Tetrahedron Letters, Vol.31, No.40, pp 5701-5704, 1990
Printed in Great Britain

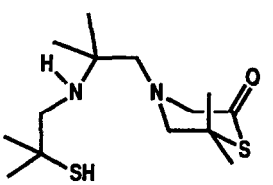
0040-4039/90 $3.00 + .00
Pergamon Press plc

DESIGN AND SYNTHESIS OF A VERSATILE PRECURSOR TO NEUTRAL TECHNETIUM AND RHENIUM COMPLEXES[1]

Kwamena E. Baidoo and Susan Z. Lever*
Division of Radiation Health Sciences, Department of Environmental Health Sciences, The Johns Hopkins University, Baltimore, MD 21205, USA.

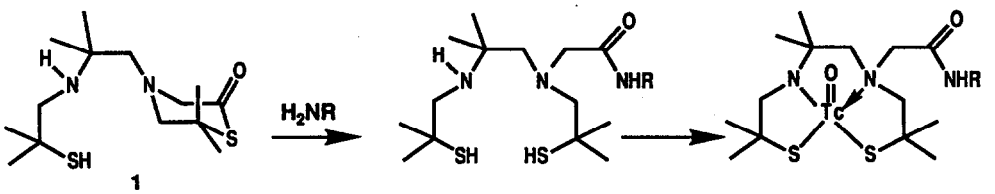
Summary. The design and synthesis of a novel bifunctional chelating agent (BCA) is described which allows convenient one-step preparation of organic ligands for subsequent formation of neutral complexes with group VIIB metals of biomedical interest, such as technetium and rhenium.

Radionuclides of the group VIIB elements possess useful physical characteristics for medical applications. Technetium-99m (^{99m}Tc) is the ideal radionuclide for routine diagnostic nuclear medicine scintigraphic imaging,[2] while rhenium-186 (^{186}Re) has been judged appropriate for cancer radiotherapy.[3] For biomedical applications, stable complexes of these metals are required. Such complexes can be prepared from tetradentate diaminedithiol (DADT) chelating ligands.[4-7] Complexes derived from DADT ligands in which one of the coordinating nitrogens is a secondary amine are neutral, lipid soluble and thus cross intact membranes.[5,6,8,9] Consequently, these ligands show great promise for the generation of novel Tc and Re radiopharmaceuticals. For example, ^{99m}Tc complexes of N-ethylpiperidinyl[5,9] and diester[10] DADT ligands have been shown to be useful as brain perfusion imaging agents, whereas simple N-alkyl DADT derivatives are taken up in pulmonary tissue.[11,12] As the nature of the organic substituent in such complexes is the critical feature which determines *in vivo* biodistribution, it is important to develop new synthetic routes to allow the rapid preparation of a variety of chelating ligands which can form neutral complexes. To date, the usual methods of preparation of DADT ligands involve lengthy linear syntheses, utilize strong reducing agents or require acid hydrolysis.[5,6,8,9] These drawbacks currently limit the variety of chelating ligands available for study. In this report, we describe the synthesis of a convenient precursor, **1**, which obviates these synthetic constraints and allows a facile one step route to DADT ligands suitable for the preparation of neutral, lipid soluble Tc and Re complexes.



1

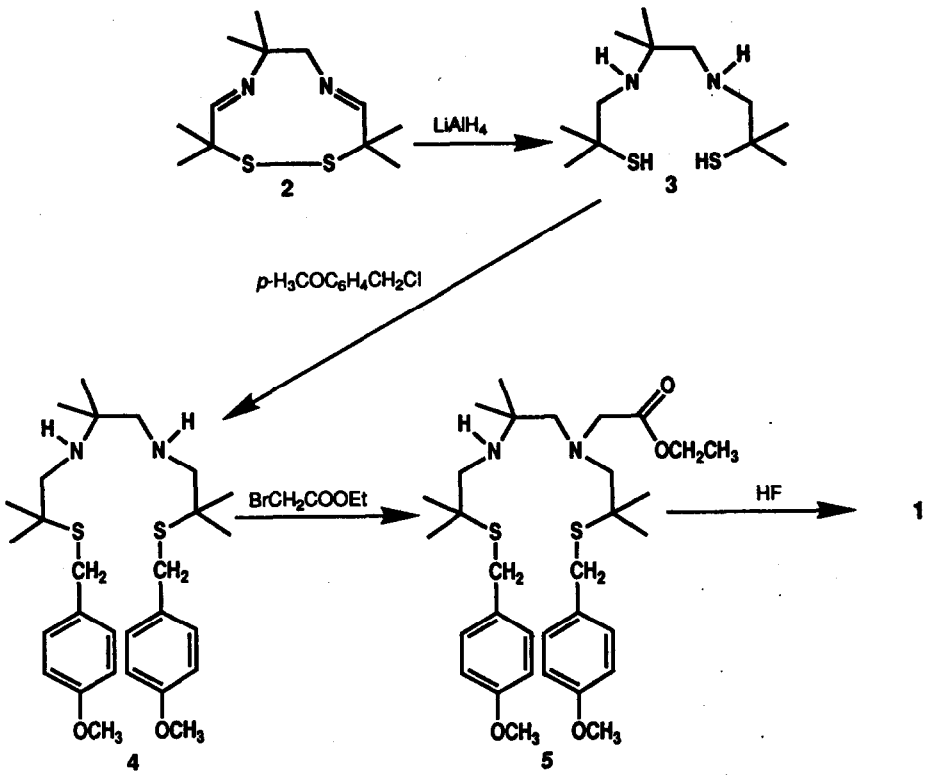
Several key features were considered when BCA **1** was designed. First, a thiolactone was chosen as the coupling functionality capable of reaction with nucleophiles such as amines. Thus, the ligand and substrate become attached through a built-in two carbon spacer *via* a stable amide bond, and the thiol released in the reaction completes the coordinate core of the strongly chelating DADT ligand (Scheme 1). Another essential feature is the introduction of a geminal dimethyl group on the ethylene bridge. We reasoned that its presence α to nitrogen would impart sufficient steric bulk to allow differentiation of the two nitrogens in the required chemoselective synthesis (*cf.* Scheme 2). In addition, this group should minimize potential intra- and intermolecular reactions of the final product. This design of **1** represents a modification of the BCA we recently developed for labeling antibodies and other proteins with Tc and Re radionuclides.[13,14] In that case, the two coordinating nitrogens are tertiary amines which leads to positively charged metal complexes. Thus, the previous methodology is not amenable for the preparation of neutral complexes, and is limited to situations where charge does not adversely affect the biodistribution of the labeled product.



Scheme 1

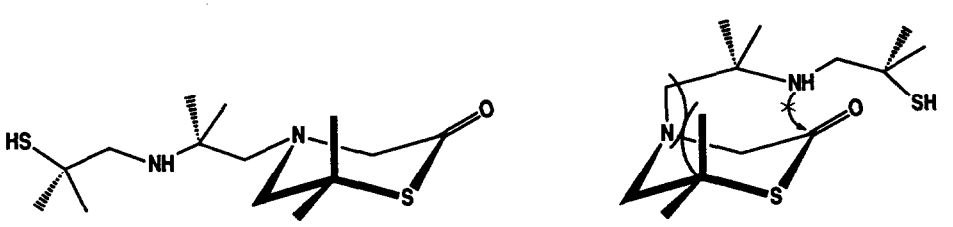
The synthesis of **1** is depicted in Scheme 2.[15] The components which eventually become the coordination backbone were assembled by the condensation reaction of 1,2-diamino-2-methylpropane with 2,2'-dithio-*bis*-(2-methylpropanal) to yield **2**.[5] The reduction of **2** with lithium aluminum hydride (THF, reflux, 18 hr) afforded **3** in 76% yield. The thiol groups in **3** were selectively protected as *p*-methoxybenzyl thioethers, **4**, at room temperature using *p*-methoxybenzyl chloride in aqueous ethanolic sodium hydroxide solution in 83% yield. Reaction of **4** with ethyl bromoacetate (K_2CO_3, EtOH, reflux, 24 hr) produced precursor **5**, in 69% yield. As anticipated, the presence of the geminal dimethyl group on the ethylenediamine bridge provided sufficient steric hindrance to di-alkylation.

The preparation of **1** was accomplished by hydrolysis of **5** in anhydrous hydrogen fluoride (0°C, 2 hr) in the presence of anisole as a radical scavenger.[13,14] The thiolactone **1** was isolated in 73% yield at pH 8 from the residue left after flushing the HF with a stream of nitrogen into a potassium hydroxide trap. The compound exhibited an N-H stretch at 3300 cm^{-1} and a carbonyl stretching frequency at 1655 cm^{-1} characteristic of six membered ring thiolactones.[13,14,16] The ^1H NMR (300 MHz) and elemental analysis (C,H,N,S) were also consistent with the assigned structure.



Scheme 2

Even though a secondary amine is present in 1, intermolecular reactions have not been observed. Presumably, the geminal dimethyl group hinders attack on the carbonyl carbon. This would also retard intramolecular S→N acyl transfer to some degree. An added deterrent to intramolecular reaction is the conformational constraint imparted on the N-substituent due to its spatial relationship to the ring geminal dimethyl moiety. In order to avoid unfavorable 1,3-diaxial interactions, the side chain prefers an equatorial position which places the secondary amine out of proximity for nucleophilic attack.



Reaction with benzylamine (CH_3CN, rt., 3 hr) gave an adduct in 74% yield with the expected spectral and precise elemental analysis data. Preliminary experiments indicate that the benzylamine adduct can be labeled in high yield (> 88%) using no-carrier-added technetium-99m. Further, the product is stable in human serum at 37°C with no evidence of decomposition over an 8 hr study period. The partition coefficient of the ^{99m}Tc complex was determined to be 101.4 ± 6.2 in octanol/pH 7.0 phosphate buffer, which indicates that the complex is neutral and lipophilic. The reaction of 1 with other nucleophiles is currently being assessed.

Recently, we showed that rhenium complexes formed with the DADT ligand system are similar to those derived from technetium.[7] Thus, this BCA should be applicable to the preparation of analogous Re-186 and Re-188 complexes for applications in therapeutic oncology. In summary, the BCA reported here should aid in the syntheses of new neutral DADT complexes of both Tc and Re radionuclides for evaluation as radiopharmaceuticals.

References and Notes

1. This work was supported by USPHS grant CA 32845. A portion of this work was presented at the 37th Annual Meeting of the Society of Nuclear Medicine, Washington, D.C. June, 1990; *J. Nucl. Med.* **1990**, 31, 806 [Abstract].
2. Pinkerton T.C., Dislets C.P., Hock D.J., Mikelson M.V., Wilson G.M. *J. Chem. Educ.* **1985**, 62, 965.
3. Wessel B.W., Rogus R.D. *Med Phys.* **1984**, 11, 638.
4. Epps L.A. Ph.D. Thesis, The Johns Hopkins University, Baltimore, **1984**.
5. Lever S.Z., Burns H.D., Kervitsky T.M., Goldfarb H.W., Woo D.V., Wong D.F., Epps L.A., Kramer A.V., Wagner H.N. *J. Nucl. Med.* **1985**, 26, 1287.
6. Kung H.F., Molnar M., Billings J., Wicks R., Blau M. *J. Nucl. Med.* **1984**, 25, 326.
7. Mahmood A., Baidoo K.E., Lever S.Z. In Technetium In Chemistry And Nuclear Medicine **1990**, 3 Cortina International, Verona. *In Press.*
8. Epps L.A., Burns H.D., Lever S.Z., Goldfarb H., Wagner. H.N. *Appl. Radiat. Isot. (Int. J. Radiat. Appl. Instrum. Part A)* **1987**, 38, 361.
9. Scheffel U., Goldfarb H.W., Lever S.Z., Gungun R.L., Burns H.D., Wagner, Jr. H.N. *J. Nucl Med.* **1988**, 29, 73.
10. Leveille J., Demonceau G., De Roo M., Rigo P., Taillefer R., Morgan R.A., Kupranick D., Walovitch R.C. *J. Nucl. Med.* **1989**, 30, 1902.
11. Baidoo K.E., Epps L.A., Scheffel U., Burns H.D., Lever S.Z., Kramer A.V., Goldfarb H., Gungun R., Wagner H.N. *J. Nucl. Med.* **1987**, 28, 729.
12. Lever S.Z., Sun S.-Y., Kaltovich F., Scheffel U., Goldfarb H., Mahmood A., Baidoo K.E., Wagner H.N. *J. Nucl. Med.* **1988**, 29, 789.
13. Lever S.Z., Baidoo K.E., Kramer A.V., Burns H.D. *Tet. Lett.* **1988**, 29, 3219.
14. Baidoo K.E. Ph.D. Thesis, The Johns Hopkins University, Baltimore, **1988**.
15. All new compounds were characterized by IR, ^1H NMR and elemental analysis.
16. Korte F., Christoph H. *Chem. Ber.* **1961**, 94, 1966.

(Received in USA 25 July 1990)