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AN EXPEDITIOUS ROUTE TO 7α-SUBSTITUTED ESTRADIOL DERIVATIVES

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Abstract: 6-Ketoestradiol derivatives are converted in 7α-alkyl substituted estradiol derivatives selectively by alkylation of the generated enolate followed by deoxygenation-deprotection with $BF_3{\cdot}Et_2O/Et_3SiH$. © 1997 Elsevier Science Ltd.

7α-Substituted estradiols are a class of compounds of considerable pharmaceutical interest. A 7α-methyl group has been used to enhance the binding affinity and specificity of estradiol derivatives designed as radiotracers for the imaging of estrogen receptor (ER)-positive breast tumors.[1-4] A number of estradiol derivatives with longchain 7α substituents (e.g., **1d**) have pure antiestrogenic activity.[5,6]

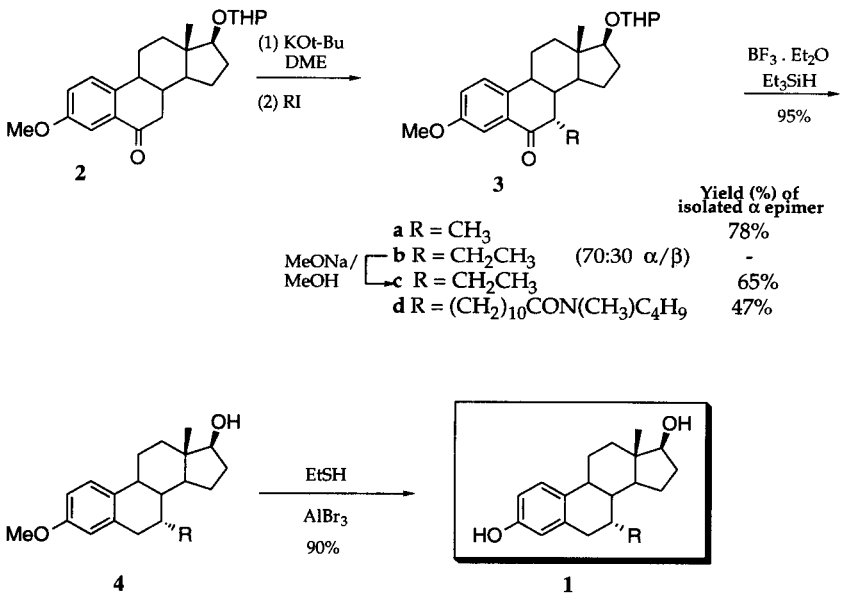
Traditionally, the synthesis of 7-alkyl estradiol derivatives has been accomplished by Cu(I) catalyzed 1,6-conjugate addition to steroidal 4,6-dien-3-ones, such 17β-hydroxyestra-4,6-dien-3-one[7,8] or 6-dehydrotestosterone.[9] This approach is, however, non stereoselective, leading to a mixture of 7α and 7β epimers. In addition, the generation of the cyclic dienone system from a precursor with an aromatic A-ring, as well as the final rearomatization step, make this approach generally inefficient.

Kunzer and co-workers have proposed two synthetic approaches for the introduction of a 7α chain in estradiol derivatives without altering the aromatic A-ring.[10,11] One is based on a Lewis acid-promoted Prins reaction involving a 7-dehydroestrogen that gives access to certain 7α-hydroxymethyl derivatives.[10] In the second and more recent approach, 6-ketoestradiol is converted into 6-(phenylsulfonyl)-6-dehydroestradiol, which undergoes conjugate addition of organolithium reagents to the C-7 position. However, except for the introduction of a 7α-ethynyl group, this method suffers from low stereoselectivity, and additional steps are required to introduce and remove the sulfone group.[11] Our interest in the synthesis of 7,11-dialkyl substituted estradiols led us to explore a more direct and versatile approach to the synthesis of 7α-substituted estradiols.

Our earlier work provided us with a convenient synthesis of the 6-ketoestradiol derivative **2**.[12] The alkylation of its enolate followed by deoxygenation of the carbonyl group appeared quite an obvious

choice for the introduction of an alkyl chain at C-7 (Scheme 1). Thus, treatment of ketone **2** with either potassium *t*-amylate[12] or potassium *t*-butoxide (commercially available as a 1M solution in THF) in dry 1,2-dimethoxyethane followed by quenching of the intermediate enolate with MeI, afforded the methylated derivative **3a** (78 % yield), uncontaminated by the β epimer. Careful control of the quantity of the base (0.99 equiv) and temperature (-78 °C) was necessary in order to avoid dialkylation. Ethylation of the potassium enolate with ethyl iodide required higher temperatures (0 °C) to obtain satisfactory conversion, and this led to a mixture of α and β epimers in a 70:30 ratio. These could be separated by chromatography. However, we made no effort to improve the selectivity of this reaction, since the 7β epimer (and hence the mixture) could be quantitatively converted into the thermodynamically more stable 7α epimer by treatment with NaOMe in MeOH.

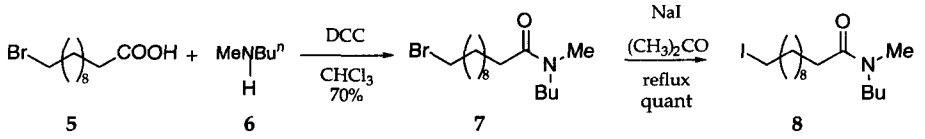
Scheme 1



In order to extend our approach to the synthesis of the pure antiestrogen ICI 164,384, we required the iodo amide **8**, which was obtained from the commercially available 11-bromoundecanoic acid by

1,3-dicyclohexylcarbodiimide (DCC)-mediated condensation with N-butyl-N-methylamine[13] followed by halogen exchange of the intermediate bromoamide **7** with excess of NaI in acetone (Scheme 2). Under optimized conditions (1.15 equiv. of base, 0 °C), 6-ketoestradiol (**2**) was alkylated with the iodoamide **8** to give the 7α-alkylated estradiol derivative **3d** as the sole epimer; this product was readily separated by chromatography from unreacted starting ketone and traces of O-alkylated material.

Scheme 2



5 6 7 8

The three alkylated ketones **3a**, **3c**, **3d** were deoxygenated by treatment with BF_3·Et_2O/Et_3SiH, conditions under which the THP protecting group is also removed; final deprotection of the methyl ether with $AlBr_3$/EtSH or BBr_3 in CH_2Cl_2 gave the target compounds **1**. In cases in which the 3- and 17β-hydroxyl groups do not need to be differentiated, 6-keto-3,17β-bis(2-tetrahydropyranyloxy)estradiol can be used as starting material, and the 7-substituted estradiol can be obtained from intermediate **3** in a single reduction step.

In conclusion, we have reported here the first stereoselective synthesis of 7α-methylestradiol, along with a new, efficient and versatile method for the synthesis of other 7α-substituted estradiols based on the alkylation of the C-6 ketone.[14] Although the yields of the alkylation step range from modest to good, our approach provides a number of advantages: the conditions are simple and the starting materials readily available; the approach allows the introduction of complex and functionalized side chains; although elimination reactions of the alkylating agent as well as O-alkylation have been observed as side reactions, unreacted steroidal ketone can be easily recovered, and the O-alkylated product can be reconverted into the 6-keto derivative by acid treatment. These features have been demonstrated by the efficient synthesis of the antiestrogen ICI 164,384.

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14. **General conditions for the alkylation of the ketone 2.** To a solution of potassium *t*-butoxide [0.130 mL (1 equiv, for methylation with excess MeI) or 0.150 mL (1.15 equiv, for alkylation with excess RI) of a 1 M solution in THF] in 4 mL DME, cooled at 0 °C, was added **2** (50 mg, 0.130 mmol). The solution was stirred at 0 °C for 40 min, and then cooled at -78 °C (dry ice-isopropyl alcohol bath), before adding the appropriate alkyl iodide. The reaction was quenched with water 10 min after the addition of MeI, or 2 hr after warming to 0 °C when the other alkylating agents were used. When the reaction was complete, water was added and the mixture extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure to leave a residue from which **3** was isolated by flash chromatography (0.5 % Et_3N in hexane/ethyl acetate 9:1 for **3a** and **3c**; 0.5 % Et_3N in hexane/ethyl acetate 7:3 for **3d**). (When **3c** is the desired product, the residue obtained (**3b**) can be dissolved in a solution of NaOMe/MeOH and stirred at 25 °C for 5 h).
    General conditions for the deoxygenation of the ketones 3a, 3c, 3d. To a solution of **3** (0.1 mmol) and Et_3SiH (1 mL) in 5 mL CH_2Cl_2 cooled at 0 °C was added $BF_3{\cdot}Et_2O$ (2 mL) dropwise. The reaction was warmed to 25 °C and stirred for 12 h. K_2CO_3 (10% aqueous solution) was then added and the mixture extracted with ethyl acetate. The combined organic phases, washed with water and then, with brine, were dried over $MgSO_4$ and evaporated at reduced pressure to give a residue. The methyl derivative **4a** (95 % yield) was obtained by recrystallization from ethyl ether. The ethyl derivative **4c** and the antiestrogen **4d** were obtained by chromatography using hexane/ethyl acetate 7:3 and hexane/ethyl acetate 1:1, respectively, as eluent.

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