Receptor-Targeted Imaging Agents that Utilize Cyclopentadienyl Tricarbonyl Rhenium and Technetium Complexes

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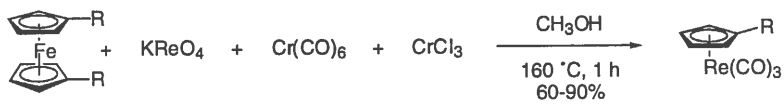
The extensive use of metallic radionuclides in nuclear medicine is dominated by technetium-99m (γ, $t_{1/2}$ = 6 h), and technetium-99m-based radiopharmaceuticals are used in approximately 80% of all diagnostic imaging procedures.[1] For tumor radiotherapeutic purposes, rhenium-186 (β, $t_{1/2}$ = 91 h) and rhenium-188 (β, $t_{1/2}$ = 17 h) have shown great promise.[2,3] The ongoing development of receptor-targeted radiopharmaceuticals that incorporate these radiometals is directly due to their proven utility.

Recently, a large number of publications have appeared describing the preparation and use of low-valent (i.e., $M(CO)_3^+$) technetium and rhenium for radiopharmaceutical purposes.[4-11] In this regard, our group has been focused upon the development of novel methods for the generation of stable substituted η^5-cyclopentadienyltricarbonyl rhenium and technetium (CpTM) complexes for radiolabeling biologically interesting molecules. Our interest in this system derived from the favorable structural and chemical properties of the CpTM system, when compared to the more widely used high-oxidation state metal-oxo complexes.[12-14] However until recently, the preparation of these organometallic species has required harsh conditions and multi-step procedures which do not lend themselves to radiopharmaceutical application.

The first practical radiochemical preparation of substituted CpTT complexes was the double ligand transfer reaction (DLT), originally reported by Martin Wenzel in 1992.[15] A revised synthetic sequence, developed previously in our group, is depicted in Scheme 1.[16] This reaction involves the in situ reduction/carbonylation of the permetallate species, followed by selective ring transfer from an appropriately substituted ferrocene precursor. To extend the DLT methodology further, we have chosen to synthesize a number of appropriately substituted ferrocenyl phenyl-tropanes for use as substrates in a *direct double ligand transfer reaction* (Scheme 2). These CpTR phenyl-tropane conjugates were then evaluated as potential dopamine transporter (DAT) imaging agents.

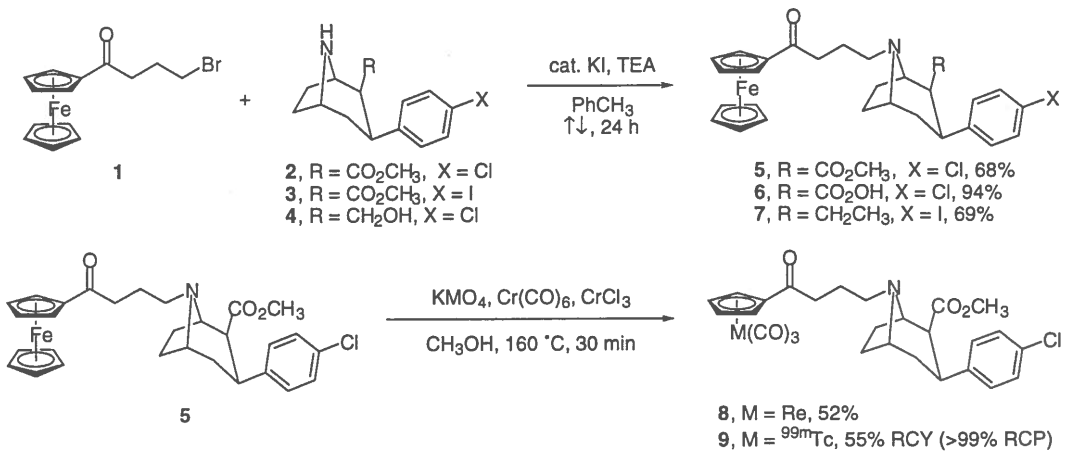


R = ketone, ester or amide

Scheme 1

DAT affinity (K_i ± SE) of *N*-[4-Oxo-4-cyclopentadienyltricarbonyl rhenium butyl]-2β-carbomethoxy-[3β-(4-chlorophenyl)] tropane) (**8**) in rat brain tissue homogenate was found to be 5.95 ± 0.93 nM. The corresponding technetium congener **9** could be obtained by *direct* DLT of ferrocene **5** with $[^{99m}Tc]NaTcO_4$ in the presence of $CrCl_3$ and $Cr(CO)_6$ in CH_3OH for 40 min at 160°C in 55% radiochemical yield (RCY) and >99% radiochemical purity (RCP). Regional cerebral uptake and distribution of the technetium analog was evaluated in vivo in mouse brain. Mice were given 2 MBq (54 μCi) of **9** with and without pretreatment

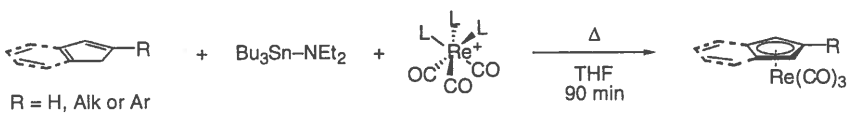
(15 min) with DAT ligand β-CIT (2 mg/kg, ip). At 60 and 90 min after iv injection, the mouse striatum/cerebellum radioactivity ratio was 2.0 and 2.3 respectively, and was reduced to unity in presence of β-CIT at 60 min.



Scheme 2

Although the DLT reaction has continued to show excellent functional group tolerance, the requirements of high temperatures and an electron-withdrawing substituent are still significant limitations. In an effort to develop milder methods for the preparation of substituted CpTM complexes, we have chosen to investigate the utility of known latent cyclopentadienyl anions, those of the metalloids silicon and tin.

The reaction of tributyltin-diethylamine, a *fac*-$Re(CO)_3^+$ precursor, and a cyclopentadiene has proved to be a mild and efficient method for the preparation of substituted CpTR complexes (Scheme 3). The reaction can be extended to the use of indenyl ring systems and shows excellent tolerance of a variety of substitution patterns. The reaction is unaffected by a number of functional groups, including ethers, esters, halides and amines. The main limitation of the reaction is the yield, which is modest when the reaction time needs to be truncated for the requirements of efficient radiochemical synthesis with a short-lived radionuclide. The solvent acetonitrile gives the best yields of CpTR, although this solvent proved to be incompatible with the indenyl ring system. In THF, the reaction can be carried out in a single pot, and in this solvent it can be extended to more complex systems.



Scheme 3

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