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SYNTHESIS OF RHENIUM(I) AND TECHNETIUM(I) CARBONYL/DITHIOETHER LIGAND COMPLEXES BEARING 3,17β-ESTRADIOL

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Abstract: Tricarbonyldithioethermetal(I) complexes of rhenium and technetium with a pendant 3,17β-estradiol have been synthesized and characterized. The steroid ligand was bound to the metal centre by the two sulfur atoms of a 4,7-dithiaoct-1-ine spacer. © 1997 Elsevier Science Ltd.

Radiolabelled steroidal estrogens are of great interest because of their potential as *in vivo* imaging agents for hormone receptor-positive breast tumours[1,2]. In particular, current research is focused on coupling ^{99m}Tc as the preferred diagnostic radionuclide to various estrogen derivatives in order to obtain small-sized neutral complexes capable of binding to the corresponding receptor. The link between the metal centre and the estrogens can be realized either by the construction of a chelate[3] or by using a organometallic coordination approach[4].

Recently we have synthesized non radioactive "3+1"-mixed-ligand oxorhenium(V) complexes, in which the binding of the metal is accomplished by mercapto functionalized estradiol[5]. Additionally, it has been proposed to apply the organometallic technetium or rhenium aquo-complex $[M(OH_2)_3(CO)_3]^+$, which synthesis has been established on the macroscopic and the no carrier added level, for the same purpose[6-11]. Due to the known tendency to bridge the Re(I) or Tc(I) center[12], the mercapto group did not seem to be a very advantagous linker. Therefore we have chosen a bidentate thioether group, which strong interaction under exclusion of pH *equilibria* to $[M(OH_2)_3(CO)_3]^+$ is known from literature. In the present article we describe the first example of a coordination of the tricarbonylrhenium(I) and -technetium(I) core to a steroid via a small-sized dithioether unit.

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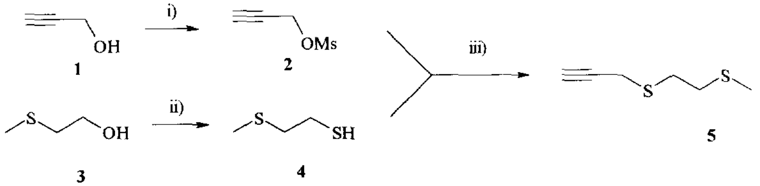
Tricarbonylrhenium and -technetium moieties are easily available as $(NEt_4)_2[ReBr_3(CO)_3]$ and $(NEt_4)_2[TcCl_3(CO)_3]$ precursors[6]. Thioether ligands with their soft donor properties substitute two of the three halogen atoms.

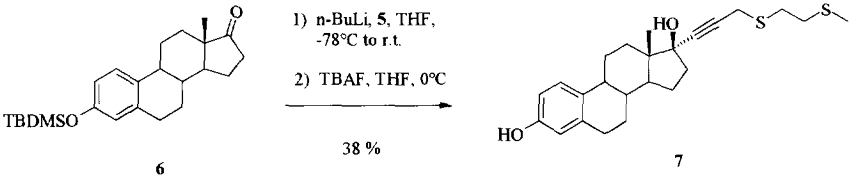
For the development of high affinity metal estradiol complexes the metal unit must be leashed to the steroid at a position which least interferes with the binding to the receptor. Earlier studies showed that substitutions by neutral bulky organometallic moieties will be fairly tolerated by the 17α-position of 3,17β-estradiol[4,13]. Therefore we concentrated on the 17α-linkage of a dithioether containing side chain. The principle of the introduction of a 17α-substituent consists in the 1,2-addition of in-situ generated lithium acetylide of **5** on *tert.*-butyldimethylsilyl protected estrone **6**[14]. The dithioether **5** was easily obtained in a 78 % yield by the reaction of propargyl mesylate **2** and 2-(methylmercapto)-ethanethiol **4** with *t*BuOK in DMF at r.t. (Scheme 1).



Scheme 1

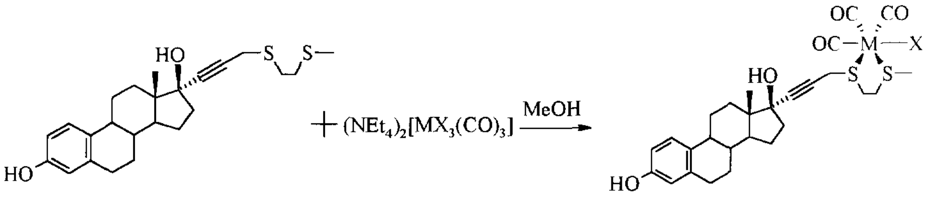
i) MsCl, Et_3N, CH_2Cl_2, (85 %); ii) 1. $SOCl_2$, $CHCl_3$, DMAP; 2. $(H_2N)_2CS$, EtOH; 3. 5N NaOH (42 %) iii) *t*BuOK, DMF, r.t. (78 %)

The introduction of the dithioether unit into the 17α-position of 3,17β-estradiol was achieved by the slow addition of the ketone **6** at r.t. to the lithium acetylide of **5** in THF. The lithium acetylide of **5** was generated subsequently by treatment of **5** with 1 equiv. of n-BuLi at -78°C in THF. The following cleavage of the silyl ether of the corresponding acetylenic carbinol by tetra-n-butyl-ammoniumfluoride (TBAF) in THF at 0°C yielded the desired dithioether **7** in a total yield of 38 % related to protected estrone **6** (Scheme 2). The formation of the 17α-substituted steroid **7** was proved by ^{13}C-NMR spectroscopy. The chemical shifts of the carbon atoms C17 (80.1), C13 (47.3), C12 (33.8) and C18 (12.8) correlate with the proposed structure of **7** in comparison with the unsubstituted 3,17β-estradiol (17α-H).



Scheme 2

The synthesis of the complexes **8**[15] and **9**[16] was performed by the reaction of the steroid **7** with the precursors $(NEt_4)_2[ReBr_3(CO)_3]$ and $(NEt_4)_2[TcCl_3(CO)_3]$ in methanol (Scheme 3). After work-up in dry THF the neutral [ReBr(SS-estradiol)$(CO)_3$] **8** and [TcCl(SS-estradiol)$(CO)_3$] **9** complexes occured nearly quantitative as white precipitates.



7

8 M = Re, X = Br
9 M = Tc, X = Cl

Scheme 3

Elemental analyses are in good agreement with the proposed formulations. The infrared spectra of **8** and **9** show a strong band at 2928 cm^{-1} due to the skeleton vibration of the steroidal methylene groups. The strong vibration bands at 2032 cm^{-1}, 1944 cm^{-1}, and 1908 cm^{-1} characterize the tricarbonylrhenium core of the formed complex **8**. In the IR spectrum of the related technetium complex **9** the CO-absorption bands are at 2048 cm^{-1}, 1960 cm^{-1}, and 1920 cm^{-1}.

The described combination of a steroidal dithioether ligand and a tricarbonyl metal core opens a new approach for the labelling bioactive molecules with radioactive metals. In further investigations we want to extend these first results aiming at other thioether modified receptor binding ligands containing rhenium- and technetiumtricarbonyl moieties.

Acknowlegdment

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15. 59 mg (140 µmol) **7** dissolved in 1 ml methanol was added to a solution of 109 mg (140 µmol) $(NEt_4)_2[ReBr_3(CO)_3]$ in 2 ml methanol. After stirring for 1 h at r.t. the solvent was evaporated. 2 ml dry THF as added and the precipitate was filtered off. The solvent of the filtrate was reduced, and the oily residue was washed with diethylether to give 101 mg (93 %) analytical clean **8**.

    Elemental analysis: calcd: C 42.29, H 4.21, S 8.36 %;
    found: C 42.14, H 4.78, S 8.23 %.

    IR (KBr): $\tilde{\nu}$ = 2032, 1944, 1908 cm^{-1}. F_p: 166-168°C.

    ^{13}C-NMR (acetone d_6; 125.77 MHz; number of steroid carbon atoms in brackets)
    δ = 198.1, 191.9, 187.9 ($C{\equiv}O$); 155.9 (3); 138.4 (5); 127.0 (1); 115.9 (4); 113.5 (2); 92.0 ($-\underline{C}{\equiv}C-CH_2-$); 80.0 ($-C{\equiv}\underline{C}-CH_2-$); 78.9 (17); 50.4 (14); 44.5 (9); 40.6 (8); 39.7 (16); 36.9, 35.3 ($-S-\underline{C}H_2-\underline{C}H_2-S-CH_3$); 34.0 (12); 30.3 (6); 29.1 ($-C{\equiv}C-\underline{C}H_2-$); 28.2 (7) 27.3 (11); 23.5 (15); 17.8 ($S-\underline{C}H_3$); 13.3 (18).

16. 19 mg (46 µmol) **7** dissolved in 1 ml methanol was added to a solution of 25 mg (46 µmol) $(NEt_4)_2[TcCl_3(CO)_3]$ in 1 ml methanol. After stirring for 1 h the solvent was reduced by N_2. The residue was collected in THF and filtrated. The filtrate was reduced to dryness and washed with diethylether. Purifying by silica gel column (chloroform/ethylacetate/methanol 9:3:1) yielded after evaporation of the eluate 26 mg (91 %) **9**.

    Elemental analysis: calcd: C 51.14, H 5.09, S 10.11 %;
    found: C 51.03, H 5.11, S 8.99 %.

    IR (KBr): $\tilde{\nu}$ = 2048, 1960, 1920 cm^{-1}. F_p: 193-195°C.

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