Direct Synthesis of Tricarbonyl(cyclopentadienyl)rhenium and Tricarbonyl(cyclopentadienyl)technetium Units from Ferrocenyl Moieties − Preparation of 17α-Ethynylestradiol Derivatives Bearing a Tricarbonyl(cyclopentadienyl)technetium Group

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The preparation of new tricarbonyl(cyclopentadienyl)rhenium and tricarbonyl(cyclopentadienyl)technetium derivatives is described. The approach used was applied to a cold target model, 17α-ethynylestradiol substituted at the 17α position by a ketotricarbonyl(cyclopentadienyl)rhenium group. The novel organometallic reaction applied here, when extended to potential radiopharmaceuticals, consists of a cyclopentadienyl-ligand transfer between ketoferrocenes and *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ in a water/DMSO 1:1 mixture. This reaction lead to the synthesis of a new estradiol derivative, labeled with ^{99m}Tc. The synthesis of another product was performed by using $[^{99}TcCl_3(CO)_3]^{2-}$ as the Tc precursor and its X-ray crystal structure was determined. In each case high yields were obtained.

Introduction

The synthesis of new radiolabeled estrogen derivatives has generated much interest during the last decade.[1] The design of new molecules labeled with technetium, ^{99m}Tc, or rhenium, ^{188}Re, for imaging and therapy of breast tumors, respectively, is of current interest since most of the compounds prepared have not yet shown enough affinity or selectivity towards estrogen receptors (ER) and, in addition, their synthesis is rather circuitous. Many different systems have been envisaged for the labeling of ligands with technetium or rhenium. One general approach is the coordination of a Tc^V moiety through chelation with heteroatom systems, but the molecules obtained are not always stable in solution.[1,2] Therefore, we have elaborated an organometallic approach, in which a low-oxidation-state-rhenium core is tethered to a cyclopentadienyl (Cp) ligand.[3] The organometallic tether using this ligand seems to be particularly attractive. This group has the advantage of being lipophilic, fairly small in size and very robust. Furthermore, this approach can be easily extended to the preparation of tricarbonyl(cyclopentadienyl)technetium compounds because Re and Tc complexes exhibit very similar chemical behavior.

The search for an easy route to $CpM(CO)_3$ complexes (where M = Re, Tc) bearing a functional substituent on the Cp ring, with the purpose of being compatible with the handling of radioactive compounds, has attracted much interest.[4] Wenzel reported a unique double ligand-transfer reaction where the technetium source is $[^{99m}TcO_4]^-$.[5] More recently, Alberto et al. reported the preparation of different $[(R\text{-}Cp)^{99m}Tc(CO)_3]$ molecules (R = ketone), where the *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ compound, generated in physiological media, is the ^{99m}Tc precursor.[6] With regard to rhenium, Top et al. reported various syntheses of $[(R'\text{-}Cp)Re(CO)_3]$ molecules (R′ = organic fragment) based on the use of $[Re(CO)_6][BF_4]$ with particular monosubstituted ferrocene compounds in DMSO. This method is compatible with aqueous media as we obtained promising results in a water/DMSO 1:1 mixture.[7]

The first step in the transformation of $[Re(CO)_6][BF_4]$ in DMSO seems to be the departure of three carbonyl ligands from the $[Re(CO)_6]^+$ cation. Thus, we postulated the formation of the *fac*-$[Re(DMSO)_3(CO)_3]^+$intermediate. It is believed that *fac*-$[Re(DMSO)_3(CO)_3]^+$ may react with the cyclopentadienyl ligands the same way that *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ does.[6,7] Combining these aspects, we decided to extend our work with ferrocene derivatives and the $[Re(CO)_6]^+$ cation to the preparation of [(R-

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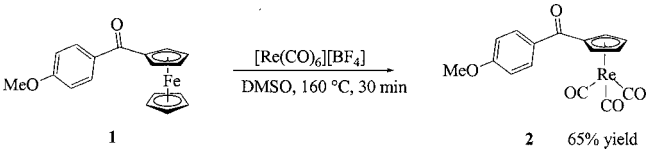
Cp)^{99m}Tc(CO)$_3$] from the same ferrocene derivatives and using *fac*-[^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ as the reagent.

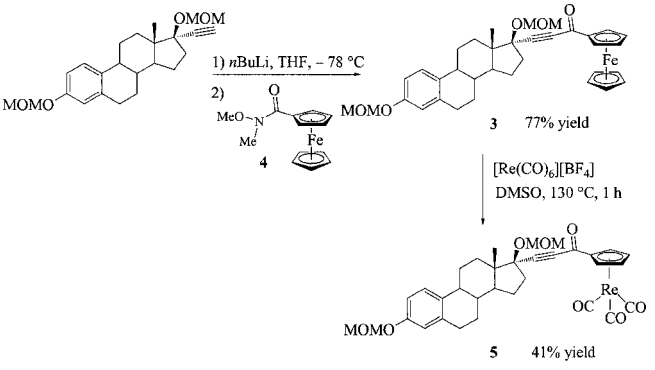
Results and Discussion

The ketoferrocene **1** was first used as a model for the reaction between [Re(CO)$_6$][BF$_4$] and *fac*-[^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$. It was prepared from ferrocene and *p*-anisoyl chloride following the procedure described in the literature.[8] The reaction with [Re(CO)$_6$]$^+$ was carried out by heating the DMSO solution of **1** and [Re(CO)$_6$]$^+$ at 160 °C for 30 min and **2** was obtained in 65 % yield (see Scheme 1).



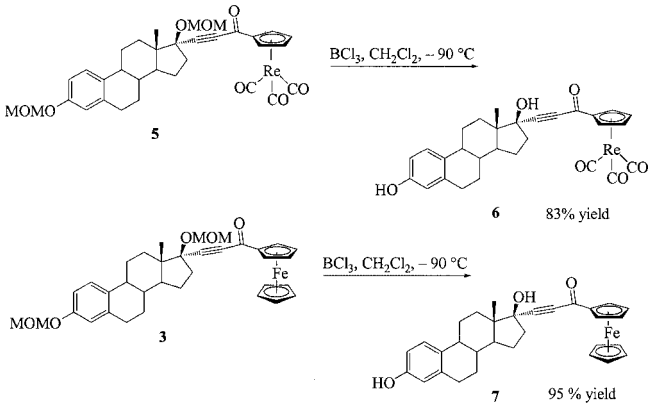
Scheme 1. Ligand-transfer reaction between ketoferrocene **1** and the hexacarbonylrhenium cation

In the hormone series, the ferrocenyl-β-estradiol derivative, **3**, was prepared. The amidoferrocene **4**, prepared according to the Weinreb method,[9] was reacted with the lithium compound generated from 17α-ethynylestradiol, diprotected with methylmethoxy (MOM) to produce **3** (see Scheme 2). Heating **3** with [Re(CO)$_6$][BF$_4$] in DMSO for one hour affords the rhenium compound **5** in 41 % yield.

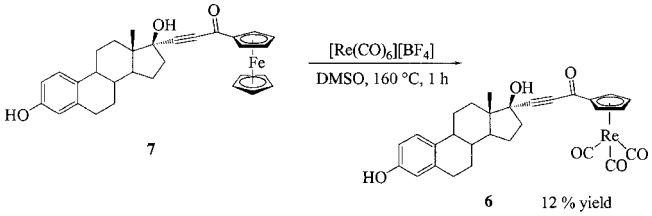


Scheme 2. Synthesis of tricarbonyl(cyclopentadienyl)rhenium derivative **5**

The removal of the methoxymethyl groups was achieved by using BCl$_3$ in dichloromethane (see Scheme 3). The rhenium compound **6** and the ferrocenyl derivative **7** were obtained in good yields. Compound **6** had already been prepared by another method.[10] Heating the unprotected ferrocenyl steroid **7** with [Re(CO)$_6$][BF$_4$] also gives the rhenium complex **6** but in low yield (12 %) (see Scheme 4).

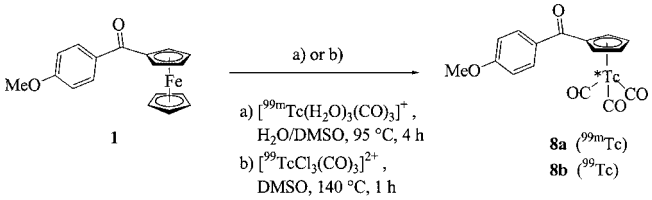


Scheme 3. Deprotection of the ethynyl estradiol derivatives



Scheme 4. Ligand-transfer reaction between **7** and the rhenium-hexacarbonyl cation

Since the chemistry of Re is similar to that of Tc, the above reaction between [Re(CO)$_6$]$^+$ and the ferrocenyl derivative may be adapted to Tc analogs. Recently, Alberto et al. have found a very convenient synthetic method for [^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ starting from ^{99m}TcO$_4^-$.[11] Therefore, it would be interesting to use the reagent [^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ in the exchange reaction. According to the procedure already described for the reaction of *fac*-[^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ with NaCp derivatives,[6] an aliquot of 0.5 mL of an aqueous solution containing [^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ (nM–μM range) was mixed with 0.5 mL of a DMSO solution, where an excess of **1** had been previously dissolved (1.5–2 μmol). The mixture was heated at 95 °C and the reaction was monitored by HPLC (high-pressure liquid chromatography) equipped with a γ radiodetector. The expected complex, **8a**, was formed in > 80 % radiochemical yield after heating for 4 h (see Scheme 5). The presence of **8a** (^{99m}Tc) was confirmed by comparing its HPLC chromatogram, measured by γ-detection, with the HPLC chromatogram of the analogous cold compound, **2** (Re). Due to the very low concentration of the ^{99m}Tc species, characterization is only possible by chromatographic comparison.



Scheme 5. Synthesis of a cyclopentadienyltechnetium derivative from the corresponding ferrocene precursor

After the successful formation of **8a** from *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$, we attempted to synthesize **8** on a larger scale, in order to identify it with more accuracy. Starting from $[^{99}TcCl_3(CO)_3]^{2-}$, larger quantities of complex **8** can be produced and handled because the long half-life of ^{99}Tc results in weak radiation of this isotope. Thus, **1** was treated in 0.5 mL of DMSO at 140 °C with $[^{99}TcCl_3(CO)_3][Et_4N]_2$. Within 1 h, **8b** had formed in about 74 % yield and was crystallized from a diethyl ether/hexane 2:1 solution. The reaction was monitored with HPLC equipped with a β radiodetector. The retention time of the isolated **8b** (^{99}Tc) is very close to that of **8a** (^{99m}Tc) (24.3 min for **8b** and 24.4 min for **8a**, respectively), thus proving the identity of **8a**. The structure of **8b** was elucidated by an X-ray study. An ORTEP representation of this complex is given in Figure 1.

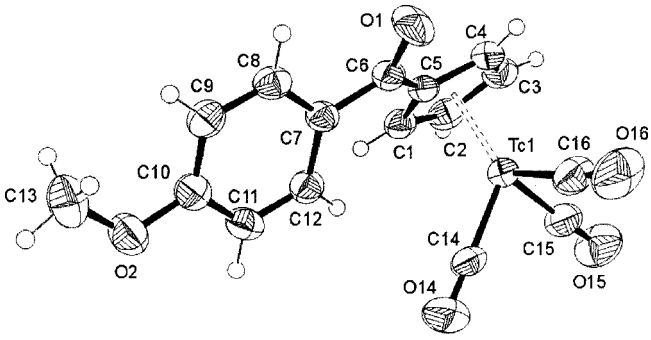
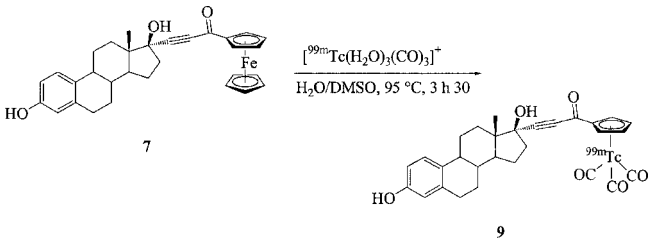


Figure 1. Ortep plot of **8b**, ellipsoids drawn with 50 % probability

We next applied the reaction between ketoferrocene compounds and the reagent *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ to steroid **7** and obtained molecule **9** with excellent yields. Thus, using the conditions described above with **1** and heating for 3 h 30 min, allowed us to form **9** in quantitative yield (> 90%) (see Scheme 6). It is remarkable that such a mild and efficient reaction has never been reported for the synthesis of molecules belonging to the class of ethynylestradiol. Additionally, it is noteworthy that our approach for the labeling of ^{99m}Tc on (bio)organic molecules constitutes a real improvement, with regard to the transformations of ferrocene derivatives into corresponding tricarbonyl(cyclopentadienyl)technetium derivatives, described in the literature.[5,12]



Scheme 6. Synthesis of a novel 17α-ethynyl estradiol derivative labeled with ^{99m}Tc, in a water/DMSO 1:1 mixture at atmospheric pressure

Conclusion

In summary, we have presented the synthesis of new complexes bearing tricarbonyl(cyclopentadienyl)rhenium or tricarbonyl(cyclopentadienyl)technetium functionalities, where the target molecules belong to the estradiol series. In addition, the first synthesis of tricarbonyl(cyclopentadienyl)-technetium derivatives from the organometallic aqua complex *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ and ferrocene-containing compounds has been successfully investigated. Thanks to this convenient method, the efficient radiochemical synthesis of a novel 17α-ethynylestradiol derivative can be achieved in aqueous media under mild conditions, without protecting the estradiol substituents. On the basis of these encouraging results, the reaction should be useful in the development of a wide variety of radiolabeled compounds in aqueous media.

Experimental Section

DMSO was used without any purification. TLC chromatography was performed on silica gel 60-GF254. Infrared spectra were recorded on an IR-FT BOMEM Michelson-100 spectrometer. ^1H- and ^{13}C NMR spectra were recorded on 200 MHz and 400 MHz Bruker spectrometers. Mass spectrometry was performed with a Nermag R 10−10C spectrometer. Melting points were measured with a Kofler device. Elemental analyses were performed by the regional microanalysis department of Université Pierre et Marie Curie.

1: $AlCl_3$ (0.477 g, 3.49 mmol) was added to a 5 mL dichloromethane solution of ferrocene (0.5 g, 2.69 mmol). *p*-Anisoyl chloride (0.305 g, 1.79 mmol) was then added dropwise and the resulting solution was stirred for 4 h at room temperature. The mixture was hydrolyzed with water (40 mL) and the aqueous solution was extracted with diethyl ether (3 × 80 mL). All the organic fractions were combined, dried over magnesium sulfate, filtered and the solvents evaporated. The compound was purified by a silica-gel plate (dichloromethane) to give **1** (0.18 g, 31% yield); m.p. 74−76 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, -OCH_3), 4.13 (s, 5 H, Cp), 4.49 (s, 2 H, 2,5-H of C_5H_4), 4.83 (s, 2 H, 3,4-H of C_5H_4), 6.89 (d, *J* = 8.0 Hz, 2 H, Ar), 7.88 (d, *J* = 8.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.4 (-OCH_3), 70.1 (C_{Cp}), 71.4 (C_{Cp}), 72.1 (C_{Cp}), 113.4 (C_{Ar}), 130.4 (C_{Ar}), 162.4 (C_{Ar}), 197.3 (CO) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1635 (ν_{CO}) cm^{-1}. MS (EI): *m*/*z* = 56 $[Fe]^+$, 77, 92, 121, 135 $[M - Fc]^+$, 171, 277, 320 $[M]^+$.

2: $[Re(CO)_6][BF_4]$ (0.073 g, 0.166 mmol) was dissolved in DMSO (1 mL) in a 5 mL round-bottomed flask equipped with a magnetic stirring bar. Compound **1** (0.166 g, 0.518 mmol) was added and the solution was heated for 30 min at 160 °C. The mixture was allowed to warm to room temperature and then water (10 mL) was added. The product was extracted with dichloromethane (2 × 50 mL). The organic phase was washed, dried ($MgSO_4$), filtered and concentrated. The mixture was purified by chromatography on a silica-gel plate (ethyl acetate/petroleum ether 1:7) to give **2** (0.051 g, 65 % yield); m.p. 186 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, -OCH_3), 5.45 (t, *J* = 2.2 Hz, 2 H, 3,4-H of C_5H_4), 6.05 (t, *J* = 2.2 Hz, 2 H, 2,5-H of C_5H_4), 6.95 (d, *J* = 8.0 Hz, 2 H, Ar), 7.83 (d, *J* = 8.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.4 (-OCH_3), 85.1 (2 C_{Cp}), 89.4 (2 C_{Cp}), 113.8 (2 C_{Ar}), 130.8 (2

C_{Ar}) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2030 s, 1938 s, 1652 w (ν_{CO}) cm^{-1}. MS (EI): *m/z* = 386 [M − 3 CO]$^+$, 412, 442 [M − CO]$^+$, 469 [M]$^+$. $C_{16}H_{11}O_5Re$ (469.46): calcd. C 40.93, H 2.36; found C 40.97, H 2.29.

4: The synthesis of **4** was performed using the procedure for the preparation of *N*-methoxy-*N*-methylamides (see reference [9]). Oxalyl chloride (7.250 g, 57 mmol) was added to ferrocenecarboxylic acid (0.550 g, 2.39 mmol) placed in a Schlenk tube and cooled in an ice bath. The mixture was stirred for 3 h, then the excess oxalyl chloride was removed under vacuum. Chloroform (20 mL) was added, followed by addition of *N*,*O*-dimethylhydroxyamine hydrochloride (0.260 g, 2.63 mmol). Anhydrous pyridine (0.420 g, 5.26 mmol) was added dropwise to the mixture, cooled in an ice bath. The mixture was stirred for 2 h 30 min to allow the temperature to rise to room temperature. Then, dichloromethane (200 mL) was added and the solution obtained was washed with a saturated K_2CO_3 solution, dried over magnesium sulfate, filtered and the solvents were evaporated. The compound obtained was crystallized in pentane to give **4** (0.524 g, 83 % yield); m.p. 28 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.31 (s, 3 H, -NCH_3), 3.74 (s, 3 H, -$NOCH_3$), 4.22 (s, 5 H, Cp), 4.39 (t, *J* = 1.8 Hz, 2 H, 3,4-H of C_5H_4), 4.91 (t, *J* = 1.8 Hz, 2 H, 2,5-H of C_5H_4) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.4 (-NCH_3), 61.0 (-$NOCH_3$), 69.5 (C_{Cp}), 70.6 (C_{Cp}), 71.0 (C_{Cp}), 73.0 (C_{Cp}), 171.0 (CO) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1616 s (ν_{CO}) cm^{-1}. MS (EI): *m/z* = 56 [Fe]$^+$, 65 [Cp]$^+$, 121 [FeCp]$^+$, 129, 185 [Fc]$^+$, 213 [FcCO]$^+$, 273 [M]$^{+\cdot}$. $C_{13}H_{15}FeNO_2$ (273.05): calcd. C 57.17, H 5.54, N 5.13; found C 57.02, H 5.73, N 5.15.

3: In a Schlenk tube, 17α-ethynylestradiol diprotected with a methoxymethyl group (0.665 g, 1.73 mmol) was dissolved in THF (6 mL) and cooled to −78 °C. *n*BuLi (0.8 mL, 2.05 mmol, 2.5 M solution in hexane) was added dropwise and the mixture was stirred for 1 h. By that time the temperature had risen to −50 °C. Then, a solution of **4** (0.429 g, 1.57 mmol) in THF (4 mL) was added dropwise. After 15 min of stirring, the ice bath was removed and the stirring was maintained for two more hours . Then, dichloromethane (200 mL) was added and the solution obtained was washed with water, dried over magnesium sulfate, filtered and the solvents were evaporated. The crude product was purified by chromatography on a silica-gel plate (diethyl ether/petroleum ether 1:1) to give **3** (77 %); m.p. 102 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (s, 3 H, CH_3-18), 2.88 (m, 2 H, H-6), 3.47 (s, 3 H, -OCH_3), 3.48 (s, 3 H, -OCH_3), 4.28 (s, 5 H, Cp), 4.61 (t, *J* = 2 Hz, 2 H, 3,4-H of C_5H_4), 4.90 (d, *J* = 6.6 Hz, 1 H, -OCH_2O-17), 4.94 (t, *J* = 2 Hz, 2 H, 3,4-H of C_5H_4), 5.13 (d, *J* = 6.6 Hz, 1 H, -OCH_2O-17), 5.16 (s, 2 H, -OCH_2O-3), 6.79 (d, *J* = 2.6 Hz, 1 H, H-4), 6.84 (dd, *J* = 8.4, 2.6 Hz, 1 H, 2-H), 7.24 (d, *J* = 8.4 Hz, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.0 (C-18), 29.6 (C-6), 23.1, 26.3, 27.3, 33.5 and 37.3 (C-7, C-11, C-12, C-15 and C-16), 39.1, 43.7, 49.3 (C-8, C-9 and C-14), 48.5 (C-13), 55.8 and 56.0 (2 MeO-3), 70.3 and 73.3 (C_{Cp}), 85.4 and 87.4 (C_{Cp} and C-17), 91.0, 93.9 and 94.4 (C-19, C-20, and -OCH_2O-), 113.7 (C-2), 116.2 (C-4), 126.3 (C-1), 133.5 (C-10), 137.9 (C-5), 155.1 (C-3) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2207 w ($\nu_{C\equiv C}$), 1623 s (ν_{CO}) cm^{-1}. MS (EI): *m/z* = 45 [CH_2OCH_3]$^+$, 596 [M]$^{+\cdot}$. MS (IC, DCI/NH_3): *m/z* = 597 [M + H]$^+$. $C_{35}H_{40}FeO_5$ (596.22): calcd. C 70.47, H 6.76; found C 70.17, H 7.17.

5: [$Re(CO)_6$][BF_4] (0.540 g, 1.22 mmol) was dissolved in DMSO (1 mL) in a 5 mL round-bottomed flask equipped with a magnetic stirring bar. Compound **3** (0.640 g, 1.07 mmol) was added and the solution was heated for 1 h at 130 °C. The mixture was allowed to warm to room temperature and then water (10 mL) was added. The product was extracted with dichloromethane (2 × 150 mL). The organic phase was washed, dried ($MgSO_4$), filtered and concentrated. The mixture was purified by chromatography on a silica-gel plate (ethyl acetate/petroleum ether 1:5) to give **5** (0.331 g, 41 % yield); m.p. 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 3 H, CH_3-18), 2.85 (m, 2 H, H-6), 3.43 (s, 3 H, -OCH_3), 3.47 (s, 3 H, -OCH_3), 4.84 (d, *J* = 7.2 Hz, 1 H, -OCH_2O-17), 4.99 (d, *J* = 7.2 Hz, 1 H, -OCH_2O-17), 5.15 (s, 2 H, -OCH_2O-3), 5.41 (m, 2 H, 3,4-H of C_5H_4), 6.21 (m, 2 H, 2,5-H of C_5H_4), 6.78 (d, 1 H, 4-H), 6.83 (dd, *J* = 8.4 Hz, 1 H, 2-H), 7.20 (d, *J* = 8.4 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2 (C-18), 29.8 (C-6), 23.1, 26.3, 27.2, 33.7 and 37.4 (C-7, C-11, C-12, C-15 and C-16), 39.1, 43.5 and 49.5 (C-8, 9 and C-14), 48.8 (C-13), 56.0 (2 CH_3O), 85.1 and 85.4 (C_{Cp} and C-17), 85.5, 89.2 and 89.3 (C_{Cp}), 94.0 (-OCH_2O-17), 94.5 (-OCH_2O-3), 94.3 and 96.5 (C-19 and C-20), 113.8, 116.3 and 126.5 (C-1, C-2, and C-4), 133.4 (C-10), 138.0 (C-5), 155.1 (C-3), 171.3 (CO, ketone), 191.4 (Re-CO) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2205 w ($\nu_{C\equiv C}$), 2032 s, 1940 vs, 1642 w (ν_{CO}) cm^{-1}. MS (EI): ^{187}Re *m/z* = 45 [CH_2OCH_3]$^+$, 746 [M]$^+$. MS (IC, DCI/NH_3): ^{187}Re *m/z* = 747 [M + H]$^+$, 764 [M + NH_4]$^+$. $C_{33}H_{35}O_8Re$ (746.19): calcd. C 53.14, H 4.73; found C 53.07, H 5.00.

6: The deprotection of **5** was carried out according to a procedure described in the literature.[13] Under an inert atmosphere, **5** (0.070 g, 0.094 mmol) was dissolved in 8 mL of dichloromethane. The solution was cooled to −90 °C and BCl_3 (1 mL, 1 M in CH_2Cl_2) was added dropwise. A rapid evolution of the color from beige to orange was observed. The solution was stirred for 30 min, the temperature of the cooling bath was thus −30 °C. The bath was removed and dichloromethane (150 mL) was poured into the mixture. This organic phase was washed with water (50 mL) and neutralized with 50 mL of K_2CO_3 (10 %). The organic phase was washed, dried ($MgSO_4$), filtered and concentrated. The mixture was purified by silica-gel chromatography (diethyl ether/petroleum ether 2:1) to give **6** (0.051 g, 83% yield); m.p. 156 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (s, 3 H, CH_3-18), 2.75 (m, 2 H, 6-H), 5.78 (m, 2 H, 3,4-H of C_5H_4), 6.34 (m, 2 H, 2,5-H of C_5H_4), 6.53 (d, 1 H, 4-H), 6.59 (dd, 1 H, 2-H), 7.09 (d, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (C-18), 23.1 (C-15), 26.3, 27.1 (C-7 and C-11), 29.6 (C-6), 33.3 (C-16), 39.0 and 39.4 (C-12 and C-8), 43.5 (C-9), 48.1 (C-13), 50.3 (C-14), 80.4 (C-17), 85.5 and 89.4 (4 C_{Cp}), 83.0, 96.3 and 96.6 (1 C_{Cp} and C≡C), 112.8 (C-2), 115.3 (C-4), 126.7 (C-1), 132.3 (C-10), 138.3 (C-5), 153.5 (C-3), 171.4 (CO), 191.5 (Re-CO) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2033 s, 1943 vs, 1653 w (ν_{CO}) cm^{-1}. MS (IC, DCI/NH_3): ^{187}Re *m/z* = 659 [M + H]$^+$, 676 [M + NH_4]$^+$. $C_{29}H_{27}O_6Re$ + 1 Et_2O (732.21): calcd. C 54.16, H 5.10; found C 54.35, H 5.01.

7: The deprotection of **3** was carried out according to the procedure described above for the deprotection of **5**. The crude material was purified by silica-gel chromatography (diethyl ether/petroleum ether 1:1) to give **7** (0.081 g, 95% yield); m.p. 143 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (s, 3 H, CH_3-18), 2.84 (m, 2 H, 6-H), 4.28 (s, 5 H, Cp), 4.63 (t, 2 H, 3,4-H of C_5H_4), 4.93 (t, 2 H, 2,5-H of C_5H_4), 6.59 (d, 1 H, 4-H), 6.64 (dd, *J* = 8.4 Hz, 1 H, 2-H), 7.17 (d, *J* = 8.4 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (C-18), 23.0 (C-15), 26.3, 27.3 (C-7 and C-11), 29.6 (C-6), 33.2 (C-16), 39.0 and 39.3 (C-12 and C-8), 43.5 (C-9), 47.9 (C-13), 50.2 (C-14), 70.6 (C_{cp} and 2 $C_{cp'}$), 73.7 (2 $C_{cp'}$), 80.1 (C-17), 84.9 and 94.8 (1 $C_{Cp'}$ and C≡C), 112.8 (C-2), 115.3 (C-4), 126.5 (C-1), 131.8 (C-10), 137.9 (C-5), 153.9 (C-3), 181.7 (CO) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1623 s (ν_{CO}) cm^{-1}. MS (EI): *m/z* = 43, 73, 147, 207, 221, 281, 508 [M]$^{+\cdot}$. $C_{31}H_{32}FeO_3$ + H_2O (526.43): calcd. C 70.72, H 6.52; found C 71.33, H 6.78.

6 from 7: The compound **6** was also prepared according to the procedure described above for the synthesis of **2** or **5** (see also Scheme 4). 12 % yield of **6** was obtained.

8a: 0.5 mL of an aqueous solution containing the starting material $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was prepared as described in the literature.[11] Compound **1** (0.6 mg, 1.9 μmol) in 0.5 mL of DMSO was added to the aqueous solution. Subsequent heating at 95 °C for 4 h afforded **8a** in an overall yield of > 80%.

8b: Compound **1** (0.0170 g, 0.053 mmol) in 0.5 mL of DMSO was added to $[NEt_4]_2[TcCl_3(CO)_3]$ (0.0225 g, 0.041 mmol) in a Schlenk tube equipped with a magnetic stirring bar. The mixture was heated for 1 h at 140 °C, yielding a brownish precipitate containing the product, as shown by HPLC analysis. The crude product was purified by column chromatography on a silica-gel plate (ethyl acetate/petroleum ether 1:7). Yield: 74 %. The product was dissolved in a diethyl ether/hexane 2:1 solution, slow evaporation of the solvents gave crystals suitable for an X-ray study. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, -OCH_3), 5.37 (t, J = 2.4 Hz, 2 H, 3,4-H of C_5H_4), 6.01 (t, J = 2.4 Hz, 2 H, 2,5-H of C_5H_4), 6.96 (d, J = 9.0 Hz, 2 H, Ar), 7.84 (d, J = 9.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.5 (-OCH_3), 87.0 (2 C_{Cp}), 91.85 (2 C_{Cp}), 113.8 (2 C_{Ar}), 130.7 (2C_{Ar}), 163.2 (CO, ketone) ppm. ^{99}Tc NMR (740 Hz, $CDCl_3$): δ = −2478 ppm. IR (KBr): $\tilde{\nu}$ = 2040 s, 1957 vs, 1930 vs, 1631 w (ν_{CO}) cm^{-1}. MS (FAB): m/z = 382 $[M]^+$.

X-ray Crystal-Structure Determination of 8b: ($C_{16}H_{11}O_4Tc$), orange needle, 0.3 × 0.1 × 0.1 mm^3, Stoe IPDS diffractometer, λ = 0.71073 Å, φ oscillation scan, monoclinic, space group $P21/c$, a = 18.2751(5), b = 13.1242(8), c = 6.1913(17) Å, β = 90.380(11)°, V = 1484.9(4) Å^3, Z = 4, $D_{calcd.}$ = 1.634 g cm^{-3}, $R_1(I \geq 2\sigma(I)]$ = 0.0437, $wR_2(F^2, I \geq 2\sigma(I)]$ = 0. 0995 for 2595 data (total 14235 reflections collected, 4435 independent (R_{int} = 0.0984), 2595 observed (I, ≥ 2σ(I)]), θ range: 3.10 to 30.55°, completeness 97.4 %, 200 parameters, refinement with SHELXL-97[14] against F^2, calculated positions of hydrogen atoms, no absorption correction, μ = 0.981 mm^{-1}. CCDC-209247 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

9: 0.5 mL of an aqueous solution containing the starting material $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was prepared as described in the literature.[11] Compound **7** (0.8 mg, 1.6 μmol) in 0.5 mL of DMSO was added to the aqueous solution. Subsequent heating at 95 °C for 3 h 30 min afforded **9** in an overall yield of > 90%.

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[1] [1a] F. Wust, H. Spies, B. Johannsen, *Bioorg. Med. Chem. Lett.* **1996**, *22*, 2729−2734. [1b] M. Reisgys, F. Wust, R. Alberto, R. Schibli, P. A. Schubiger, H. J. Pietzsch, H. Spies, B. Johannsen, *Bioorg. Med. Chem. Lett.* **1997**, *17*, 2243−2246. [1c] F. Wust, D. Scheller, H. Spies, B. Johannsen, *Eur. J. Inorg. Chem.* **1998**, 789−793. [1d] J. B. Arterburn, C. Corona, K. Venkateswara Rao, K. E. Carlson, J. A. Katzenellenbogen, *J. Org. Chem.* **2003**, *68*, 7063−7070.

[2] [2a] S. S. Jurisson, J. D. Lydon, *Chem. Rev.* **1999**, *99*, 2205−2218. [2b] R. C. Mease, C. Lambert, *Semin. Nucl. Med.* **2001**, XXXI, 278−285.

[3] S. Top, H. El Hafa, A. Vessieres, J. Quivy, J. Vaissermann, D. W. Hugues, M. J. McGlinchey, J.-P. Mornon, E. Thoreau, G. Jaouen, *J. Am. Chem. Soc.* **1995**, *117*, 8372−8380.

[4] [4a] G. Jaouen, S. Top, A. Vessières, R. Alberto, *J. Organomet. Chem.* **2000**, *600*, 23−36. [4b] F. Le Bideau, M. Salmain, S. Top, G. Jaouen, *Chem. Eur. J.* **2001**, *7*, 2289−2294.

[5] M. Wenzel, *J. Labelled Compd. Radiopharm.* **1992**, *31*, 641−650.

[6] J. Wald, R. Alberto, K. Ortner, L. Candreia, *Angew. Chem. Int. Ed.* **2001**, *40*, 3062−3066.

[7] S. Top, S. Masi, G. Jaouen, *Eur. J. Inorg. Chem.* **2002**, 1848−1853.

[8] A. F. Cunningham, *Organometallics* **1994**, *13*, 2480−2485.

[9] S. Nahm, S. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

[10] T. W. Spradau, J. A. Katzenellenbogen, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3235−3240.

[11] R. Alberto, K. Ortner, N. Wheatley, R. Schibli, A. P. Schubiger, *J. Am. Chem. Soc.* **2001**, *123*, 3135−3136.

[12] M. Wenzel, C. Klinge, *J. Labelled Compd. Radiopharm.* **1994**, *34*, 981−987.

[13] D. R. William, P. D. Lowder, Y.-U. Gu, *Tetrahedron Lett.* **2000**, *41*, 9397−9401.

[14] Sheldrick, G. M. SHELXL-97, University of Göttingen: Germany, **1997**.

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