. Calcd for $C_{12}H_{22}N_2OS_2Re$: C, 31.22; H, 5.02; N, 6.07; S, 13.88. Found: C, 31.52; H, 5.16; N, 6.08; S, 13.56.

4-Nitro-2-picoline *N*-Oxide (11). *Note: 2-Picoline N-oxide is extremely hygroscopic.* 2-Picoline *N*-oxide (**10**, 13.1 g, 0.12 mol) and concentrated sulfuric acid (30 mL) were thoroughly mixed and then heated to 85−95 °C. A mixture of nitric (55 mL) and sulfuric acid (44 mL) was added slowly dropwise with stirring. The mixture was maintained at the above temperature for 16 h before cooling in an ice bath. The acid was neutralized carefully using 30% potassium hydroxide solution. The precipitate was filtered, and the resulting solids were washed with CH_2Cl_2. The remaining aqueous layer was also extracted with CH_2Cl_2. The organic layers were collected, dried ($NaSO_4$), and concentrated. Recrystallization from $CHCl_3$ gave product **11** as yellow crystalline needles (14.1 g, 76%): R_f 0.28 in 2% EtOH/CH_2Cl_2; mp 154−156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, CH_3, 3), 8.00 (dd, J = 7.2, 3.2 Hz, C_5-H, 1), 8.15 (d, J = 3.1 Hz, C_3-H, 1), 8.32 (d, J = 7.2 Hz, C_6-H, 1); MS (EI, 70 eV) (*m*/*z*) 154 (M^+, 100), 137 (42), 108 (21), 91 (37); Anal. Calcd for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.67; H, 3.89; N, 18.05.

4-(Benzyloxy)-2-picoline *N*-Oxide (12). To the nitropicoline *N*-oxide **11** (10.1 g, 65.5 mmol) in benzyl alcohol (40 mL) at 80 °C was added a premixed solution of sodium benzyl alkoxide (1.5 g sodium, 70 mL benzyl alcohol) over 30 min. Immediately after addition, TLC indicated complete conversion of starting material (R_f 0.24 in 5% EtOH/CH_2Cl_2). Benzyl alcohol was removed by vacuum distillation, and the mixture was diluted with 1:1 CH_2Cl_2/H_2O. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with brine solution, and concentrated. The material obtained from flash chromatography (0−10% EtOH/CH_2Cl_2 elution) was recrystallized from acetone to give product **12** as fluffy white crystals (7.4 g, 52%): mp 154−156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (s, CH_3, 3), 5.09 (s, CH_2, 2), 6.77 (dd, J = 7.2, 3.4 Hz, C_5-H, 1), 6.86 (d, J = 3.4 Hz, C_3-H, 1), 7.40 (b s, Ar-H, 5), 8.18 (d, J = 7.2 Hz, C_6-H, 1); MS (EI, 70 eV) (*m*/*z*) 215 (M^+, 4), 91 (100), 65 (12). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.45; H, 6.09; N, 6.46.

4-(Benzyloxy)-2-(hydroxymethyl)pyridine (14). To benzyl ether **12** (1.13 g, 5.25 mmol) in acetic anhydride (6 mL) was added concentrated sulfuric acid (3 drops) at room temperature. This mixture was then heated to 110 °C for 3 h and then allowed to stand at room temperature overnight. The reaction mixture was washed ($NaHCO_3$, H_2O, brine) and extracted with EtOAc, and the organic solution was dried (Na_2SO_4) and concentrated, leaving acetate **13** as a dark brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, CH_3, 3), 5.12 (s, CH_2, 2), 5.17 (s, CH_2, 2), 6.81 (dd, J = 5.7, 2.4 Hz, C_3-H, 1), 6.95 (d, J = 2.4 Hz, C_5-H, 1), 7.36−7.42 (m, Ph-H, 5), 8.41 (d, J = 5.7 Hz, C_2-H, 1).

Crude acetate **13** was taken up in 2:1 MeOH/H_2O (30 mL), and K_2CO_3 (1 g, crude excess) was added. After 15 min, solvent was evaporated, and the residue was dissolved in CH_2Cl_2. This solution was dried (Na_2SO_4) and concentrated, and flash chromatography (R_f 0.42 in 5% MeOH/CH_2Cl_2) yielded **14** as a solid waxy product (752 mg, 67% by ^{1}H NMR): mp 102.5−103.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.69 (s, CH_2, 2), 5.10 (s, CH_2, 2), 6.76 (dd, J = 5.7, 2.4 Hz, C_5-H, 1), 6.91 (d,

J = 2.2 Hz, C_3-H), 7.35−7.41 (m, Ar-H, 5), 8.32 (d, J = 5.7 Hz, C_6-H, 1); MS (EI, 70 eV) (*m*/*z*) 215 (M^+, 4), 109 (4), 91 (100). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.50; H, 6.37; N, 6.45.

4-Benzyloxy-2-[(acetylthio)methylpyridine (15). To a flask containing triphenylphosphine (1.02 g, 3.9 mmol) in THF (10 mL) at 0 °C was added diisopropyl azodicarboxylate (761 μL, 3.9 mmol). This was allowed to stir at 0 °C for 30 min after which the mixture became a white suspension. A solution of crude alcohol **14** (416 mg, 1.93 mmol) in THF (5 mL) was then added. After another 30 min, thiolacetic acid (277 μL, 3.9 mmol) was added, causing the mixture to turn dark orange. This mixture was allowed to stir at 0 °C for 1 h and then at rt for 1 h. Concentration and flash chromatography of the residue (R_f 0.41 in 60% EtOAc/hexanes) afforded product **15** as a slightly yellow oil (500 mg, 95%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, CH_3, 3), 4.20 (s, CH_2, 2), 5.09 (s, CH_2, 2), 6.75 (dd, J = 5.6, 2.4 Hz, C_5-H, 1), 6.96 (d, J = 2.4 Hz, C_3-H, 1), 7.34−7.41 (m, Ar-H, 5), 8.34 (d, J = 5.6 Hz, C_6-H, 1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.2, 35.4, 69.8, 109.2, 109.8, 127.431, 127.438, 127.5, 128.3, 128.7, 135.4, 158.9, 165.3, 195.0; MS (EI, 70 eV) (*m*/*z*) 273 (M^+, 5), 231 (15), 91 (100), 65 (13). Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.92; H, 5.53; N, 5.12; S, 11.72. Found: C, 65.73; H, 5.40; N, 5.27; S, 11.50.

***N*-Methyl-2-(mercaptomethyl0-4-pyridone Hydrochloride (9·HCl).** To a solution of thiolacetate **15** (1.93 g, 7.1 mmol) in acetone (7 mL) at rt was added by syringe methyl iodide (6.6 mL, 106 mmol). This was allowed to stir at rt for 2.5 hand then at reflux for 1 h. Concentration *in vacuo* provided the methiodide as a hygroscopic, slightly yellow foam. This material was taken immediately to the next reaction: ^{1}H NMR (CD_3OD, 400 MHz) δ 2.30 (s, $COCH_3$, 3), 4.08 (s, N-CH_3, 3), 4.41 (s, CH_2S, 1), 4.78 (s, CH_2S, 1), 5.35 (s, CH_2O, 2), 7.23−7.37 (m, ArH, 3), 7.38−7.45 (m, ArH, 3), 7.54 (d, J = 2.9 Hz, C_3-H, 1), 8.56 (d, J =7.6 Hz, C_6-H, 1); MS (FAB) (*m*/*z*) 288 (M^+, 100), 214 (39); HRMS calcd for $C_{16}H_{18}NO_2S^+$ 288.1058, found 288.1057.

Pyridinium iodide **16** was dissolved in MeOH (20 mL), and to it was added sodium borohydride (490 mg, 13.0 mmol) in portions at 0 °C. After gas evolution ceased, the reaction was heated to reflux for 30 min. Flash chromatography (R_f 0.46 in 10% MeOH/CH_2Cl_2; 2−5% MeOH/CH_2Cl_2 elution; $KMnO_4$) yielded the tetrahydropyridine **17** and **18** as a slightly yellow oil (1.13 g, 64%). The residue was dissolved in THF (20 mL) and added to a suspension of lithium aluminum hydride (175 mg, 4.6 mmol) in THF (15 mL) at 0 °C. After 10 min, TLC indicated only free thiol in solution. This reaction was diluted with diethyl ether and quenched by addition of 1 :1 sodium sulfate decahydrate/Celite until a white precipitate settled. The suspension was filtered through Celite and concentrated to give amino thiol **17** as a slightly yellow oil (887 mg, 78%): ^{1}H NMR ($CHCl_3$, 300 MHz) δ 1.60−1.80 (m, 1), 2.05−2.25 (m, 1), 2.39 (s, CH_3, 3), 2.55−2.70 (m, 2), 2.75−3.40 (m, 3), 4.62 (s, C=CH, 1), 4.79 (s, $ArCH_2$, 2), 7.20−7.45 (m, ArH, 5); MS (CI, CH_4) (*m*/*z*) 250 (($M + H)^+$, 33), 248 (37), 202 (100), 126 (53), 91 (96), 90 (56).

Amino thiol **17** (887 mg, 3.6 mmol) was taken up in THF (50 mL), and water (64 μL, 3.6 mmol) was added. To this solution was added 1 N HCl in ether (7 mL, 7 mmol) at 0 °C. This solution was allowed to stir at 0 °C for 1 h. The mixture was then concentrated and washed with dry diethyel ether to give product **9**·HCl as an off-white solid (893 mg, 128%, contaminated by BnOH and H_2O). Silica gel chromatography afforded a small sample of free amine **9**: ^{1}H NMR (CD_3OD, 400 MHz) δ 1.67−1.77 (m, 1), 1.86 (d, B of AB q, J = 11.6 Hz, 1), 1.90−2.02 (m, 1), 2.14 (dt, A of AB q, J = 11.7, 3.7 Hz, 1), 2.29 (s, CH_3, 3), 2.80−2.90 (m, 2), 2.95−3.10 (m, 2), 3.42−3.48 (m, 1); MS (CI, CH_4) (*m*/*z*) 161 (26), 160 (($M + H)^+$, 100), 142 (32), 112 (26), 102 (39); HRMS calcd for $C_7H_{14}NOS^+$ 160.0796, found 160.0795.

5-Methyl-1-aza-3-oxabicyclo[3.3.0]octane-2,6-dione (21). Compound **20**[11] (2.0 g, 12.7 mmol) was dissolved in CH_2Cl_2 (200 mL), and solid NaOAc (10.7 g, 130 mmol) was added. The reaction vessel was then covered with aluminum foil. To this vigorously stirred suspension was added pyridinium chlorochromate (PCC) (13.6 g, 63 mmol) in portions. After 3 h, TLC indicated complete conversion of the starting alcohol to the corresponding ketone (R_f 0.48 in 5% MeOH/CH_2Cl_2; $KMnO_4$). This mixture was then added slowly to a rapidly stirring suspension of Celite/Et_2O (800 mL), and filtered through a pad of silica gel, which was washed with 4:1 Et_2O/CH_2Cl_2. Concentration of the organic layers and flash chromatography yielded the title compound (1.36 g, 69%) as a white solid: mp 102.5−103.3 °C; IR (cm^{-1}, KBr pellet) 3480, 1777, 1753, 1745, 1406, 1390, 1342, 1184, 1077, 1031; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, CH_3, 3), 2.45−2.64 (m, C_7-H, 2), 3.54 (ddd, J = 12.8, 9.1, 8.0 Hz, C_8-H 1), 4.13 (d, J = 8.9 Hz, 1), 4.24 (ddd, J = 12.8, 4.0, 3.6 Hz, 1), 4.45 (d, J = 8.9 Hz, 1); MS (CI, CH_4) (*m*/*z*) 156 (M + H^+, 100), 127 (12). HRMS calcd for $C_7H_{10}NO_3^+$ 156.0661, found 156.0654. Anal. Calcd for $C_7H_{10}NO_2$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.18; H, 5.88; N, 9.07.

***cis*-6-Hydroxy-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-2-one (22).** To ketone **21** (1.36 g, 8.7 mmol) in THF (50 mL) at 0 °C was added, in portions, LiAl(O-*tert*-Bu)$_3$H (2.74 g, 10.4 mmol). This reaction was allowed to stir for 2 h after which TLC analysis indicated complete conversion to the alcohol (R_f 0.14 in 5% MeOH/CH_2Cl_2; $KMnO_4$). Ether was then added, and reaction was quenched slowly with addition of saturated sodium potassium tartrate solution. The precipitated salts were filtered through Celite, and the filtrate was concentrated. Flash chromatography (5% MeOH/CH_2Cl_2) yielded the desired alcohol **22** (1.31 g, 95% yield, 94% de; minor isomer separable by chromatography) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, CH_3, 3), 1.83−2.00 (m, H_β of C-7, 1), 2.35 (ddt, J = 12.5, 9.0, 3.5 Hz, H_α of C-7, 1), 3.31 (ddd, J = 12.0, 10.1, 3.7 Hz, H_β of C-8, 1), 3.37 (b s, OH, 1), 3.58 (ddd, J = 12.0, 9.0, 7.6 Hz, H_α of C-8, 1), 4.058 (d, J = 9.0 Hz, H_β of C-4, 1), 4.061 (t, J = 8.8 Hz, H_α of C-6, 1), 4.36 (d, J = 9.0 Hz, H_α of C-4, 1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.3 (CH_3), 31.8, 42.0, 66.5, 73.1, 74.9, 161.6 (C=O); MS (CI, CH_4) (*m*/*z*) 159 (9), 158 (M+H^+, 100), 85 (5); HRMS calcd for $C_7H_{12}NO_3^+$ 158.0817, found 158.0820. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.20; H, 7.25; N, 8.97.

***cis*-6-(Benzyloxy)-5-methyl-1-aza-3-oxabicyclo[3.3.0]-octan-2-one (23).** To a solution of alcohol **22** (1.18 g, 7.5 mmol) in DMF (15 mL) at room temperature was added NaH (60% dispersion in mineral oil, 382 mg, 9.6 mmol) in one portion. This mixture was allowed to stir for 15 min to permit H_2 gas evolution to proceed to completion. Benzyl bromide (1.1 mL, 9.3 mmol) was then added by syringe, in the process, warming the solution. A catalytic amount of *n*-BuNI (32 mg) was added, and the mixture was allowed to stir at room temperature for 90 min. Reaction was quenched by addition of MeOH (5 mL). The mixture was concentrated and flash chromatography (R_f 0.19 in 2:1 hexanes/ethyl acetate; 33−50% EtOAc/hexanes elution; $KMnO_4$) yielded product **23** (1.67 g, 90%) as a white solid: mp 71.0−71.5 °C; IR (cm^{-1}, KBr pellet) 2985, 2974, 2912, 1764, 1456, 1395, 1343, 1308, 1125, 1101, 1067, 761; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, CH_3, 3), 1.87−2.02 (m, $H_{C\text{-}7}$, 1), 2.30−2.44 (m, $H_{C\text{-}7}$, 1), 3.32 (ddd, J = 11.9, 10.3, 3.6 Hz, $H_{C\text{-}8}$, 1), 3.62 (ddd, J = 11.9, 9.2, 7.6 Hz, $H_{C\text{-}8}$, 1), 3.79 (t, J = 8.5 Hz, $H_{C\text{-}6}$, 1), 4.04 (d, J = 8.9 Hz, H_β of C-4, 1), 4.20 (d, J = 8.9 Hz, H_α of C-4, 1), 4.45 (d, J = 11.8 Hz, CH_2 of Bn, 1), 4.58 (d, J = 11.8 Hz, CH_2 of Bn, 1), 7.27−7.40 (m, Ar-H, 5); MS (CI, CH_4) (*m*/*z*) 276 (22), 249 (21), 248 (M + H^+, 100), 91 (24). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.00; H, 6.92; N, 5.69.

***trans*-3-(Benzyloxy)-*N*-(benzyloxycarbonyl)-2-(hydroxymethyl)-2-methylpyrrolidine (25).** According to a modified procedure of Hirai et al.,[19] a solution of **23** (1.67 g, 6.8 mmol) in 1 N KOH in MeOH (60 mL) was heated to gentle reflux for 16 h. TLC then indicated complete conversion (R_f 0.26 in 18:2:80 MeOH:NEt_3:CH_2Cl_2; ninhydrin). This reaction was concentrated and flash chromatography (10−35% MeOH/CH_2Cl_2) yielded *trans*-3-(benzyloxy)-2-(hydroxymethyl)-2-methylpyrrolidine (**24**) as a clear, slightly yellow gel (1.15 g, 77%): ^{1}H NMR (CD_3OD, 400 MHz) δ 1.19 (s, CH_3, 3), 1.78−1.87 (m, $H_{C\text{-}4}$, 1), 1.94−2.04 (m, $H_{C\text{-}4}$, 1), 2.96−3.10 (m, $H_{C\text{-}5}$,

(19) Hirai, Y.; Terada, T., Amemiya, Y.; Momose, T. *Tetrahedron Lett.* **1992**, *31*, 7893.

(20) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

2), 3.25 (s, CH_2-OH, 2), 3.68 (dd, J = 5.6, 4.9 Hz, CH-OBn, 1), 4.18 (d, J = 11.7 Hz, CH_2 of Bn, 1), 4.30 (d, J = 11.7 Hz, CH_2 of Bn, 1), 6.92−7.04 (m, ArH, 5); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.9 (CH_3), 30.1 (C-3), 43.2 (C-4), 65.0, 71.2, 73.0, 80.8, 125.0, 128.9, 129.5, 139.3; MS (CI, CH_4) (m/z) 222 (M + H^+, 100), 114(22), 107(29), 91(47), 61 (62); HRMS calcd for $C_{13}H_{20}NO_2^+$ 222.1494, found 222.1493.

To amino alcohol **24** (613 mg, 2.8 mmol) in 1:1 THF:H_2O (60 mL) was added K_2CO_3 (2.33 g, 16.9 mmol). This mixture was stirred vigorously as benzyl chloroformate (1.7 mL, 11.9 mmol) was added *via* syringe at room temperature. The reaction was allowed to stir for 1 h, after which TLC (R_f 0.32 in 40% EtOAc/hexanes; $KMnO_4$) indicated complete conversion of starting material. The layers were separated, and the aqueous phase was back-extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (40% EtOAc/hexanes) yielded the title compound **25** as a clear, colorless oil (835 mg, 84%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, CH_3, 3), 1.65−1.92 (m, C_4-H, 1), 2.05−2.15 (m, C_4-H, 1), 3.30 (dt, J = 7.6, 10.8 Hz, C_5-H, 1), 3.55−3.70 (m, C_5-H, one CH_2-OH, and C_3-H, 3), 3.83 (d, J = 11.7 Hz, CH_2-OH, 1), 4.30 (br s, OH, 1), 4.51 (d, J = 11.9 Hz, CH_2 of Bn, 1), 4.62 (d, J = 11.9 Hz, CH_2 of Bn, 1), 5.11 (s, CH_2 of Cbz, 2), 7.25−7.43 (m, ArH, 10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (CH_3), 26.4, 43.7, 66.5, 66.9, 68.0, 72.0, 80.1, 127.4, 127.7, 128.0, 128.4, 128.5, 136.5, 137.9, 155.6 (C=O); MS (CI, CH_4) (m/z) 356 (M + H^+, 47), 324 (25), 313 (23), 312 (86), 276 (15), 248 (71), 91 (100), 79 (13); HRMS calcd for $C_{22}H_{26}NO_4^+$ 356.1862, found 356.1861. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.23; N, 3.94. Found: C, 71.00; H, 7.23; N, 4.03.

***trans*-3-(Benzyloxy)-*N*-(benzyloxycarbonyl)-2-methyl-2-[(acetylthio)methyl]pyrrolidine (26).** To triphenylphosphine (589 mg, 2.2 mmol) in THF (30 mL) was added diethyl azodicarboxylate (354 μL, 2.2 mmol) at 0 °C. After 30 min, alcohol **25** (662 mg, 1.9 mmol) in THF (10 mL) was added to this solution, followed by thiolacetic acid (170 μL, 2.3 mmol). This mixture was allowed to stir at 0 °C for 1 h and then at rt for 32 h. TLC showed partial conversion to product (R_f 0.39 in 20% EtOAc/hexanes; UV/$KMnO_4$). Flash chromatography (20−30% EtOAc/hexanes) yielded product **26** (364 mg, 87% based on consumed starting material) and unreacted alcohol **25** (302 mg, 48%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, CH_3 of a rotamer, 1), 1.41 (s, CH_3 of a rotamer, 2), 1.72−1.84 (m, CH_2CH, 1), 2.00−2.10 (m, CH_2CH, 1), 2.32 (s, SCOMe, 3), 3.20−3.30 (m, NCH_2, 1), 3.58 (s, CH_2S, 2), 3.56−3.68 (m, NCH_2, 1), 3.74 (dd, J = 8.1, 6.4 Hz, CHOBn, 1), 4.57 (s, CH_2 of Cbz, 2), 5.08−5.14 (m, CH_2 of Bn, 2), 7.25−7.42 (m, Ar-H, 10); MS (CI, CH_4) (m/z) 414 (M + H^+, 9), 370 (19), 354 (39), 328 (15), 324 (21), 295 (17), 264 (28), 119 (15), 91 (100); HRMS calcd for $C_{23}H_{28}NO_4S^+$ 414.1739, found 414.1731. Anal. Calcd for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39; S, 7.75. Found: C, 66.40; H, 6.85; N, 3.26; S, 7.40.

***trans*-3-Hydroxy-2-methyl-2-(mercaptomethyl)pyrrolidine Hydrochloride (19·HCl).** Into a solution of acetate **26** (653 mg, 1.6 mmol) in THF (5 mL), ammonia (45 mL) was condensed at −78 °C in a dry ice-2-propanol bath. The solution was then allowed to warm to reflux (dry ice−cold finger condenser), at which time sodium (234 mg, 10.2 mmol) was added in pieces. The blue solution was allowed to stir at reflux for 20 min, and reaction was then quenched by slow addition of degassed methanol (4 mL). Solvent was evaporated by nitrogen overflow, and the residue was passed through a silica gel plug (2 cm) with 20% MeOH/CH_2Cl_2 elution. The resulting solution was then acidified with 1 N HCl in ether (5 mL) and concentrated under vacuum leaving **19**·HCl as a white gum (330 mg, 114%, contaminated with MeOH). This material was used in the complexation reaction without further purification: ^{1}H NMR (CD_3OD, 400 MHz) δ 1.29 (s, CH_3, 3), 1.89 (dddd, J = 13.7, 9.1, 5.8, 4.5 Hz, C_4-H, 1), 2.24 (dddd, J = 13.8, 9.2, 7.2, 5.9 Hz, C_4-H, 1), 2.68 (AB q, $\Delta\nu$ = 22.0 Hz, J = 14.7 Hz, CH_2-S, 2), 3.18−3.33 (m, C_5-H, 2), 4.05 (dd, J = 5.8, 4.4 Hz, CH-OH, 1); MS (CI, CH_4) (m/z) 148 ((M + H^+), 100), 146 (20), 130 (68), 116 (27), 114 (67), 100 (92), 70 (42); HRMS calcd for $C_6H_{14}NOS^+$ 148.0796, found 148.0795.

[*trans*-*N*-Methyl-2-(mercaptomethyl)-4-pyridonato][*trans*-3-hydroxyl-2-methyl-2-(mercaptomethyl)pyrrolidinato]oxorhenium(V) (3a) and [*cis*-*N*-Methyl-2-mercaptomethyl-4-pyridonato][*trans*-3-hydroxyl-2-methyl-2-(mercaptomethyl)pyrrolidinato]oxorhenium(V) (3b). Amino thiol compound **19**·HCl (150 mg, 0.82 mmol) was dissolved in MeOH (10 mL). To this solution were added, in succession, amino thiol **9**·HCl (156 mg, 0.80 mmol), 1 N NaOAc/MeOH (10 mL, 10 mmol), and trichlorobis(triphenylphosphine)oxorhenium(V) (950 mg, 1.14 mmol). The suspension was then refluxed for 20 min and then allowed to cool to rt. Concentration and flash chromatography on a cyanopropyl silica gel column yielded an orange solid product (53.2 mg, 13%) as a mixture of diastereomers, which could be separated by normal phase HPLC (30% (5% *i*-PrOH/CH_2Cl_2)/70% hexane elution; **3b**, t_R = 13.87 min; **3a**, t_R = 17.20 min).

For the *cis* compound **3b**: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.01 (d, J = 0.7 Hz, 13-CH_3, 3), 1.24−1.35 (m, 2α, 1), 2.04 (ddq, J = 12.0, 9.7, 0.7 Hz, 9β, 1), 2.16 (ddd, M of AMX, J = 16.0, 3.8, 2.6 Hz, 4β, 1), 2.33 (s, N-CH_3, 3), 2.37−2.50 (m, 2β, 9α, 2), 2.77 (dd, B of ABX, J = 11.2, 0.7 Hz, 12β, 1), 2.82 (d, B of ABX, J = 13.2 Hz, 6β, 1), 2.87−3.00 (m, 5β, 1), 3.03 (dd, A of ABX, J = 11.0 Hz, 12α, 1), 3.27 (ddd, A of AMX, J = 15.9, 13.0, 0.7 Hz, 4α, 1), 3.33−3.47 (m, 1β, 1), 4.15−4.32 (m, 10β, 8β, 1α, 3), 4.60 (ddd, J = 13.6, 9.3, 7.9 Hz, 8α, 1); HRMS calcd for $C_{13}H_{24}N_2O_3S_2{}^{187}Re^+$ 507.0786, found 507.0779.

For the *trans* compound **3a**: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.99 (d, J = 0.7 Hz, 13-CH_3, 3), 2.01 (dq, J = 12.0, 9.2 Hz, 1), 2.33−2.50 (m, 9β+2, 3), 2.46 (s, NCH_3, 3), 2.73−2.79 (m, 1), 2.78 (d, B of AB q, J = 13.0 Hz, 12α, 1), 2.84 (dd, B of AB q, J = 11.0, 0.7 Hz, 12β, 1), 2.85−3.00 (m, 9α, 1), 3.20 (d, A of AB q, J = 11.0 Hz, 12α, 1), 3.23 (dd, J = 13.0, 5.0 Hz, 6α, 1), 3.95−4.02 (m, 5α, 1), 4.00−4.10 (m, 1), 4.16−4.26 (m, 2), 4.44 (ddd, J = 13.8, 9.3, 7.8 Hz, 8β, 1), 4.52 (ddd, J = 13.9, 6.7, 1.6 Hz, 8α, 1); HRMS calcd for $C_{13}H_{24}N_2O_3S_2{}^{187}Re^+$ 507.0786, found 507.0779.

HPLC Determination of Stability. Stability of complexes **3a** and **3b** were determined by the following procedure. Samples of 0.2 mg of rhenium complex, 0.2 mg estriol (as internal standard), and 0.1 mg bovine albumin (fraction V) were combined in a vial with 1 mL androgen receptor assay buffer (0.01 M Tris, 0.0015 M EDTA, 0.02% NaN_3, 0.01 M thioglycerol, 20 mM sodium molybdate, 10% (v/v) glycerol; pH 7.4)[16] and incubated at 0 °C. At various time intervals samples were then extracted with CH_2Cl_2 (3 × 1 mL), and concentrated to 0.5 mL, and an aliquot (10 μL) was injected into an analytical HPLC column with isocratic elution (35% (5% *i*-PrOH/CH_2Cl_2)/65% hexane).

Androgen Receptor Binding Affinity. These values were determined by a competitive radiometric binding assay, using rat prostate cytosol as a source of receptor, tritium-labeled R1881 as tracer, according to a previously published method.[16]

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Supporting Information Available: Proton NMR spectra for compounds **3a**, **3b**, **9**, and **16** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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