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SYNTHESIS OF TETRADENTATE BISAMINO-BISTHIOL COMPLEXES OF OXORHENIUM(V) AS STRUCTURAL MIMICS OF STEROIDS.

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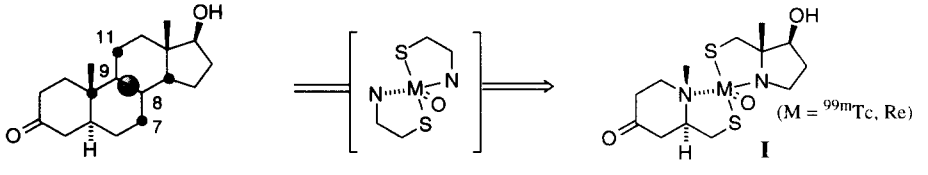
Abstract: Two tetradentate chelate systems have been synthesized in order to prepare metal complexes with oxorhenium(V) whose structures will mimic that of steroids. The chelate system with amide/amine/thioether/thiol donor sites failed to give a stable complex, but the corresponding diamine chelate gave a stable complex.

Until recently, radiopharmaceuticals prepared from the widely available radionuclide technetium-99m have generally been rather simple inorganic complexes or organometallic species, and their distribution for imaging has been based on differential permeability and metabolism.[1] Because of their bulk and hydrophobicity, these complexes are poorly suited for the labeling of receptor-binding radiopharmaceuticals, such as ligands for steroid or neurotransmitter receptors, by a simple *conjugate* approach: The attachment of the receptor ligand to the metal complex results in conjugates that are so large (MW generally exceeds 700) that their receptor binding is often low, their non-specific binding is high, and their transport and distribution properties are poor.[2] Such considerations led us to design metal-labeled steroid receptor radiopharmaceuticals in which the metal complex was *integrated* into the structure of the steroid.[3]

Our initial design paradigm (Design A) involved the replacement of the *trans*-decalin BC ring system of a steroid with a prototypical bis(aminothiol) complex of oxorhenium or oxotechnetium; this approach recognized that the dimensions of such a square planar complex closely matched the dimensions of the decalin system. This design leads to metal complexes of a *heterobisbidentate* amino thiol nature, such as **I**, whose structure—that is, overall size, shape, and A- and D-ring peripheral functionality—mimics that of a steroid quite closely. Recently, we have overcome a number of synthetic and stereochemical problems and have succeeded in preparing both model systems as well as steroid mimics according to this design,[3] including the synthesis of complex **I** itself.[3c,d]

Design A

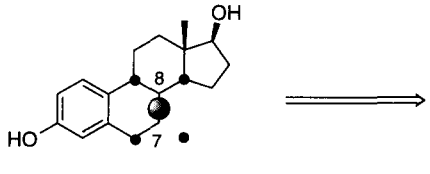


I

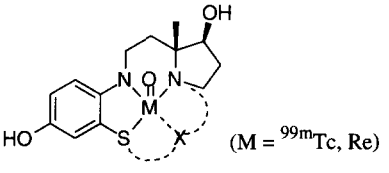
C_8-C_9 Metal Centered Prototypical $(NS)_2$ Complex Bisbidentate $(NS)_2$ Complex

In all of the complexes prepared according to Design A, the metal occupies a position that corresponds to the midpoint of the C_8-C_9 bond, thereby effectively bisecting the carbon structure of the steroid molecule and giving a complex of a *heterobisbidentate* structure (**I**). We recognized that stability was one aspect in which the complexes of the bisbidentate design might be inferior to those of tetradentate design.[4] While some of the model bis-bidentate complexes related to **I** were relatively stable,[3b] complex **I** itself proved to be insufficiently stable for in vitro receptor binding measurements and in vivo biodistribution studies.[3d] Therefore, in a modification of Design A, we have considered complexes in which the metal might be centered at the C_7-C_8 bond (Design B). The off-center nature of this design does not bisect the steroid structure and leaves the upper atom periphery intact (**II**). As a result, with the addition of a few atoms to provide the fourth chelation site, one can obtain various designs for *tetradentate* metal complexes that resemble steroids having only minor structural perturbation at the lower periphery of either the B- or D-ring regions (**III**, **IV**).

Design B

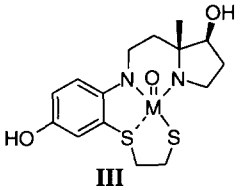


C_7-C_8 Metal Centered

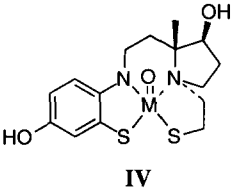


(M = ^{99m}Tc, Re)

II



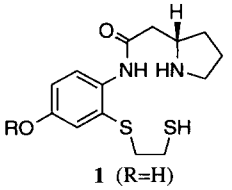
III



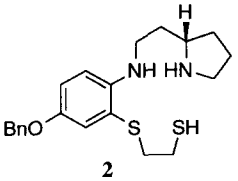
(M = ^{99m}Tc, Re)

IV

In this work, we describe the synthesis of compounds **1**, **1'** and **2**, which represent, respectively, "amide" and "amine" model systems for one of the most accessible of these metal complexes (**III**), and the preparation of the corresponding oxorhenium(V) complexes. The chelate systems **1** and **2** are not of the conventional N_2S_2 design, as they have a thiol and a *thioether* as donor sites, rather than two thiols, a facet that affects the stability of their metal complexes.



1 (R=H)
1' (R=Bn)



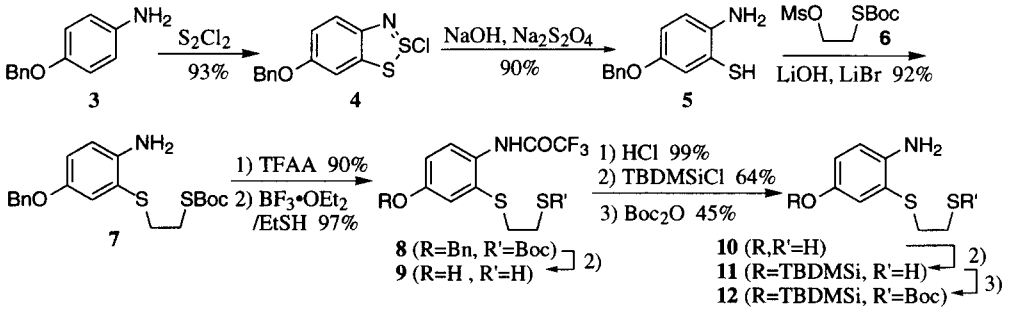
2

Synthesis of Tetradentate Chelates 1 and 2

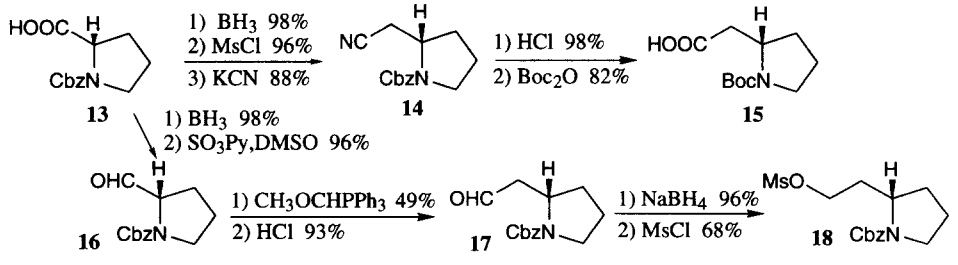
The synthesis of the two tetradentate complexes **1** and **2** involved the coupling of an AB-ring mimic system (**7** or **12**) with a CD-ring mimic system (**15**). The AB-ring mimics were prepared from 4-benzyloxyaniline (**3**). Treatment of **3** with sulfur monochloride produced the benzodithiazole **4**,[5] which was converted to the aminothiol **5** by reductive hydrolysis.[5] Selective S-alkylation of **5** with the S-Boc protected methanesulfonate **6** gave thioether **7**. Attempted alkylation with the corresponding Cbz-protected methanesulfonate resulted in S-benzylation.

Because of problems we encountered in removal of the O-benzyl group later in the synthesis, we chose to replace it at this stage with a bulky tert-butyldimethylsilyl (TBDMSi) group. We surmised that it was the electron rich aromatic ring that made the benzyl ether **7** resistant to acid and reductive cleavage (with HBr; HOAc; H_2, Pd/C; Na, tBuOH; Na, NH_3). Furthermore, we found that an N-acetyl analog related to **7** readily underwent debenzylation with BF_3•OEt_2/EtSH. Therefore, we converted the aniline **7** to its corresponding trifluoroacetanilide **8**, which readily underwent debenzylation (with simultaneous S-Boc cleavage) under similar conditions. Cleavage of the N-acyl group in the free phenol **9** gave the fully deprotected intermediate **10**, which was selectively O-protected as the tert-butyldimethylsilyl (TBDMSi) derivative, and S-protected as the Boc-derivative, giving the doubly protected aniline **12**. In the latter step, the thiol function proved to be more reactive than the aniline. While the O,S-bistriisopropylsilyl derivative as well as the other bis silanes were investigated, the S-silane group in these systems proved to be too reactive in subsequent acylation reactions. Thus, the O-silyl S-Boc derivative **12** was used in the subsequent construction of the tetradentate chelate system (cf. Scheme 3).

Scheme 1

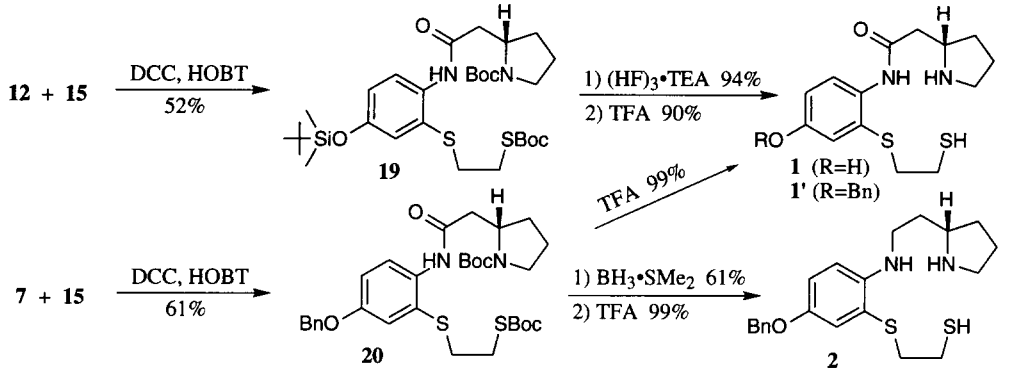


Scheme 2



The CD-ring mimic portion of the chelate system (**15**) was prepared from N-Cbz proline **13** by the route shown in Scheme 2, using standard 1-carbon homologation sequences. In addition to the acid **15**, we also prepared the corresponding aldehyde **17** and methanesulfonate **18** as potential reagents for constructing the tetradentate system. Neither of these latter two reagents, however, proved to be useful: In our hands, the aldehyde **17** was too unreactive to undergo a reductive amination with aniline **12** ($NaBCNH_3$), and the methanesulfonate **18** suffered internal attack by the Cbz group, forming the cyclic carbamate, in preference to N-alkylation of the aniline nitrogen. Nevertheless, we were successful in constructing the desired tetradentate chelate system **1** by DCC/HOBT mediated coupling of acid **15** with the O,S-protected aniline **12** (Scheme 3). Subsequent treatment with HF•triethylamine complex and trifluoroacetic acid gave the fully deprotected chelate system **1**.

Scheme 3



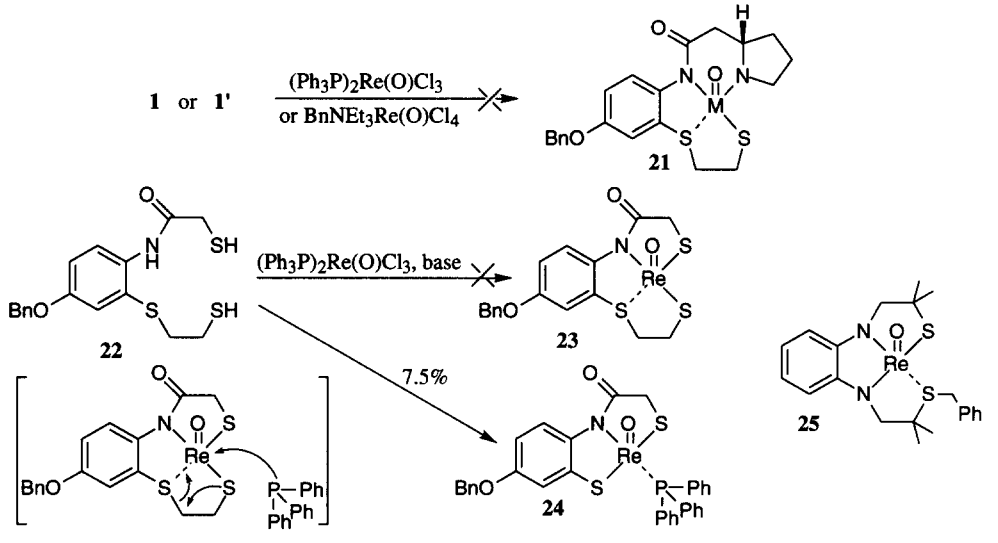
In order to investigate a related chelate system in which the amide function in **1** is replaced by a potentially stronger amine donor function, we also prepared chelate system **2**. In this case, for synthetic simplicity, we left the phenolic function protected as the benzyl ether. Thus, intermediate **7** (Scheme 1) was coupled with acid **15**. Deoxygenation of the adduct **20** with diborane, followed by both S- and N-deprotection with trifluoroacetic acid, furnished the free chelate system **2**. Direct TFA deprotection of intermediate **20** also furnished **1'**, the O-benzyl ether analog of chelate **1**, which is the direct "amide" analog of the "amine" chelate system **2**.

Formation of Oxorhenium(V) Complexes with Chelates 1 and 2

We have investigated the formation of oxorhenium(V) complexes with the "amide" (**1** and **1'**) and the "amine" (**2**) chelate systems, using as metal precursors either the stable, but relatively inert species $(Ph_3P)_2Re(O)Cl_3$,[6] as well as the more reactive species $BnNEt_3Re(O)Cl_4$[7] (Schemes 4 and 5). Under a variety of conditions (in NaOAc/MeOH; iPr_2NEt/EtOH, CH_3CN or CH_2Cl_2), we were unable to obtain a tetradentate complex from the amide systems **1** or **1'**. This may be a consequence of the relatively poor donor ability of the amide and thioether sites in this chelate. Another potential problem with the mercaptoethylsulfide linkage in our complex system is its potential for dealkylation. For example, under the relatively harsh conditions required to effect reaction of a related NS_3 chelate **22** (synthesis not described) with $(Ph_3P)_2Re(O)Cl_3$, we obtained the very

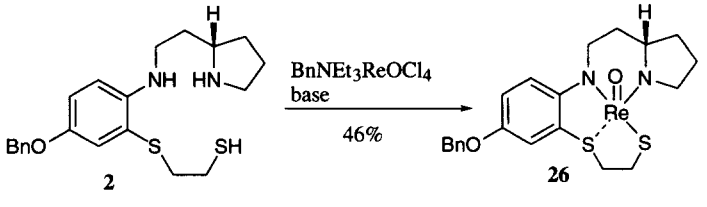
stable "3 + 1" complex **24**,[8] rather than the tetradentate complex **23**. A plausible mechanism for dethioethylation of the chelate **22** is shown in Scheme 4. On the other hand, isomeric N_2S_2 oxorhenium complexes with one thioether donor are known (e.g. complex **25**).[9]

Scheme 4



In contrast to our experience with the amide chelate systems **1** and **1'**, we were able to prepare a tetradentate oxorhenium(V) complex **26** from the amine chelate **2** with the more reactive rhenium metal source. This complex (**26**) was characterized spectroscopically[10]. Despite its tetradentate nature, the stability of complex **26** is not high. It may be purified by normal phase chromatography on silica gel, but it decomposes upon prolonged exposure to chromatographic media. Perhaps, despite its tetradentate nature, the weakness of the thioether donor site and its potential for dealkylation (cf. Scheme 4), coupled with the larger than normal "bite size" for the diamine portion of the chelate (6 in complex **26** vs. 5 in the most N_2S_2 complexes), contribute to the limited stability of this system.

Scheme 5



Based on these observations, we have embarked upon the synthesis of both tetradentate and "3 + 1" chelate systems of alternate design, in our continuing efforts to prepare rhenium and technetium complexes whose structures mimic those of hormonal steroids.

Acknowledgements

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References and Notes

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8 (200 MHz, $CDCl_3$) δ 4.36 (s, 2, SCH_2), 5.07 (s, 2, $PhCH_2$), 6.79 (dd, 1, *J*=9.4, 3.4 Hz, Ar-5-H), 7.07 (d, 1, *J*=3.4 Hz, Ar-3-H), 7.28-7.82 (m, 20, $\underline{Ph}CH_2$-, PPh_3), 8.5 (d, 1, *J*=9.4 Hz, Ar-6-H); MS(FAB) 768 (M^++1, 93), 676 (M^++1-Bn, 21); Anal(HRFAB) calcd for $C_{33}H_{28}NO_3PS_2Re$ 768.0806 found 768.0804.
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10. (200 MHz, $CDCl_3$) δ 0.73-2.45 (m, 10, CCH_2CH_2C, CCH_2C and SCH_2CH_2S), 3.15-4.70 (m, 5, 2 NCH_2 and NCH), 5.02 (s, 2, $PhCH_2$), 6.91-7.02 (m, 2, 2 Ar-H), 7.12 (bs, 1, Ar-H), 7.31-7.52 (m, 5, Ph); MS(FAB) 589 (M^++1, 11); Anal (HRFAB) calcd for $C_{21}H_{26}N_2O_2S_2$ 589.0993 found 589.0982.

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