Preparation and Structural Characterization of Monoamine–Monoamide Bis(thiol) Oxo Complexes of Technetium(V) and Rhenium(V)

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We report the design and synthesis of a novel N_2S_2 ligand system for the formation of Re(V) oxo and ^{99}Tc(V) oxo complexes. An *S*,*S*′-bis(trityl) *N*-benzyl monoamine–monoamide (Bn-MAMA′-Tr_2) complex was prepared in four steps from commercially available cysteamine hydrochloride. *S*-Trityl protection of cysteamine hydrochloride followed by N-acylation of the amine function with bromoacetyl bromide provided the corresponding primary bromide, which was then reacted with additional *S*-trityl-protected cysteamine to provide the *S*,*S*′-bis(trityl) monoamine–monoamide ligand (MAMA′-Tr_2). N-Alkylation by nucleophilic displacement with the methanesulfonate of benzyl alcohol gave the *N*-benzyl MAMA′ ligand in the thiol-protected form. Metal incorporation to provide the title compounds consisted of deprotection of the sulfur atoms with $Hg(OAc)_2$ followed by H_2S to provide free bis(thiol) which could then be reacted with the corresponding metals in basic methanolic medium to provide a mixture of *syn*- and *anti*-substituted metal(V) oxo products (Bn-MAMA′–M=O, metal = Re, ^{99}Tc). The two diastereomers could be differentiated by proton NMR due to the upfield shifts of the methylene protons on the endo (*anti*) phenylmethyl substitutent (2.7 and 3.4 ppm) relative to those of the exo- (*syn*-) substituted isomer (4.7 and 5.1 ppm). An unambiguous structural assignment of the *N*-benzyl-MAMA–metal(V)–oxo compounds was established by an X-ray diffraction study on the rhenium compounds **8a-Re** (syn) and **8b-Re** (anti). Crystal data for **8a-Re** (syn): $C_{13}H_{17}N_2O_2S_2Re \cdot {}^1/_6C_2H_6O$, trigonal, $R\bar{3}$ $a = b = 25.961(7)$ Å, $c = 12.392(4)$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$, $V = 7233(12)$ Å^3, $Z=18$, $R = 2.7\%$. Crystal data for **8b-Re** (anti): $C_{13}H_{17}N_2O_2S_2Re$, triclinic, $P\bar{1}$ $a = 6.696(2)$ Å, $b = 8.494(1)$ Å, $c = 13.981(3)$ Å, $\alpha = 104.25(2)°$, $\beta = 103.19(2)°$, $\gamma = 93.38(2)°$, $V = 744.8(6)$ Å^3, $Z = 2$, $R = 1.6\%$.

Introduction

A great number of chelates of technetium and rhenium have been prepared in the search for novel, selective, and effective agents for diagnostic imaging and therapy.[1] Perhaps the most common chelate system used to bind technetium and rhenium in these agents is some form of the N_2S_2 metal(V) oxo system, exemplified by compounds (**1–5**) shown in Figure 1.[2] Quite a variety of these BAT (bis(aminoethanethiol)) and DADT (diamide dithiol) complexes have been prepared, containing the nitrogen function either as an amine or an amide. In most cases, the complexes bearing both nitrogens as amino functions provide neutral metal(V) oxo complexes, as the amines are sufficiently basic that one will remain protonated. By contrast, in the diamide complexes, both of the more acidic amide functions deprotonate, resulting in an anionic metal(V) oxo salt. One example of a MAMA (monoamine–monoamide) complex (**5**) bearing one of the nitrogens as an amine and the second nitrogen as an amide has been reported.[3]

In connection with our interest in the preparation of technetium- and rhenium-labeled steroids as agents for the diagnosis and therapy of breast cancer, we recently reported the synthesis of three conjugates between a progestin and a BAT complex.[4] Although the metal complex has a molecular mass and a steric volume nearly equal to those of the steroid, one of these systems **6** (Figure 2), based on the antiprogestin RU486, maintains a nanomolar binding affinity for the progesterone receptor. In fact, one diastereomer of **6** binds to the progesterone receptor with 3-fold higher affinity than the natural hormone itself. This conjugate, however, is very lipophilic, as the metal chelate system increases the octanol/water partition coefficient by a factor of 100. As a result, in tissue distribution studies carried out in rats, the nonspecific binding levels of this compound are quite high.[5]

As an attempt to lower the lipophilicity of this high-binding progestin–metal complex conjugate, we sought to develop a more

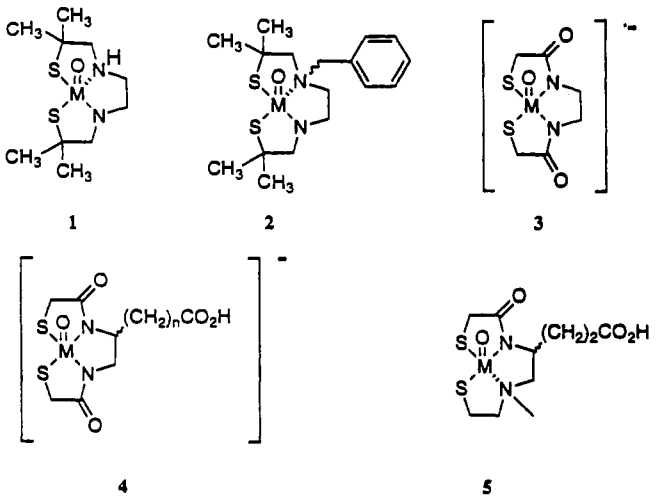

Figure 1. Representative tetradentate N_2S_2–technetium(V) and –rhenium(V) oxo complexes.

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(4) DiZio, J. P.; Fiaschi, R.; Davison, A.; Jones, A. G.; Katzenellenbogen, J. A. *Bioconjugate Chem.* **1991**, *2*, 353–366.

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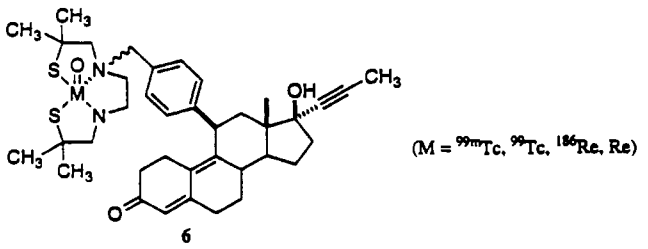

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Figure 2. Structure of the previously reported[4,5] conjugate between a progestin and an N_2S_2 (BAT) metal complex.

7, R= H, R'= H
7a, R= H, R'= CPh_3
7b, R= CH_2Ph, R'= CPh_3
7c, R= CH_2Ph, R' = H

8a, R = CH_2Ph (syn)
8b, R = CH_2Ph (anti)

Figure 3. Structures of the MAMA′ ligand system and the corresponding *N*-benzyl metal(V) oxo complexes.

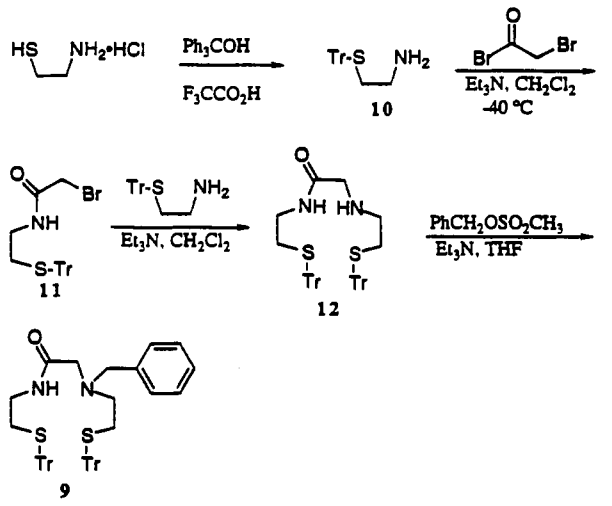
polar yet neutral chelate system for which we envisioned a bifunctional system combining both an amine and an amide in the molecule (a MAMA system). A search of the literature led to only one neutral compound containing both an amine and amide function in the same chelate core, the MAMA complex **5**. The monoamine–monoamide bis(ethanethiol) compound **7a** (Figure 3), which we had chosen to attatch to the steroid, is isomeric with this MAMA chelate and has not been reported or fully characterized;[6] we give it the designation MAMA′ to indicate its isomeric relationship to the MAMA chelate. Thus, herein we report the synthesis of the MAMA′ chelate system in its *S*-trityl-protected form **7a** and its *N*-benzyl analog **7b**, as well as the preparation and spectroscopic and structural characterization of the oxo metal complexes **8a** (syn) and **8b** (anti) (M = ^{99}Tc, Re). This ligand system has now been used to prepare a conjugate analogous to **6** containing Re, ^{99}Tc, and ^{99m}Tc. The synthesis as well as in vitro and in vivo biological studies on these progestin–MAMA′ metal complexes will be reported elsewhere.

Results and Discussion

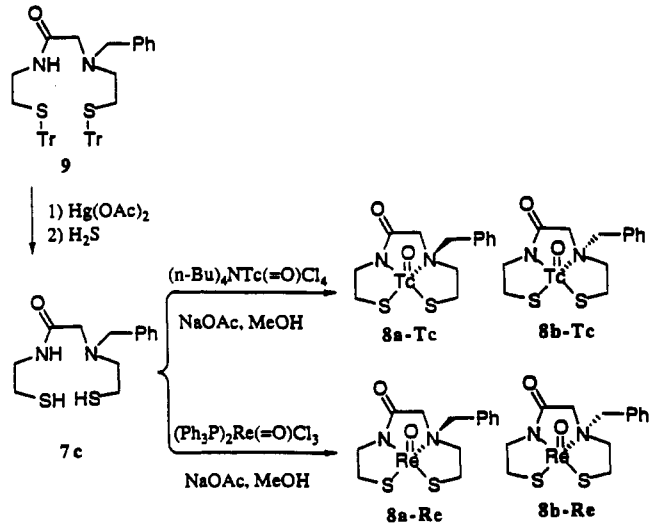
Synthesis of the Monoamine–Monoamide Bis(thiol) Chelate and Its Oxorhenium(V) and Oxotechnetium(V) Complexes. The synthesis of *S*,*S*′-bis(trityl)-*N*-benzyl-MAMA′ (**9**) is shown in Scheme 1. Cysteamine hydrochloride was *S*-trityl-protected by allowing it to react with triphenylmethanol in trifluoroacetic acid, to provide upon basic workup the crystalline free amine **10**. N-Acylation of amine **10** with bromoacetyl bromide in the presence of triethylamine provided the primary bromide **11**, which was then treated with an additional equivalent of amine **10** under more vigorous conditions, to give the *S*,*S*′-bis(trityl) monoamine–monoamide ligand (MAMA′-Tr_2) **12**. Nucleophilic displacement of the methanesulfonate of benzyl alcohol gave the *S*,*S*′-bis(trityl) *N*-benzyl monoamine–monoamide ligand (Bn-MAMA′-Tr_2) **9**.

Incorporation of the metal(V) oxo core into the ligand system (Scheme 2) requires prior deprotection of the sulfur atoms of **9**, which is accomplished by mercury salt formation (treatment with $Hg(OAc)_2$) followed by cleavage of the salt with H_2S. This

Scheme 1



Scheme 2



provided the corresponding bis(thiol) **7c**, which was used directly in the metal incorporation reactions. Rhenium(V) oxo incorporation consisted of incubation of the ligand in basic methanolic solution with trichlorobis(triphenylphosphine)rhenium(V) oxide[7] and isolation of the resulting metal–oxo chelates **8a** and **8b** by silica gel column chromatography. The *syn* **8a** and *anti* **8b** products (*N*-alkyl substituent relative to the metal–oxo bond) could be separated by flash column chromatography, although HPLC was used to determine the product ratio of the two stereoisomers. In a similar manner, the technetium-99 complexes could be formed by treating the free bis(thiol) **7c** with tetrachloro(tetra-*n*-butylammonium)technetium(V) oxide in basic methanol. The product isomers could be isolated and separated in a manner similar to that for the analogous rhenium compounds, while exercising the precautions necessary for working with radioactive compounds.

X-ray Crystallographic Study of 8a-Re (*Syn*) and 8b-Re (*Anti*). Proposed structural models for **8a-Re** (syn) and **8b-Re** (anti) show the metal in the V oxidation state with the two sulfur atoms as well as the amide nitrogen bound to the rhenium oxo metal center (Figure 4). Details of the crystal data, measurement of intensities, and data processing are summarized in Table 1. The final atomic coordinates with thermal parameters, bond distances, and bond angles are listed in Tables 2–4, respectively. The Re=O distances of 1.683(4) and 1.680(2) Å, respectively, are consistent

(5) DiZio, J. P.; Anderson, C. J.; Davison, A.; Ehrhardt, G. J.; Carlson, K. E.; Welch, M. J.; Katzenellenbogen, J. A. *J. Nucl. Med.* **1992**, *33*, 558–569.

(6) We recently learned from A. Davison (MIT) that the MAMA′ chelate and its oxo-^{99}Tc complex have been prepared and characterized in his laboratories; only the more abundent *syn* diastereomer was isolated (Joel Wolfe, Ph.D. Thesis, Massachusetts Institute of Technology, 1991).

(7) Johnson, N. P.; Lock, C. J. L.; Wilkinson, G. *Inorg. Synth.* **1967**, *9*, 145–148.

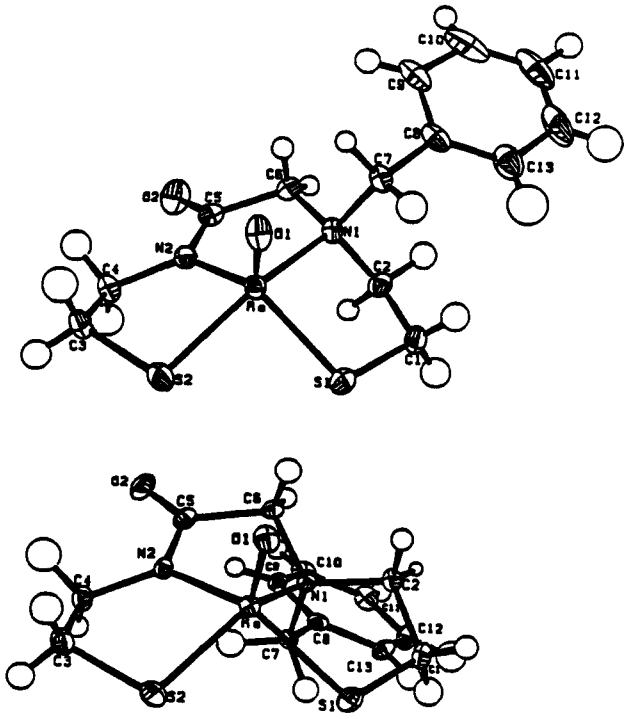


Figure 4. ORTEP drawings of compounds **8a-Re** (syn) (top) and **8b-Re** (anti) (bottom).

Table 1. Summary of Crystallographic Data for Compounds **8a–Re** and **8b–Re**

	8a	**8b**
formula	$C_{13}H_{17}N_2O_2S_2Re \cdot {}^1/_6C_3H_6O$	$C_{13}H_{17}N_2O_2S_2Re$
crystal system	trigonal	triclinic
space group	$R\bar{3}$	$P\bar{1}$
a, Å	25.961(7)	6.696(2)
b, Å	25.961(7)	8.494(1)
c, Å	12.392(4)	13.981(3)
α, deg	90	104.25(2)
β, deg	90	103.19(2)
γ, deg	120	93.38(2)
V, Å^3	7233(12)	744.8(6)
Z	18	2
density calcd, g/cm^3	2.038	2.154
crystallizing solvent	acetone	acetone
crystal habit	prismatic (purple-red)	prismatic (orange-red)
crystal dimens, mm	0.2 × 0.3 × 0.4	0.2 × 0.2 × 0.3
μ, cm^{-1}	79.17	85.31
transm factor range	0.301–0.143 (numerical)	0.316–0.152
extinction	not applied	1.1(1) × 10^{-7}
2θ limit, deg (octants)	48.0 ($\pm h,-k,-l$)	49.0 ($\pm h,\pm k,-l$)
intensities (unique, R_i)	4183 (2519, 0.030)	2670 (2471, 0.015)
intensities > $2.58\sigma(I)$	2140	2311
R (all intensities)	0.027 (0.035)	0.016 (0.018)
R_w (for $w = 1/\sigma^2(F_o) + pF_o^2$)	0.029 (p = 0.01)	0.020 (p = 0.01)
max/min density of ΔF map, e/Å^3	0.82/–0.86	0.70/–0.84

with a rhenium–oxygen bond order of 2.[8] The tertiary amine nitrogen–metal center bond order is low, with interatomic Re–N distances of 2.182(5) and 2.151(3) Å, respectively. The four heteroatom metal core of the complexes is oriented in a piano stool-like conformation with the metal center residing 0.75 Å above a best fit plane through the heteroatoms. The most significant difference between the two compounds is the orientation of the *N*-benzyl moiety. The *syn* isomer extends the bulky aromatic ring away from the central core, while the *anti* isomer is forced to position the bridging methylene group under the Re=O bond in order to minimize the interactions of the aromatic ring with the rest of the complex.

(8) Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1991**, *16*, 146–153.

Nuclear Magnetic Resonance Spectroscopy. Complete proton chemical shift assignments of the *syn*-(benzyl-substituted-MAMA′)Re=O complex were based on data obtained from 2D NMR (COSY, HETCOR) experiments, as well as single resonance proton–proton decoupling experiments and 1D nOe difference spectra. Proton assignments were coupled with carbon assignments in the following manner. Analysis of the proton 2D COSY indicated four isolated aliphatic spin systems—two methylene and two ethylene—as well as the aromatic protons. The positional assignment of protons within the ethylenic spin systems relied on ^{13}C chemical shift data to assign the upfield carbons next to the sulfur atoms, followed by ^{13}C–^1H HETCOR data to identify the specific protons coupled to these carbons. Once the protons of each ethylene unit were assigned to specific carbons, the regio position of each ethylenic spin system (amino or amido) was determined by proton 1D nOe experiments: the amino ethylene protons displayed marked nOe interactions with both of the methylene units, while the amido ethylene side showed no observable nOe interactions with other protons in the molecule. Assignment of the proton-coupling constants was made more difficult by the compact tricyclic chelate center, which caused significant deviations from simple first-order coupling patterns. Theoretical vicinal coupling constants, obtained by entering torsional angles measured from the X-ray crystal coordinates into the Karplus equation,[9] were compared to experimental NMR data and also used to verify assignments.

Protons residing on the endo face of the tricyclic ring system showed significant upfield shifts from their geminally coupled counterparts residing on the exo face. This phenomenon has been previously noted for *N*-methyl substituted diaminedithiol complexes of technetium.[10] Confirmation of this trend was accomplished by the analysis of nOe interactions of the proton at 3.08 ppm of C_2. Since this proton shows nOe to both the aromatic ring and one of the C_7 benzylic protons, it was assigned to the exo face of the molecule. Thus, upfield chemical shift of the remaining C_2 proton (δ 1.5) caused by anisotropic effects of the Re=O core was consistent with assignment of the proton to the endo face of the molecule. The remaining protons of this ethylene unit on C_1 were assigned by coupling constant information, while the protons of C_3 and C_4 were assigned by chemical shift analogy. The benzylic methylene protons are of particular interest, since the chemical shifts are also unique for each diastereoisomer, due to similar anisotropy effects caused by the Re=O core. The protons associated with the *syn* diastereomer **8a** resonate at 5.1 and 4.7 ppm, while the methylene protons tucked completely under the Re=O core of the *anti* diastereomer **8c** show significant upfield shifts to 3.4 and 2.7 ppm. These characteristic chemical shifts can be used as a tool in determining the orientation of the *N*-alkyl substituent relative to the rhenium oxo core in these diastereomers as well as in related compounds.

Experimental Section

General Procedures. All operations were carried out under an atmosphere of dry nitrogen gas unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane (CH_2Cl_2), triethylamine, and 1,2-dichloroethane were distilled from calcium hydride, while other reagents were used as received, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel F-254 glass-backed plates and visualized by UV illumination at 254 nm and/or staining with phosphomolybdic acid (PMA), anisaldehyde, or iodine reagents. Flash chromatography was performed according to the method of Still,[11] using Merck silica gel (0.040–0.063 mm). High-performance liquid chromatography (HPLC) was performed isocratically on a Spectra Physics Model 8700 liquid chromatograph with an analytical (4.6 × 250 mm Whatman

(9) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11; *J. Am. Chem. Soc.* **1963**, *85*, 2870.

(10) Lever, S. Z.; Baidoo, K. E.; Mahmood, A. *Inorg. Chim. Acta* **1990**, *176*, 183–184.

(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

Table 2. Fractional Atom Coordinates and Isotropic Thermal Parameters from the Refined Anisotropic Parameters ($\times 10^3$ Å^2) for the Non-Hydrogen Atoms (with Esd's; U_{eq} Estimated as $^1/_3$[trace(U)])

	8a-Re				8b-Re			
atom	*x*	*y*	*z*	U_{eq}	*x*	*y*	*z*	U_{eq}
Re	0.17448(1)	0.28047(1)	0.52657(2)	23.6(8)	0.89905(2)	0.54895(2)	0.76954(1)	16.13(3)
S1	0.26570(8)	0.35445(7)	0.4776(1)	32.6(8)	0.8037(2)	0.4684(1)	0.59514(7)	24.61(6)
S2	0.19406(9)	0.31762(8)	0.6969(1)	37(9)	0.7721(2)	0.3057(1)	0.78146(8)	27.28(6)
O1	0.1177(2)	0.2880(2)	0.4803(3)	39(2)	1.1584(4)	0.5735(3)	0.8063(2)	27(5)
O2	0.1430(2)	0.1129(2)	0.5874(4)	48(5)	0.7435(5)	0.8745(3)	0.9980(2)	32(5)
N1	0.1869(2)	0.2317(2)	0.3954(4)	24(8)	0.7651(4)	0.7621(3)	0.7411(2)	15(8)
N2	0.1562(2)	0.2061(2)	0.6022(4)	24(8)	0.7874(4)	0.6342(4)	0.8901(2)	18(8)
C1	0.2824(3)	0.3239(3)	0.3596(5)	32(8)	0.7963(6)	0.6668(5)	0.5639(3)	25(2)
C2	0.2519(3)	0.2573(3)	0.3709(5)	29(2)	0.8504(6)	0.8074(5)	0.6600(3)	21(8)
C3	0.1452(3)	0.2488(3)	0.7694(5)	37(2)	0.7544(7)	0.3610(5)	0.9148(3)	28(8)
C4	0.1528(3)	0.1999(3)	0.7218(5)	33(2)	0.6925(6)	0.5299(5)	0.9422(3)	26(5)
C5	0.1529(3)	0.1595(3)	0.5472(5)	25(5)	0.7843(5)	0.7989(5)	0.9206(3)	20(5)
C6	0.1604(3)	0.1682(3)	0.4279(5)	26(8)	0.8367(6)	0.8825(5)	0.8427(3)	18(5)
C7	0.1538(3)	0.2370(3)	0.2969(5)	30(8)	0.5290(5)	0.7344(4)	0.7103(3)	17(8)
C8	0.1582(3)	0.2062(3)	0.1975(5)	40(5)	0.4266(5)	0.8835(4)	0.6986(3)	16(8)
C9	0.1196(4)	0.1462(4)	0.1809(6)	55(5)	0.3749(5)	0.9880(5)	0.7815(3)	19(5)
C10	0.1272(5)	0.1200(5)	0.0876(7)	83(5)	0.2729(6)	1.1213(5)	0.7687(3)	22(8)
C11	0.1694(5)	0.1514(5)	0.0133(7)	87(8)	0.2208(6)	1.1518(5)	0.6748(3)	28(2)
C12	0.2048(4)	0.2101(5)	0.0278(6)	75(8)	0.2669(6)	1.0482(5)	0.5920(3)	28(5)
C13	0.2003(3)	0.2381(4)	0.1203(6)	55(2)	0.3713(6)	0.9154(5)	0.6048(3)	21(2)

Table 3. Intramolecular Distances (Å, with Esd's) between Non-Hydrogen Atoms

	8a-Re	8b-Re		8a-Re	8b-Re
Re–S1	2.262(2)	2.2886(9)	Re–N1	2.182(5)	2.151(3)
Re–S2	2.270(2)	2.2464(10)	Re–N2	1.978(5)	1.990(3)
Re–O1	1.683(4)	1.680(2)			

Table 4. Selected Intramolecular Bond Angles (deg, with Esd's)

	8a-Re	8b-Re
S1–Re–S2	88.39(6)	92.49(4)
S1–Re–O1	114.6(2)	107.78(10)
S1–Re–N1	84.1(1)	80.66(8)
S1–Re–N2	126.4(1)	141.84(9)
S2–Re–O1	106.9(2)	110.36(10)
S2–Re–N1	150.8(1)	134.44(8)
S2–Re–N2	82.4(1)	82.96(9)
O1–Re–N1	101.9(2)	114.6(1)
O1–Re–N2	118.6(2)	109.3(1)
N1–Re–N2	79.6(2)	76.1(1)

Partisil-5 silica gel) or a semipreparative (9.2 × 500 mm Whatman Partisil-5 silica gel) column with the elutent monitored at 254 nm. Melting points were recorded on a Thomas Hoover Uni-Melt apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity 400 (400 MHz) spectrometer with chemical shifts reported relative to a tetramethylsilane internal standard or the proton resonance resulting from incomplete deuteration of the NMR solvent (δ scale; *J* values in hertz). Low-resolution electron impact mass spectra (LREIMS) were obtained on a Finnigan MAT-CH-5 spectrometer. High-resolution EIMS (HREIMS) were obtained on a Varian MAT-731 spectrometer. Both low- and high-resolution fast atom bombardment (FAB) MS were obtained on a VG instrument (ZAB HF), employing a dithioerythritol matrix. Technetium-99 as sodium pertechnetate was obtained from A. Davison (MIT); *caution must be exercised in handling this radioisotope.* Elemental analyses were performed by the Microanalytical Service of the University of Illinois. Crystallographic measurements were made on an Enraf-Nonius CAD4 automated κ-axis diffractometer equipped with graphite monochromated Mo radiation, $\lambda(K\bar{\alpha})$ = 0.710 73 Å.

Preparation of *S*-(Triphenylmethyl)-2-aminoethanethiol (10). To a stirred room-temperature solution of cysteamine hydrochloride (11.36 g, 0.100 mol) in trifluoroacetic acid (116 mL, 1.50 mol) was added triphenylmethanol (26.0 g, 0.100 mol) as a solid. After being stirred 1 h, the reaction mixture was concentrated under reduced pressure and the resulting dark orange oil, diluted with EtOAc (100 mL), was washed with 3 N aqueous NaOH (4 × 50 mL), water (2 × 50 mL), $NaHCO_3$(aq) (50 mL), and brine (50 mL). The aqueous washes were back-extracted with EtOAc (50 mL) and the combined organic extracts dried over $MgSO_4$. The product-containing solution was filtered through a pad of Celite, and colorless crystalline product was isolated after the solution was allowed to stand in a freezer. Two additional crops of crystals were isolated to provide 28.5 g (89%) of **10**: ^{1}H NMR (δ, $CDCl_3$) 7.75 (b s, 2H), 7.40 (b d, *J*=7.3, 6H), 7.26 (dd, *J*= 7.8, 7.3, 6H), 7.19 (ddt, *J*= 7.3, 7.1, 2.2, 3H), 2.58 (dd, *J*= 7.0, 6.9, 2H), 2.24 (dd, *J*= 7.0, 6.9, 2H); ^{13}C NMR (δ, $CDCl_3$) 144.0, 129.4, 128.2, 127.0, 67.3, 38.4, 29.0; LRFABMS (*m/z*) 321 (18) (M + 2), 320 (71) (M + 1), 275 (17), 245 (62), 244 (100), 243 (100) [$(C_6H_5)_3C^+$], 242 (58), 241 (57); HRFABMS (*m/z*) calcd for $C_{21}H_{22}NS$ 320.1473, Found 320.1485.

Preparation of *N*-(2-Bromoacetyl)-*S*-(triphenylmethyl)-2-aminoethanethiol (11). To a stirred –20 °C solution of bromoacetyl bromide (1.09 mL, 12.5 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise over 15 min a solution of protected aminoethanethiol **10** (4.0 g, 12.5 mmol) and triethylamine (1.74 mL, 12.5 mmol) in dry CH_2Cl_2 (15 mL). The mixture was allowed to warm to room temperature and stir for 15 min, at which time the reaction was quenched by the addition of water (50 mL). The layers were separated, and the organic portion was washed with 1 N aqueous HCl, water, $NaHCO_3$(aq), and brine (50 mL each). The organic solution was dried over $MgSO_4$, filtered, and concentrated to a volume of 35 mL. Trituration with hexanes (100 mL) provided white crystals (2.6 g, 47.2%) upon standing at room temperature, with a second crop of crystals (1.5 g, 27.2%) after storing overnight in the freezer: IR (cm^{-1}, KBr pellet) 3342, 3049, 1649, 1581, 1485, 1435, 700; ^{1}H NMR (δ, $CDCl_3$) 7.43 (b d, *J* = 7.1, 6H), 7.30 (b dd, *J* = 8.1, 7.0, 6H), 7.23 (ddt, *J* = 8.3, 6.1, 1.2, 3H), 6.57 (s, 1H), 3.81 (s, 2H), 3.11 (q, *J* = 6.3, 2H), 2.43 (dd, *J* = 6.3, 5.6, 2H); ^{13}C NMR (δ, $CDCl_3$) 165.1, 144.5, 129.5, 128.0, 126.8, 66.9, 38.7, 31.6, 29.1. Anal. Calcd for $C_{23}H_{22}BrNOS$: C, 62.73; H, 5.04; N, 3.18. Found: C, 62.73; H, 5.02; N, 3.16.

Preparation of *N*-[2-((2-((Triphenylmethyl)thio)ethyl)amino)acetyl]-*S*-(triphenylmethyl)-2-aminoethanethiol (MAMA′-Tr$_2$) (12). To a solution of bromide **11** (4.27 g, 9.70 mmol) and triethylamine (2 mL, 14.3 mmol) in CH_2Cl_2 (30 mL) was added amine **10** (3.10 g, 9.70 mmol) as a suspension in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 24 h, the reaction was quenched with water (50 mL), and the layers were separated. The organic portion was washed with $NaHCO_3$(aq) (2 × 50 mL), water (50 mL), and brine (50 mL) and dried over $MgSO_4$. Concentration followed by flash chromatography (silica, 50% EtOAc/hexanes) provided a white foam (4.72 g, 71.7%): ^{1}H NMR (δ, $CDCl_3$) 7.43–7.35 (m, 12H), 7.29–7.17 (m, 15H), 3.06 (ddd, *J* = 6.3, 6.3, 6.3, 2H), 3.03 (s, 2H), 2.90 (b s, 1H), 2.43 (dd, *J* = 6.4, 5.9, 2H), 2.35 (m, 4H); ^{13}C NMR (δ, $CDCl_3$) 162.7, 144.6, 129.6, 127.9, 126.7, 66.6, 57.0, 54.8, 38.5, 31.3; LRFABMS (*m/z*) 680 (23) (M + 2), 679 (46) (M + 1), 275 (30), 245 (97), 244 (100), 243 (100), 242 (71), 241 (96), 239 (56); HRFABMS (*m/z*) calcd for $C_{44}H_{43}N_2OS_2$ 679.2817, found 679.2830.

Preparation of *N*-[2-((Phenylmethyl)(2-((triphenylmethyl)thio)ethyl)-amino)]acetyl]-*S*-(triphenylmethyl)-2-aminoethanethiol (Bn-MAMA′-Tr$_2$) (9). To a stirred solution of MAMA′-Tr$_2$ (**12**) (480 mg, 0.70 mmol) in 1,2-dichloroethane (75 mL) was added benzyl methanesulfonate (66 mg, 0.35 mmol), and the mixture was heated to 65 °C for 45 min. The reaction mixture was then concentrated to dryness in vacuo and purified

by flash chromatography (silica, 25–50% EtOAc/hexanes) to provide a white foam (119 mg, 70%) along with some recovered MAMA′-Tr_2 starting material: ^{1}H NMR (δ, $CDCl_3$) 7.62 (t, J = 6, 1H), 7.52 (m, 14H), 7.35–7.30 (m, 21H), 3.54 (s, 2H), 3.12 (q, J = 6, 2H), 3.01 (s, 2H), 2.56 (t, J = 7, 2H), 2.46 (dd, J = 6, 13, 4H); ^{13}C NMR (δ, $CDCl_3$) 170.46, 144.58, 144.56, 137.31, 129.41, 128.89, 128.83, 128.36, 127.79, 127.32, 126.58, 126.56, 66.67, 66.52, 58.47, 57.47, 37.62, 31.83, 29.73; LRFABMS (m/z) 769 (M + 1) (6), 244 (22), 243 (100), 155 (14); HRFABMS (m/z) calcd for $C_{51}H_{49}N_2OS_2$ 769.3286, found 769.3298.

Preparation of *N*-[2-((Phenylmethyl)(2-mercaptoethyl)amino)acetyl]-2-aminoethanethiol (Bn-MAMA′) (7c). To a stirred solution of Bn-MAMA′-Tr_2 (**9**) (55 mg, 0.07 mmol) in a 1:1 mixture of EtOAc and EtOH (2 mL) was added a solution of mercury(II) acetate (57 mg, 0.18 mmol) in EtOH (1 mL). The reaction mixture was heated to reflux for 20 min, and after it was cooled to room temperature, gaseous H_2S was bubbled through the solution until the reaction mixture was completely black. The vessel was capped, the mixture was stirred for 10 min and passed through a pad of Celite with EtOAc (25 mL), and the solution was concentrated in vacuo. The product was purified by passing the concentrate, dissolved in $CHCl_3$, through a short plug of silica, eluting with MeOH/$CHCl_3$ (1.5:100) to provide **7c** (11.8 mg, 58%) as an oil with a strong odor. The product was used without further purification or storage in the subsequent metal incorporation reactions: LREIMS (10 eV) (m/z) 284 (M^+) (4), 251 (–HS) (25), 250 ($-H_2S$) (38), 237 ($-CH_2SH$) (100), 193 ($-CH_2Ph$) (10); HREIMS (m/z) calcd for $C_{13}H_{20}N_2OS_2$ 284.101 70, found 284.101 66.

Preparation of[*N*-(2-((Phenylmethyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (Bn-MAMA′-ReO) (8a-Re (*Syn*) and 8b-Re (*Anti*)). To a stirred solution of ligand **7c** (74 mg, 0.26 mmol) in MeOH (20 mL) was added 1 N NaOAc in MeOH (4 mL, 4 mmol) followed by solid trichlorobis(triphenylphosphine)rhenium(V) oxide (260 mg, 0.31 mmol). The reaction was heated to 80 °C for 2 h, at which time the greenish-yellow color of the starting metal compound had been replaced by a brownish-purple color. After being cooled to room temperature, the reaction mixture, diluted with EtOAc (50 mL), was washed with water, and the organic portion was separated from the mixture and dried over $MgSO_4$. Filtration through Celite followed by concentration in vacuo provided a brown oil. Flash column chromatography (silica, 1:1 EtOAc/hexanes) gave *syn* isomer **8a-Re** as a purple solid powder (85 mg, 65%) as well as *anti* isomer **8b-Re** as an orange solid powder (6 mg, 5%). The solids could be recrystallized from acetone to provide crystals of suitable quality for structural analysis.

Structures **8a-Re** and **8b-Re** were solved using Patterson methods, SHELXS-86. Compound **8a-Re** crystallized with an acetone solvate molecule disordered about the rotoinversion center; disordered solvate H atoms were not included in structure factor calculations. Least-squares refinement using SHELXS-76 for both structures included all ordered atomic positions. Final difference Fourier maps had no significant features. Final analyses of variance showed no systematic errors. HPLC analysis showed a product ratio of 14:1 *syn* to *anti*.

8a-Re (syn): IR (cm^{-1}, KBr pellet) 955; ^{1}H NMR (δ, $CDCl_3$) 7.54–7.43 (m, 5H, Ar), 5.11 (d, J = 14.2, 1H, C_7–H facing CH_2S), 5.00 (d, J = 16.2, 1H, $C_{6\beta}$–H), 4.68 (dd, J = 14.1, 1.0, 1H, C_7–H facing CH_2C=O), 4.61 (ddd, J = 13.5, 13.5, 8.0, 1H, $C_{4\beta}$–H), 4.12 (m, 1H, $C_{3\beta}$–H), 3.82 (d, J = 16.3, 1H, $C_{6\alpha}$–H), 3.72 (ddd, J = 13.3, 13.0, 3.8, 1H, $C_{1\beta}$–H), 3.23 (m, 2H, $C_{3\alpha}$–H and $C_{4\alpha}$–H), 3.08 (dd, J = 12.6, 3.8, 1H, $C_{2\beta}$–H), 2.90 (dd, J = 13.3, 4.5, 1H, $C_{1\alpha}$–H), 1.50 (ddd, J = 12.6, 13.0, 4.5, 1H, $C_{2\alpha}$–H); ^{13}C NMR (δ, $CDCl_3$) 186.80 (C=O), 131.64 (Ar), 130.28 (Ar), 130.17 (Ar), 129.48 (Ar), 66.84 (C_6), 66.70 (C_7), 62.58 (C_2), 60.07 (C_4), 48.48 (C_3), 39.53 (C_1); UV λ_{max} 236 nm, ϵ 13 480, λ_{max} 376 nm, ϵ 3794; LRCIMS (m/z) 487 (7), 486 (12), 485 (69), 484 (22), 483 (41), 482 (9); HRCIMS (m/z) calcd for $C_{13}H_{18}N_2O_2{}^{187}ReS_2$ 485.0367, found 485.0352.

8b-Re (anti): IR (cm^{-1}, KBr pellet) 980; ^{1}H NMR (δ, $CDCl_3$) 7.48–7.41 (m, 3H, Ar, 7.23–7.18 (m, 2H, Ar), 4.89 (d, J = 14.3, 1H), 4.34 (dd, J = 14.3, 1.7, 1H), 4.31 (m, 1H), 3.86 (ddd, J = 13.1, 11.3, 5.6, 1H), 3.76 (m, 1H), 3.62 (dd, J = 12.7, 5.6, 1H), 3.56 (dd, J = 13.1, 7.0, 1H), 3.38 (dd, J = 13.9, 2.1, 1H), 3.35 (m, 1H), 3.14 (m, 2H), 2.67 (dd, J = 13.9, 1.1, 1H); ^{13}C NMR (δ, $CDCl_3$) 184.58 (C=O), 132.40 (Ar), 130.26 (Ar), 129.37 (Ar), 126.45 (Ar), 65.39, 60.86, 59.82, 54.27, 47.28 (C_3), 40.38 (C_1); LRCIMS (m/z) 487 (10), 486 (19), 485 (100), 484 (30), 483 (63), 482 (11).

Preparation of[*N*-(2-((Phenylmethyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]technetium(V)-99 Oxide (Bn-MAMA′-^{99}TcO) (8a-Tc (*Syn*) and 8b-Tc (*Anti*)). To a stirred solution of ligand **7c** (14 mg, 0.05 mmol) in MeOH (4 mL) was added 1 N NaOAc in MeOH (0.2 mL, 0.2 mmol) followed by solid (tetra-*n*-butylammonium)tetrachlorotechnetium(V)-99 oxide (25 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 15 min, diluted with EtOAc (25 mL), and washed with water, and the organic portion was dried over $MgSO_4$. The dried organics were passed through a plug of silica with EtOAc and concentrated in vacuo prior to injection on the HPLC column to provide a yellow solid (16 mg, 81%). HPLC chromatography (Whatman Partisil M9 silica gel column, 35% (1:20 iPrOH/CH_2Cl_2)/65% hexanes, 5 mL/min) separated the two diastereomers. Compounds **8a-Tc** and **8b-Tc** were found to form as a 5:1 mixture. The major *syn* isomer eluted t_R = 10 min while the minor *anti* isomer eluted t_R = 29 min.

8a-Tc: ^{1}H NMR (δ, $CDCl_3$) 7.51 (b s, 5H), 5.24 (d, J = 14.2, 1H), 4.89 (d, J = 16.2, 1H), 4.84 (dd, J = 14.2, 1.2, 1H), 4.52 (d, J = 6.6, 1H), 4.00 (dd, J = 9.3, 2.4, 1H), 3.90 (td, J = 13.2, 3.8, 1H), 3.50 (d, J = 6.3, 1H), 3.49 (m, 1H), 3.38 (d, J = 16.2, 1H), 3.24 (dd, J = 12.7, 3.1, 1H), 3.04 (dd, J = 13.8, 4.0, 1H), 1.55 (tdd, J = 12.9, 4.7, 1.3, 1H); LRFABMS (m/z) 397 (M + 1) (16), 305 (M – CH_2Ph) (5); HRFABMS (m/z) calcd for $C_{13}H_{18}N_2O_2{}^{99}TcS_2$ 396.9872, found 396.9874.

8b-Tc: LRFABMS (m/z) 397 (M + 1) (23), 305 (M – CH_2Ph) (11); HRFABMS (m/z) calcd for $C_{13}H_{18}N_2O_2{}^{99}TcS_2$ 396.9872, found 396.9874.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles for compounds **8a-Re** and **8b-Re** (14 pages). Ordering information is given on any current masthead page.