New and Efficient Routes to Biomolecules Substituted with Cyclopentadienyltricarbonylrhenium and -Technetium Derivatives

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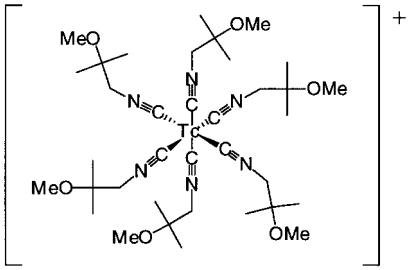
Abstract: The small, compact, robust, and nonpolar units of $[CpM(CO)_3]$ (M = Re, Tc) coupled with biomolecules may be considered as bioorganometallic entities of potential interest in the field of medicinal chemistry. However, the short half-life of useful radionuclides (^{186}Re $t_{1/2} = 3.7$ d, ^{188}Re $t_{1/2} = 16.8$ h, ^{99m}Tc $t_{1/2} = 6$ h), the risks inherent in their use, and their cost have led chemists to search for novel synthetic strategies that allow the rapid introduction of the $[CpM(CO)_3]$ moiety as a late step in the course of synthesizing the target molecule. The present paper describes different strategies recently reported in the literature to tackle this problem.

Keywords: bioorganometallic chemistry · cyclopentadienyl ligands · radiopharmaceuticals · rhenium · technetium

Introduction

The current interest in Group 7 elements as radiopharmaceuticals, whether for diagnostic (^{99m}Tc) or, more recently, therapeutic (^{186}Re, ^{188}Re) purposes, is well known.[1, 2] The available forms of these radionuclides, obtained with a generator,[3] are essentially limited to their highest accessible oxidation states (+7) such as TcO_4^- and ReO_4^-. For speed of synthesis and ease of handling in aqueous media, (N_2,S_2)- and (N_3,S)-type chelate complexes, with an intermediate degree of oxidation (e.g., +5), are frequently preferred.[4] This strategy is not without its disadvantages, which may include insufficient robustness of the chelate, a multiple-step synthesis for the chelator, stereochemical problems, or bulkiness of the complex with concomitant loss of recognition of the vector for the biological target.

Lowering the degree of oxidation of the metal still further has been shown by Davison[5] to be a useful strategy in the synthesis of robust organometallic complexes such as $[^{99m}Tc(CNR)_6]^+$ (**1**). In particular, cardiolite, a lipophilic cation, shows a regional selectively at the level of the cardiac muscle and has opened the way for an organometallic approach in this area, based on a low oxidation state of the metal and strong metal–carbon bonds.[6]



Cardiolite

In terms of using these chemically inert complexes for in vivo applications, the usefulness of Group 7 low valence (+1, 0) complexes is thus established. These oxidation states are well adapted to organometallic chemistry and its bonding modes, to the extent that ligands with acceptor properties stabilize an electron-rich metal center. Given these parameters, an interesting organometallic target is $[(C_5H_4R)M(CO)_3]$ (M = Re, Tc), since its robust and nonbulky nature as compared with (N_2,S_2) chelates[7, 8] would in principle allow it to bind to various biomolecules that could be used as biological vectors. An example of the potential benefit of the organometallic approach over the chelate route can be seen in the case of recognition of the estrogen receptor, the key protein in cancers of the breast.

Molecules **2** and **3**, derivatives of tamoxifen, the drug of reference in breast cancer therapy, have been prepared. While **2** shows a recognition level (relative binding affinity (RBA)) that is too weak relative to the estrogen receptor to be of use [RBA < 0.009 % (too low to be measured)],[9] product **3** binds to the same receptor with an RBA of 9.75 % (4-OH-tamoxifen, RBA = 38.5 %).[10] Moreover, on MCF7-type cell lines, compound **3** shows an antiproliferative activity comparable to that of tamoxifen.

To increase the potential value of this molecule **3** as well as others of the same type, the imperative now is to achieve a rapid insertion of appropriate radionuclides (^{99m}Tc = 6 h, ^{188}Re = 16.8 h), which have short half-lives. This is not a trivial problem from a synthetic point of view, and presents an interesting challenge especially because of the quasi-necessity

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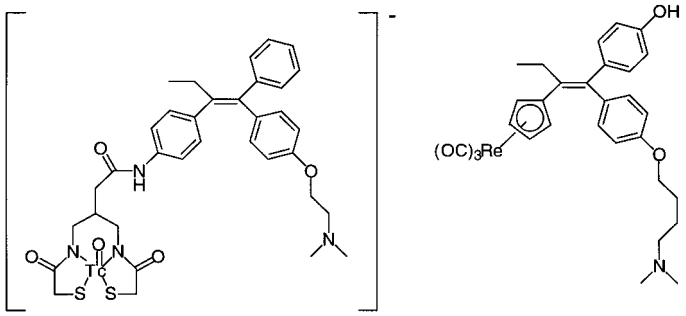

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of working in saline solution. For this or other reasons, the problem of attaching $[CpRe(CO)_3]$ and $[CpTc(CO)_3]$ onto biomolecules has recently produced an abundance of differing synthetic approaches. We present a selection of these below.

Rhenium Sources

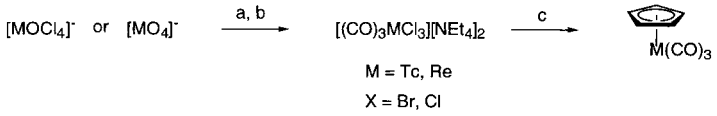
$[Re_2(CO)_{10}]$ and $[BrRe(CO)_5]$: $[Re_2(CO)_{10}]$ is the main organometallic precursor of $[CpRe(CO)_3]$ and its substituted derivatives in organic media. It is commonly prepared from perrhenate by heating under a high pressure of CO gas (100–300 atm) at high temperature (200 °C) for two days.[11–13] However, these conditions are not suitable for the synthesis of organometallic radiopharmaceuticals, which require low temperature and pressure for safety reasons and the possible sensitivity of biomolecules, and also demand short reaction times with high yields. To satisfy these requirements, it was necessary to develop a new reaction. Ammonium perrhenate, which is available in both cold and radioactive forms, was reduced by diisobutylaluminum hydride (DIBAL-H) in the presence of gaseous carbon monoxide in toluene at 70–80 °C to give $[Re_2(CO)_{10}]$ in 62 % yield (Scheme 1).[14]

Scheme 1. a) CO (1 atm), toluene, 70 – 80 °C; b) Br_2.

$[Re_2(CO)_{10}]$ can either be used directly in the cyclopentadienyl ligand-transfer reaction to give cyclopentadienyltricarbonylrhenium derivatives, or it may be converted into $[BrRe(CO)_5]$, which is a more reactive and more commonly used compound, before carrying out the complexation reaction.

$[(CO)_3ReX_3]^{2-}$ and $[(CO)_3TcX_3]^{2-}$: Alberto et al. have published a promising low-pressure approach to the synthesis of organometallic radiopharmaceuticals.[15–17]

The reagent $[(CO)_3MCl_3]$-$[NEt_4]_2$ is prepared from perrhenate or pertechnetate in 75–87 % yields, under very mild conditions, by using BH_3 under one atmosphere of CO only (Scheme 2). The advantage of this reagent is that it is possible to prepare it in its radioactive form by using $^{188}ReO_4^-$. The halide ligands are easily substituted in these species, leading to a wide range of organometallic compounds. Alberto has shown that $[(CO)_3TcCl_3][NEt_4]_2$ can react with CpTl to give $[CpTc(CO)_3]$. Dissolving $[(CO)_3ReCl_3][NEt_4]_2$ in acetonitrile quantitatively produces $[(CO)_3Re(CH_3CN)_3]^+$, a convenient precursor for substituted $[(C_5H_4R)Re(CO)_3]$ (see section on "The three-component synthesis").



Scheme 2. a) BH_3/$[NBu_4]Cl$/CO; b) $[NEt_4]Cl$, 6 h, 110 °C; c) $AgPF_6$/CpTl, THF, 60 °C.

The same author has recently prepared the aquaions $[(H_2O)_3M(CO)_3]^+$ ($M = {}^{99m}Tc$, ^{188}Re) that are currently the most promising compounds for the labeling of a variety of biomolecules.[18–20] But so far, this approach has not been applied to the synthesis of cyclopentadienylmetalcarbonyl compounds.

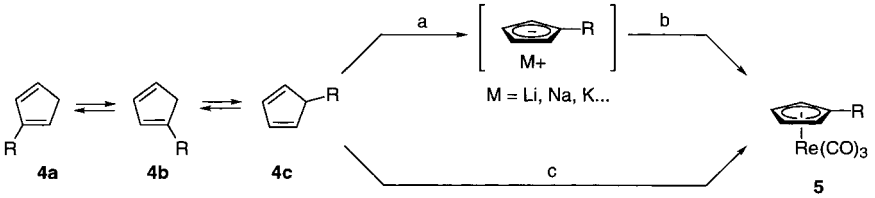
Labeling of Steroids and Specific Estrogen Receptor Modulator (SERM)

The fulvene route: The best known organometallic route to $[CpRe(CO)_3]$-substituted compounds **5** is the reaction of the cyclopentadienide salt, obtained from substituted cyclopentadiene **4**, with $[BrRe(CO)_5]$[21] or by direct reaction of $[Re_2(CO)_{10}]$ with dicyclopentadiene at high temperature (Scheme 3).[22]

However, the poor stability of the substituted cyclopentadiene compounds as well as the difficulty of their characterization (cyclopentadienes exist as a mixture of isomers as shown in Scheme 3) led us to explore a closely related strategy involving fulvenes **6** as starting materials (Scheme 4).[23] These entities are easier to synthesize and to handle than the corresponding cyclopentadienes. Thus, in the presence of a nucleophile (Scheme 4, path a), compound **6** could give **7** by a one-pot procedure involving an addition/transmetallation process. On the other hand, the action of a base, followed by addition of $[BrRe(CO)_5]$ generates **8** via the formation of an intermediate salt (Scheme 4, path b).

These strategies have been successfully applied to the synthesis of substituted organometallic steroids (Scheme 5).

We have thus provided a new and efficient route to $[CpRe(CO)_3]$-substituted steroids, with introduction of the



Scheme 3. a) base; b) $[BrRe(CO)_5]$; c) $[Re_2(CO)_{10}]$.

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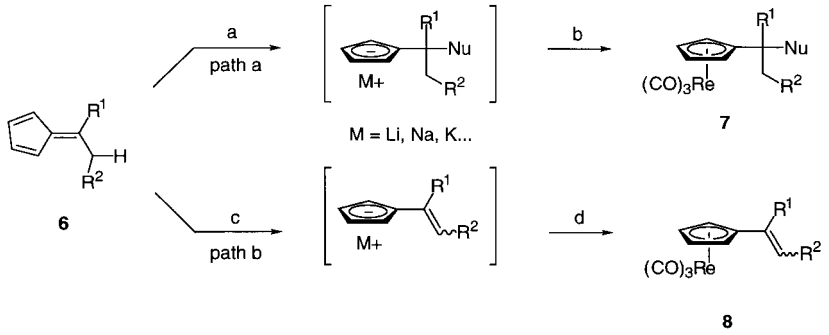
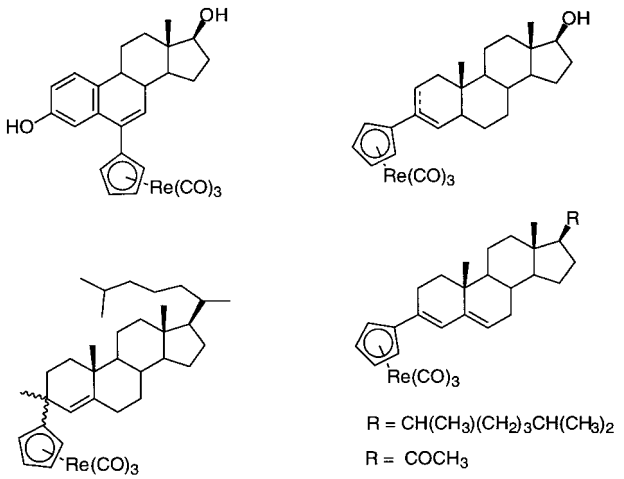


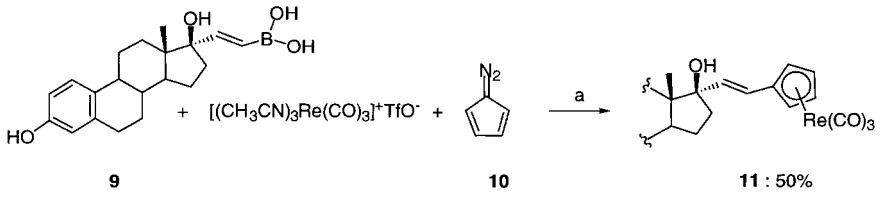
Scheme 4. a) Nucleophile; b) $[BrRe(CO)_5]$; c) base; d) $[BrRe(CO)_5]$.



Scheme 5. Structures of substituted organometallic steroids synthesized according to Scheme 4.

metal as the last step of the procedure, permitting synthesis of a large variety of products.

The three-component synthesis: Katzenellenbogen recently took advantage of Alberto's reagent for the one-pot synthesis of the estradiol analogue **11** (Scheme 6).[24]

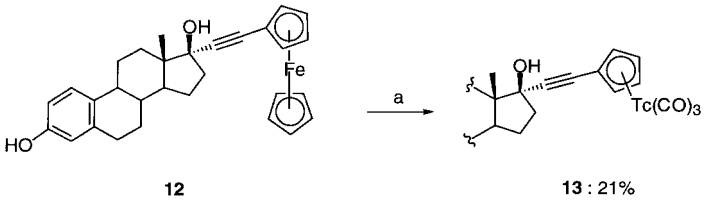


Scheme 6. a) Et_3N, Δ, 45 min, CH_3CN/acetone 1:1.

The process is based on the use of a boronic acid derivative of estradiol **9** and diazocyclopentadiene **10** as precursor of the $[CpRe(CO)_3]$ unit. This synthetic route appears as an ideal approach, since it involves a one-pot reaction and the reagent $[(CO)_3Re(CH_3CN)_3]^+$ can be obtained in its radioactive form starting from $[(CO)_3ReCl_3][NEt_4]_2$. In contrast, the marked instability of the reagent $C_5H_4N_2$ does not allow for easy handling, especially when working at low concentrations, as required for radioactive compounds.

Cyclopentadienyl transfer reaction: The transfer of an organic ligand from one transition metal unit to another is an attractive reaction when the complex cannot be prepared by conventional methods. Several examples have been discussed in the literature.[25, 26] This strategy was applied by Wenzel[27] in the one-pot synthesis of the first technetium complex of 17α-ethynylestradiol (**13**) from the corresponding ferrocenyl complex **12** (Scheme 7).

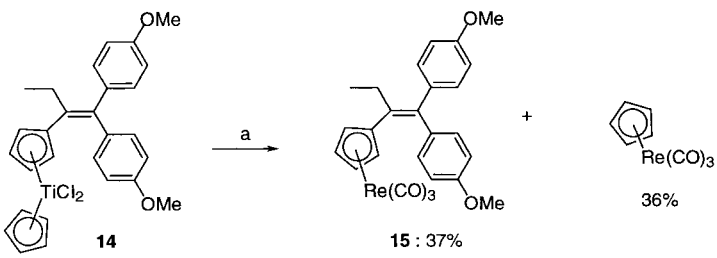
This is an elegant synthetic method for the preparation of the technetium hormone complex, although some disadvantages remain. The major drawbacks are the high temperature of the reaction and the fact that the analogous tricarbonyl complex of manganese is



Scheme 7. a) TcO_4^-, $[Mn(CO)_5Br]$, THF, 1 h, 150 °C.

produced at the same time as that of Tc. This contamination limits the usefulness of the procedure described above, since separation of the two complexes is not always straightforward. In addition, while this transfer reaction works with pertechnetate, the cyclopentadienyltricarbonylrhenium compounds can be prepared only in cases in which the ferrocene bears an electron-withdrawing substituent.[28]

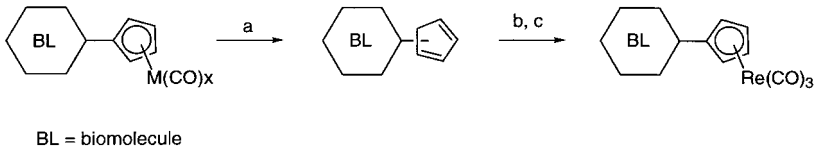
In order to find a suitable starting material for this cyclopentadienyl transfer reaction, we performed a thermal reaction of $[Re_2(CO)_{10}]$ with several cyclopentadienyl complexes of transition metals. We found that $[Cp_2TiCl_2]$ gave the best yield of $[CpRe(CO)_3]$ (82% yield).[29] This reaction also works with a more sophisticated molecule such as **14**, but in moderate yields (Scheme 8). Thus, heating **14** with $[Re_2(CO)_{10}]$ in mesitylene solution at reflux gives **15** and $[CpRe(CO)_3]$ in 37% and 36% yields, respectively. The use of this method may be limited by the



Scheme 8. a) $[Re_2(CO)_{10}]$, mesitylene, Δ, 3 h.

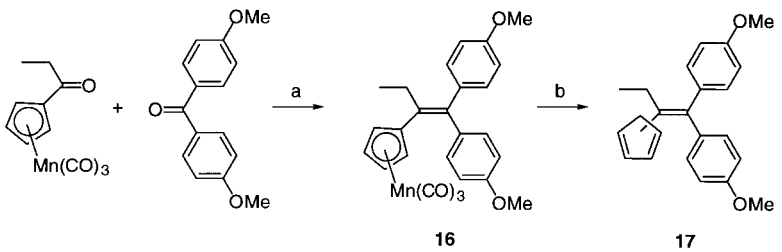
high temperature conditions and by the access to titanium complexes.

The decomplexation/recomplexation route: We next examined a new synthetic approach to the target molecules, taking into account their intended application as radiopharmaceuticals. The principle of this reaction, allowing access to substituted cyclopentadienes and hence to the desired organometallic complexes, is outlined in the general Scheme 9.



Scheme 9. a) Protic solvent, $h\nu/O_2$, RT; b) base; c) $[BrRe(CO)_5]$ or $[Re_2(CO)_{10}]$.

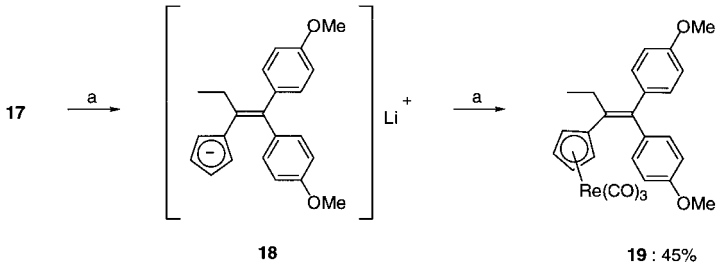
This reaction involves the photochemical decomplexation of easily handled complexed substrates in protic solvents. Thus, it is possible to keep the unstable cyclopentadiene intermediate in its stable complexed form and to generate it at the time of the reaction with a rhenium agent. Tricarbonyl-



Scheme 10. a) $TiCl_4$, Zn, THF; b) $h\nu$, Et_2O/MeOH.

manganese derivatives have proved suitable for this purpose. Thus, the photolysis of cymantrene compound **16**, which was readily accessible from a McMurry cross-coupling reaction, in diethyl ether/methanol (2:1), gives the substituted cyclopentadiene **17** in very good (81%) yield (Scheme 10).[30]

Once pure, compound **17** proved relatively stable against polymerisation and can be kept several days under refrigeration. Addition of *n*BuLi into the solution of **17** produces organolithium **18**, which reacts with $[BrRe(CO)_5]$ to form the complex **19** in 45% yield (Scheme 11).



Scheme 11. a) *n*BuLi, THF, $-70\,^{\circ}C$; b) $BrRe(CO)_5$.

This synthetic strategy has several advantages. First, it is possible to prepare the organic ligand beforehand and keep it in the form of a manganese complex until needed, at which time the cyclopentadienyl ring is liberated by photolysis, to react with the Re reagent. This means that the rhenium is introduced only at the last stage of the reaction.

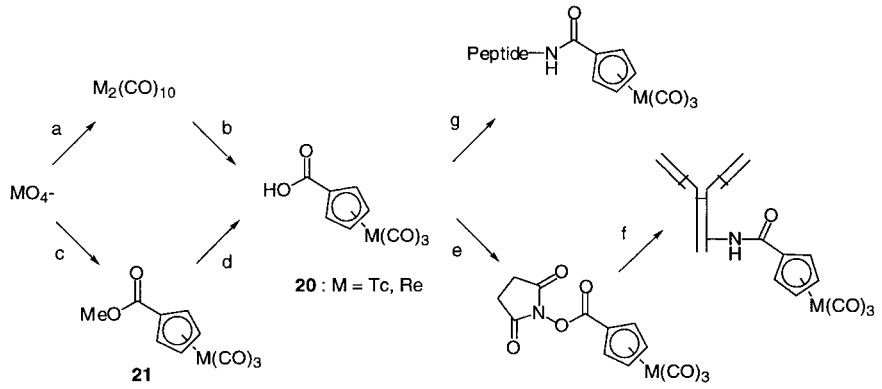
Labeling of Peptides and Proteins

Radio-imaging with labeled antibodies, antibody fragments, or peptides is one important application of the radionuclide ^{99m}Tc in nuclear medicine, more particularly in clinical oncology.[31–33] Concomitantly, adjuvant radio-immunotherapy with the β emitters ^{186}Re and ^{188}Re could benefit from the development of ^{99m}Tc labeling kits, because both elements have very similar coordination chemistries.

Methods of radio-labeling of peptides/proteins with technetium and rhenium have been categorized into three main groups: 1) direct labeling, in which coordination of the metal is ensured by particular proteins side chain functions (like the sulfhydryl group of cysteines); 2) indirect or post labeling, in which an appropriate chelate is first conjugated to the biological vehicle then coordinated with the metal at the appropriate oxidation state; and 3) labeling with a preformed complex.[34] Labeling of peptides/proteins with $[CpM(CO)_3]$ units (M = Tc, Re) belongs to the last group.

The general pathway is depicted in Scheme 12. The key intermediate is the neutral complex $[(\eta^5\text{-}CpCOOH)M(CO)_3]$ (**20**: M = Re, Tc). To generate it from MO_4^-, two strategies have been used. Strategy I is based on the conversion of pertechnetate/perrhenate to $[Re_2(CO)_{10}]$/$[Tc_2(CO)_{10}]$ by reduction in the presence of DIBAL-H, followed by complexation of C_5H_5COOH, resulting in the formation of complex **20** with a global yield of 60% from perrhenate.[35] Strategy II, developed by Katzellenenbogen and co-workers, involves the double ligand transfer (DLT) reaction with $[Cr(CO)_6]$ as carbonyl ligand donor and $CrCl_3$ as reducing agent, to yield the methyl ester **21** in 89% yield. This ester was then quantitatively saponified to **20** in a mixture of 2 M NaOH and dioxane.[36] Conjugation of **20** to protein amino groups was achieved by activation of the carboxylic acid function into an *N*-hydroxysuccinimide (NHS) ester following the classical NHS + DCC (*N*,*N*′-dicyclohexyl carbodiimide) procedure[37] or by reaction with *O*-(*N*-succinimidyl)-*N*,*N*,*N*′,*N*′-tetramethylammonium tetrafluoroborate (TSTU) in the presence of a base, then reaction in an aqueous basic buffer (pH 8). Conjugation yields were found to be dependent on the initial proportions of **20** and the protein, with high yields reached at low **20**:protein molar ratios. A slightly different route was selected for peptide labeling in which **20** was activated to give a more reactive 1-hydroxybenzotriazole

0947-6539/01/0711-2292 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 11



Scheme 12. Strategy I: a) CO (1 atm), DIBAL-H, toluene, 70–80 °C; b) $C_5H_5CO_2H$, mesitylene, 163 °C. Strategy II: c) [($\eta^5C_5H_4CO_2Me$)Fe], [$Cr(CO)_6$], $CrCl_3$, MeOH, 180 °C; d) 2 M NaOH/dioxane 1:1; e) NHS/DCC in THF or TSTU, triethylamine (TEA) in DMF; f) Buffered aqueous solution; g) HOBT or HOAT, DCC in CH_2Cl_2, then peptide in DMF.

(HOBT) or 1-hydroxy-7-azabenzotriazole (HOAT) ester in CH_2Cl_2, yielding labeled peptides with yields around 70%.

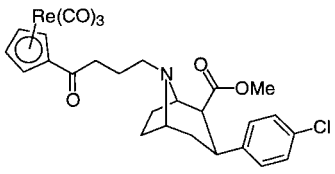
The in vitro immunological activity of one monoclonal antibody (mAb) labeled with 15 [$CpRe(CO)_3$] units was measured by an indirect radio-assay, and it was found that this mAB retained 64% of its binding activity relative to the unlabeled mAb.[37]

The biological behavior of the peptide octreotide, a somatostatin analogue, labeled at its N terminus by a [$Cp^{99m}Tc(CO)_3$] unit, has also been examined.[38] An in vitro binding experiment showed that [$CpTc(CO)_3$]-labeled octreotide displayed high affinity for a preparation of somatostatin receptors, together with a low level of nonspecific binding (5%). Following administration of the labeled peptide, fast and specific accumulation of radioisotope was observed in adrenals and pancreas, which was almost totally blocked by co-administration of octreotide. However high radioactivity levels were also measured in the liver, kidneys, and intestine; this could be problematic when imaging tumors in the abdominal region. This behavior may result from the increased lipophilicity of the labeled peptide. In fact, this phenomenon of increased lipophilicity could be detrimental to biological target selectivity and must be taken into account in the conception of a new radiopharmaceutical.

Conclusion

The variety of the recent examples mentioned above shows that synthesis of biologically interesting compounds containing the cyclopentadienyltricarbonylrhenium and -technetium groups is a very active and current area of endeavour.

This increase in interest is due chiefly to the advantages offered by this group in the development of new stable and nonbulky radiopharmaceuticals (e.g, compounds **22** and **23**).



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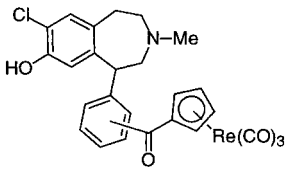

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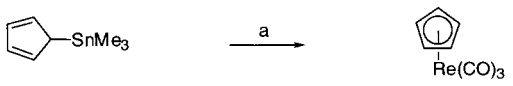
Since the first labeling of a steroid hormone with cyclopentadienyltricarbonylrhenium,[39] as part of the study of the estrogen receptor, this organometallic group has not ceased to evoke interest in finding new synthetic approaches.[40] It is currently the object of active study in the area of neurological bioligands by association with molecules such as *p*-halophenyltropane (**22**) or benzazepine (**23**).[41, 42] Although there are now several viable approaches to the preparation of target molecules containing cold rhenium, the synthesis of radioactive rhenium complexes, as well as complexes of technetium, requires the refinement of new strategies to overcome the difficulties inherent in the use of short-lived radioactive isotopes, that is, the small amounts of material available and the form of the available source. At the present time, radioactive rhenium is only available as the perrhenate, dissolved in saline solution.[3] Thanks to the relative ease with which pertechnetate can be reduced, substantial progress has already been made in the synthesis of radiopharmaceuticals based on cyclopentadienyltricarbonyltechnetium (^{99m}Tc) compounds,[43] although the ideal method has yet to be discovered. Since the chemistry of rhenium is similar to that of technetium, it is reasonable to hope that the methods developed for Tc will be adaptable to Re in the future. As ^{188}Re is produced in perrhenate form in aqueous solution, the major research challenge is to synthesize organometallic radiopharmaceuticals directly in water. It has already proved possible to synthesize the aqua ion $[Re(H_2O)_3(CO)_3]^+$, an interesting potential precursor, in the radioactive ^{188}Re form in water.[17, 18] One of the roadblocks to synthesis of cyclopentadienyltricarbonylrhenium compounds is the source of the cyclopentadienyl ligand. Cyclopentadiene, itself relatively unreactive, must be activated before it will react with the metal reagent. Alkaline salts of cyclopentadiene are often used for this purpose, but they have the disadvantage of being water sensitive. Another, less water-sensitive reagent is required for this purpose. Compounds of the (η^5-C_5H_4R)$SnMe_3$ type are currently under study by Top and Alberto.[44] Early results have shown that $CpSnMe_3$ reacts with $[Et_4N]_2[ReBr_3(CO)_3]$ in acetonitrile to give [$CpRe(CO)_3$] in 88% yield (Scheme 13).



24 **25**: 88% yield

Scheme 13. a) $[Et_4N]_2[ReBr_3(CO)_3]$, CH_3CN, Δ, 1 h.

This is a promising new approach to $Re(CO)_3$ cyclopentadienyls; however, it remains necessary to overcome the hurdle of water sensitivity in organometallic tin compounds. It is

clear that, despite the recent proliferation of activity,[45] this field of research is still in need of a practical synthetic route to radiopharmaceuticals of $[CpM(CO)_3]$ (M = Re, Tc) that would be rapid, water-based, and high in yield.

Acknowledgements

We wish to thank B. McGlinchey for correcting the manuscript.

[1] K. Schwochau, *Angew. Chem.* **1994**, *106*, 2349 – 2358; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2258 – 2267.
[2] P. A. Schubiger, R. Alberto, A. Smith, *Bioconjugate Chem.* **1996**, *7*, 165 – 179.
[3] F. F. Knapp, A. L. Beets, S. Guhlke, P. D. Zamora, H. Bender, H. Palmedo, H. J. Biersack, *Anticancer Res.* **1997**, *17*, 1783 – 1796.
[4] J. R. Dilworth, S. J. Parrott, *Chem. Soc. Rev.* **1998**, *27*, 43 – 55.
[5] B. I. Holman, Y. Sporn, A. G. Jones, S. T. Benjamin-Sin, N. Perez-Balino, A. Davison, J. Lister-James, J. F. Kronauge, A. E. A. Mitta, L. L. Camin, S. Camell, S. J. Williams, A. T. Carpenter, *J. Nucl. Med.* **1987**, *28*, 13 – 26.
[6] R. K. Hom, J. A. Katzenellenbogen, *Nucl. Med. Biol.* **1997**, *24*, 485 – 498.
[7] J. P. O'Neil, S. R. Wilson, J. A. Katzenellenbogen, *Inorg. Chem.* **1994**, *33*, 319 – 323.
[8] P. J. Fitzpatrick, Y. Le Page, J. Sedman, I. S. Butler, *Inorg. Chem.* **1981**, *20*, 2852 – 2861.
[9] D. H. Hunter, L. G. Luyt, *Bioconjugate Chem.* **2000**, *11*, 175 – 181.
[10] G. Jaouen, S. Top, A. Vessières, P. Pigeon, G. Leclercq, I. Laios, *Chem. Commun.* **2001**, 383 – 384.
[11] F. Calderazzo, R. Poli, *Gazz. Chim. Ital.* **1985**, *115*, 573 – 574.
[12] F. Calderazzo, U. Mazzi, G. Pampaloni, R. Poli, F. Tisato, P. F. Zanazzi, *Gazz. Chim. Ital.* **1989**, *119*, 241 – 247.
[13] W. Hieber, H. Fuchs, *Z. Anorg. Allg. Chem.* **1941**, *248*, 256 – 268.
[14] S. Top, P. Morel, M. Pankowski, G. Jaouen, *J. Chem. Soc. Dalton Trans.* **1996**, 3611 – 3612.
[15] R. Alberto, R. Schibli, A. Egli, P. A. Schubiger, W. A. Hermann, G. Artus, U. Abram, T. A. Kaden, *J. Organomet. Chem.* **1995**, *493*, 119 – 127.
[16] R. Alberto, R. Schibli, A. Egli, U. Abram, S. Abram, T. A. Kaden, P. A. Schubiger, *Polyhedron* **1998**, *17*, 1133 – 1140.
[17] R. Alberto, R. Schibli, P. A. Schubiger, V. Abram, R. Hübener, H. Berke, T. A. Kaden, *Chem. Commun.* **1996**, 1291 – 1292.
[18] R. Alberto, R. Schibli, A. Egli, P. A. Schubiger, U. Abram, T. A. Kaden, *J. Am. Chem. Soc.* **1998**, *120*, 7987 – 7990.
[19] R. Garcia, A. Paulo, A. Domingos, I. Santos, K. Ortner, R. Alberto, *J. Am. Chem. Soc.* **2000**, *122*, 11240 – 11241.
[20] R. Alberto, R. Schibli, R. Waibel, U. Abram, P. A. Schubiger, *Coord. Chem. Rev.* **1999**, *190 – 192*, 901 – 919.
[21] C. P. Casey, M. A. Andrews, D. R. McAlister, J. E. Rinz, *J. Am. Chem. Soc.* **1980**, *102*, 1927 – 1933.
[22] W. Tam, G.-Y. Lin, W.-K. Wong, W. A. Kiel, V. K. Wong, J. A. Gladysz, *J. Am. Chem. Soc.* **1982**, *104*, 141 – 152.
[23] F. Le Bideau, B. El Kaloun, P. Haquette, U. Kernbach, J. Marrôt, E. Stephan, S. Top, A. Vessières, G. Jaouen, *Chem. Commun.* **2000**, 211 – 212.
[24] F. Minutolo, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1998**, *120*, 13264 – 13265.
[25] A. Efraty, *J. Organomet. Chem.* **1973**, *57*, 1 – 28 and references therein.
[26] A. Z. Rubezhov, S. P. Gubin, *Adv. Organomet. Chem.* **1972**, *10*, 347 – 417.
[27] M. Wenzel, C. Klinge, *J. Labelled Compd. Radiopharm.* **1994**, *34*, 981 – 987.
[28] T. W. Spradau, J. A. Katzenellenbogen, *Organometallics* **1998**, *17*, 2009 – 2017.
[29] S. Top, C. Lescop, J.-S. Lehn, G. Jaouen, *J. Organomet. Chem.* **2000**, *593 – 594*, 167 – 174.
[30] S. Top, K. El Bachir, G. Jaouen, *J. Am. Chem. Soc.* **2000**, *122*, 736 – 737.
[31] S. Liu, D. S. Edwards, J. A. Barrett, *Bioconjugate Chem.* **1997**, *8*, 621 – 636.
[32] G. L. Griffiths, D. M. Goldenberg, A. L. Jones, H. J. Hansen, *Bioconjugate Chem.* **1992**, *3*, 91 – 99.
[33] A. J. Fischmann, J. W. Babich, H. W. Strauss, *J. Nucl. Med.* **1993**, *34*, 2253 – 2265.
[34] A. J. Fishman, J. W. Babish, H. W. Strauss, *J. Nucl. Med.* **1993**, *34*, 2253 – 2263.
[35] S. Top, P. Morel, G. Jaouen, *Inorg. Chem. Commun.* **1998**, *2*, 7 – 9.
[36] T. W. Spradau, J. A. Katzenellenbogen, *Bioconjugate Chem.* **1998**, *9*, 765 – 772.
[37] M. Salmain, M. Gunn, A. Gorfti, S. Top, G. Jaouen, *Bioconjugate Chem.* **1993**, *4*, 425 – 433.
[38] T. W. Spradau, W. B. Edwards, C. J. Anderson, M. J. Welch, J. A. Katzenellenbogen, *Nucl. Med. Biol.* **1999**, *26*, 1 – 7.
[39] S. Top, H. El Hafa, A. Vessières, J. Quivy, J. Vaissermann, D. W. Hughes, M. J. McGlinchey, J.-P. Mornon, E. Thoreau, G. Jaouen, *J. Am. Chem. Soc.* **1995**, *117*, 8372 – 8380.
[40] G. Jaouen, S. Top, A. Vessières, R. Alberto, *J. Organomet. Chem.* **2000**, *600*, 23 – 36.
[41] G. Tamagnan, Y. Gao, L. Xu, N. S Kula, R. J. Baldessarini, J. L. Neumeyer, "Parkinson's Disease": *Adv. Neurol.* **1999**, *80*, 99 – 103.
[42] G. Tamagnan, R. M. Baldwin, N. S. Kula, R. J. Baldessarini, R. B. Innis, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1113 – 1115.
[43] M. B. Skaddan, F. R. Wüst, S. Jonson, R. Syhre, M. J. Welch, H. Spies, J. A. Katzenellenbogen, *Nucl. Med. Biol.* **2000**, *27*, 269 – 278.
[44] S. Top, R. Alberto, unpublished results.
[45] N. Metzler-Nolte, *Angew. Chem.* **2001**, *113*, 1072 – 1076; *Angew. Chem. Int. Ed.* **2001**, *40*, 1040 – 1043.

  0947-6539/01/0711-2294 $ 17.50+.50/0