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SYNTHESIS OF 17α-SUBSTITUTED MERCAPTOALKYNYL DERIVATIVES OF 3,17β-ESTRADIOL

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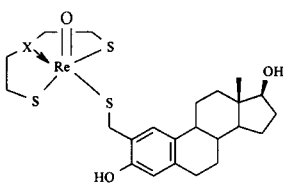
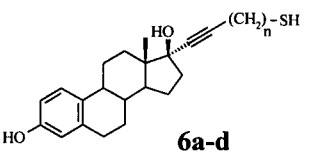
Summary: A homologous series of 17α-substituted mercaptoalkynyl estradiols have been prepared by addition of lithium acetylides to TBDMS-protected estrone

Radiopharmaceuticals which interact selectively with steroid hormone receptors are a useful tool for imaging receptor positive breast tumours. Because of its wide availability, convenient half-life and appropriate γ-energy, technetium-99m is frequently the radionuclide of choice for the application of diagnostic imaging agents in nuclear medicine[1]. Recently we reported the binding of small-sized metal chelates to modified estradiol via a single donor atom, preferably a mercaptide sulphur, for forming neutral mixed-ligand complexes of the type **A**[2].



A
X = S, O

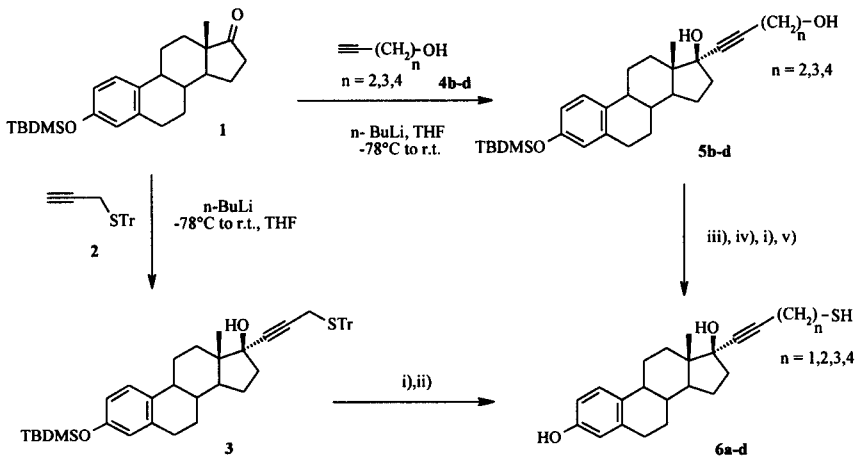


6a-d
n =1, 2, 3, 4

The present article describes the synthesis of a homologous series of 17α-substituted ω-mercaptoalkynyl estradiols **6a-d** capable of forming mixed-ligand complexes of oxorhenium(V) and oxotechnetium(V). The principle of constructing 17α substituents consists in the 1,2-addition of in-situ generated lithium acetylides on *tert*-butyldimethylsilyl-protected estrone **1**[3] (Scheme 1).

For the synthesis of thiol **6a**[4] (n=1) we used 2-propynyl trityl sulphide **2**[5] for 1,2-addition to ketone **1** followed by removal of the silyl protecting group and cleavage of the S-trityl thioether. The synthesis of thiols **6b-d** was

performed by conversion of **1** to the alcohols **5b-d**. The reaction of the dilithium derivatives of the homologues of propargyl alcohol **4b-d** (n = 2,3,4) with ketone **1** at -78°C to r.t. yielded the corresponding ω-hydroxy acetylenic carbinols **5b-d**. The subsequent conversion of **5b-d** into the desired thiols **6b-d** was achieved by mesylating the ω-hydroxy groups of **5b-d** with methanesulphonyl chloride and triethylamine in THF. Treatment of the mesylates of **5b-d** with sodium thiolacetate in DMF followed by deprotection of the silyl ethers and hydrolysis of the thiolacetate groups by sodium methoxide in methanol gave the thiols **6b-d**.



Scheme 1

i) TBAF, THF, (75%); ii) 1. $AgNO_3$, pyridine, EtOH, EtOAc; 2. HCl, acetone, (35%); iii) MsCl, Et_3N, THF (85-93%); iv) HSAc, NaH, DMF (70-85%); v) NaOMe, MeOH, (85-88%)

The compounds **6a-d** are currently being converted into the above mentioned mixed-ligand oxorhenium(V) complexes. The results from this work will be published elsewhere.

Acknowledgement

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References and Notes

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3. Fevig, T. L.; Katzenellenbogen, J. A. *J. Org. Chem.* **1987**, 52, 247-251.
4. ^{13}C-NMR data for **6a** ($CDCl_3$; 125.77 MHz; δ in ppm; number of carbon atoms of the steroid skeleton) δ = 153.4(3); 138.2(5); 132.5(10); 126.5(1); 115.2(4); 112.7(2); 80.0 (17); 84.0, 86.1(C≡C); 49.5(14); 47.4(13); 43.5(9); 39.4(8); 38.9(16); 32.9(12); 29.6(6); 27.2(7); 26.4(11); 22.8(15); 12.8(18); 12.7(CH_2SH).
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