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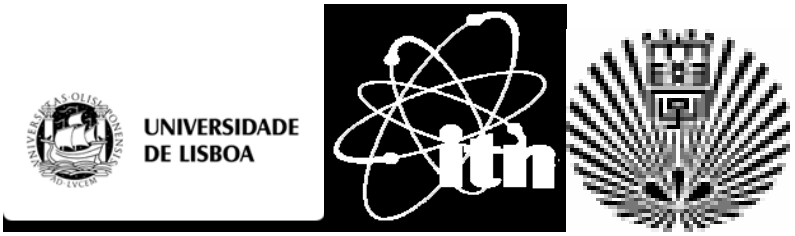

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7α-Alkoxyestra-1,3,5(10)-trienes

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Abstract: A number of α-alkoxyestradiols were prepared through $LiAlH_4$ reduction of a suitably protected 6α,7α-epoxyestra-1,3,5(10)-trien-3-ol-17-one, alkylation of the resultant 7α-hydroxyestra-1,3,5(10)-trien-3-ol-17-one derivative and subsequent transformation of the C17 functionality. The stereochemistry of the products was investigated by 2D NMR spectroscopy.

Introduction

Breast cancer remains a very serious disease and is presently the most common form of cancer among women. In 2005, 502.000 fatalities were attributed to breast cancer worldwide.[1] 60-70% of breast cancer incidents are attributed to estrogen receptor positive breast cancer.[2] In these cases, the estrogen receptor ERα, a protein, is over-expressed in the nucleus of the cancer cells. Potentially, this allows for a targeting of the breast cancer cells. Requisite for this are molecules with a high and selective binding affinity to the estrogen receptor. On this basis, one could envisage the development of diagnostic and therapeutic agents that would differentiate between the cancer cells with a relatively high concentration of estrogen receptor and healthy breast tissue normally devoid of estrogen receptor. Within the last years, much research has been addressed to the synthesis and study of molecules that interact with the estrogen receptor. Here, one may distinguish among three categories of compounds: estrogens, antiestrogens and selective estrogen receptor modulators. Basically, estrogens (= agonists) interact with the estrogen receptor, triggering the actions associated with an activated receptor-ligand complex, while antiestrogens (antagonists) interact with the receptor, but the receptor-ligand complex remains inactive. Selective estrogen receptor modulators (SERMs) act through the estrogen receptor depending on the type of tissue. Raloxifene **4** (Eli Lilly) and tamoxifene **5** (ICI, now Astra-Zeneca) are typical SERMs (Figure 1). Many of the synthetic estrogens and antiestrogens, however, base themselves on the structure of the natural ligand for the estrogen receptor ERα, estra-3,17β-diol **1** (Figure 1). A number of studies have appeared on the effect of substituents in estradiols on the *in vitro* binding of the molecules to the receptor. These studies culminated QSAR

aided compilation of the binding affinities of various substituted estradiols.[3] It has been found that substitution at C7α[4] or at C11β[5] in estradiol can be tolerated by the receptor and in some cases may lead to an increase of the binding affinity of the molecule. A number of C7α-substituted estradiols have been found to be pure antiestrogens.[4c,d]

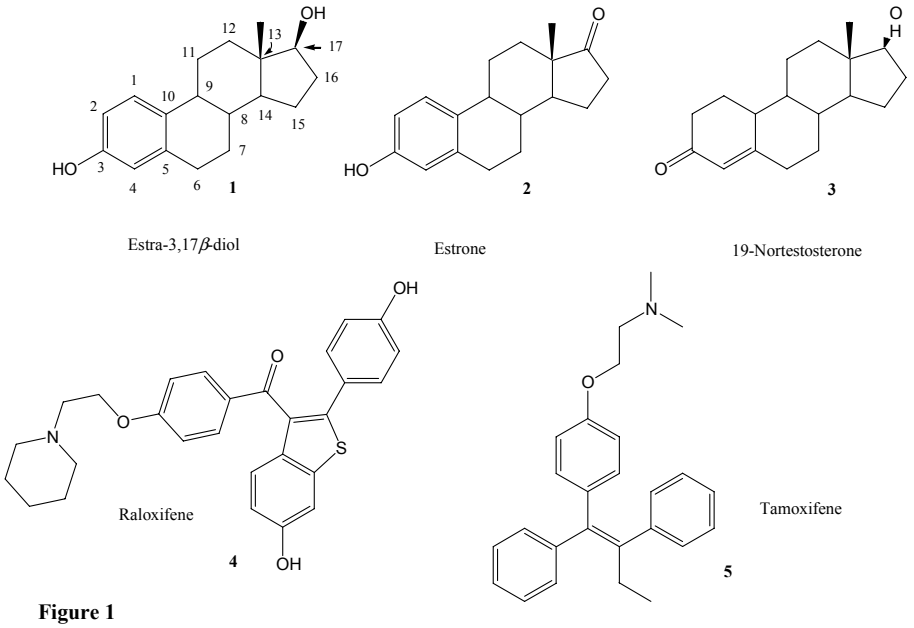


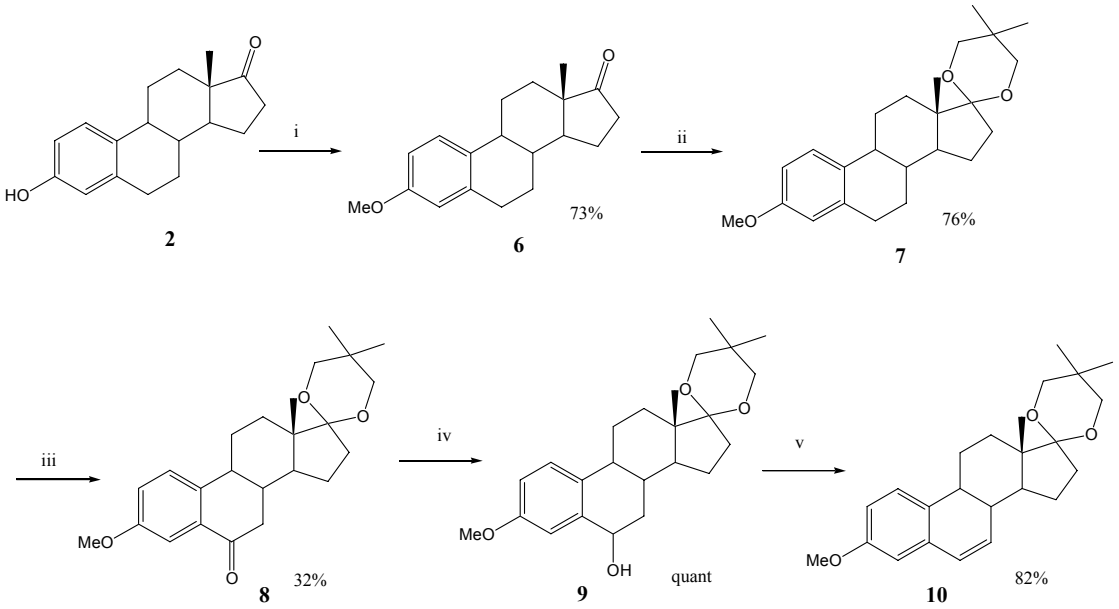
Figure 1

Until now, various approaches[6] have been followed in the synthesis of C7-substituted estranes. Both 19-nortestosterone **3** and estrone **2** itself have been used as starting materials in these preparations. The authors' recent endeavors have centered around the preparation of C7-substituted estra-1,3,5(10),6-tetraenes[7], using the conjugate addition of carbon electrophiles to the enolate of 6-ketoestrane derivatives as the key step to introduce the C7-substituent. Partly, these molecules have been radiolabelled and studied in animal models.[8]

Nevertheless, it is still of interest to have access to further, differently C7-substituted estradiols[9] in order to better understand the interaction between the C7-substituent and the receptor protein. In the following, the authors will discuss the synthesis of a number

of 7α-substituted steroidal ethers.

Results and Discussion

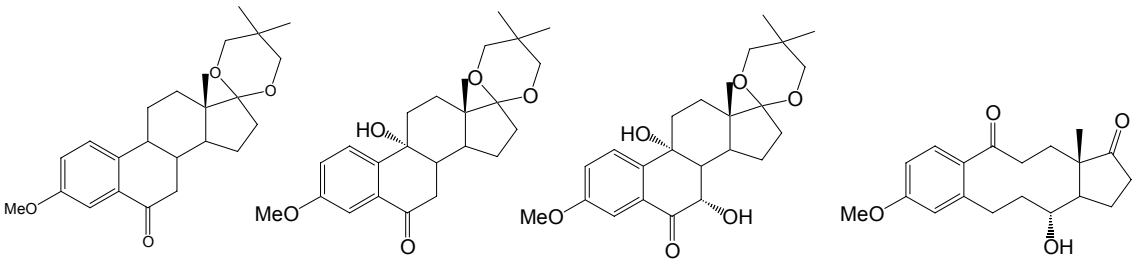


i. KOH, DMSO, MeI; ii. NPG, *p*-TsOH, benzene, refl., iii. $KMnO_4$, Adogen 464, $NaHCO_3$, benzene, H_2O; iv. $NaBH_4$, MeOH, Et_2O; v. *p*-TsOH, NPG, benzene

Scheme 1

The phenolic function at C3 of the starting material estrone **2** was protected as its methyl ether by treatment of estrone with NaOH in DMSO followed by subsequent alkylation of the phenoxide with methyl iodide to give **6**.[10] Acetalisation of the C17 keto function in **6** was carried out with neopentyl glycol (NPG) under standard conditions[11] to give the fully protected **7** (Scheme 1). In order to access the C7-position in estranes of type **7** it is necessary to activate C6. For this purpose, C6 is oxidized. The direct oxidation of estrane derivatives to 6-ketoestranes has been communicated previously.

Among the reagents used are CrO_3, CH_2Cl_2, 2,5-dimethylpyrazole,[12] AcOH, CrO_3, H_2O,[13] pyridinium chlorochromate (PCC), benzene[14] and CrO_3, H_2SO_4.[15] In our hands, the direct oxidation of fully protected **7** could best be achieved with $KMnO_4$ under PTC conditions (Adogen 464, benzene, aq. $NaHCO_3$).[16] The outcome of the reaction is dependent on reaction temperature and reaction time. The yield of **8** is similar when the reaction is run at 80 ºC for 2h or when it is run at 50 ºC for 12h. In the first case, appreciable amounts of the further hydroxylated compound **11**, 3-*O*-methyl-estra-1,3,5(10)-triene-3,9α-diol-6,17-dione 17,17-(2'-[5'5'-dimethyl-1',3'-dioxane]) are formed, of which the authors have forwarded an X-ray crystal structural analysis recently.[17]. More forced conditions lead to a further hydroxylated product, 3-*O*-methyl-estra-1,3,5(10)-triene-3,7α,9α-triol-6,17-dione 17,17-(2'-[5'5'-dimethyl-1',3'-dioxane]) **12**. No 7β-hydroxy isomer could be isolated. This forms an interesting contrast to the oxidation of estrone derivatives with *tert*-butyl hydroperoxide and cobalt acetate,[18] where the 3-*O*-methyl-estra-1,3,5(10)-triene-3,9α-diol-6,17-dione derivatives of type **11** also form, but as a mixture of α/β-isomers and where further oxidation leads to ring-cleaved compound **13** (Figure 2).[18] Incidentally, the oxidation with $KMnO_4$ in the presence of Adogen 464 works equally well with 3-*O*-benzoylestra-1,3,5(10)-trien-3,6-diol-17-one 17,17-(2'-[5'5'-dimethyl-1',3'-dioxane]).



8 **11** **12** **13**

[E. Modica et al. 2003][18]

Figure 2. Oxidation of estranes with $KMnO_4$, Adogen and with *tert*-butyl hydroperoxide/$Co(OAc)_2$[18]

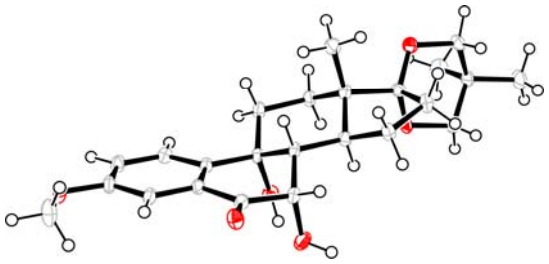
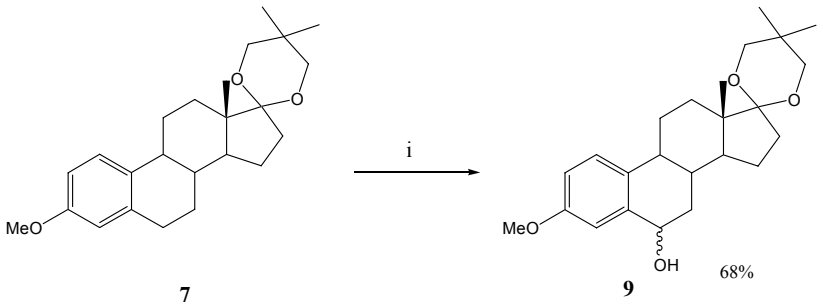


Figure 3. ORTEP drawing of an X-ray crystal structure of **12.**

Next, **8** was reduced with $NaBH_4$ in a mixture of MeOH/Et_2O to give **9** (Scheme 1). With the help of NOE experiments, the stereochemistry of **9** at C6 was determined to be α-(hydroxyl). A small amount of β-isomer also forms. **9** can be prepared alternatively by lithiation of **7**, reaction of the benzylic anion of **7** with trimethyl borate, and oxidative cleavage of the boronic ester with H_2O_2[16,19] according to a method forwarded by R. Tedesco et al (Scheme 2).[20] **9** was subjected to dehydration with *p*-TsOH (benzene, reflux) to give 3-*O*-methyl-estra-1,3,5(10),6(7)-tetraen-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) **10** (Scheme 1). In the reaction, amounts of neopentylglycol were added in order to maintain the protective group at C17.

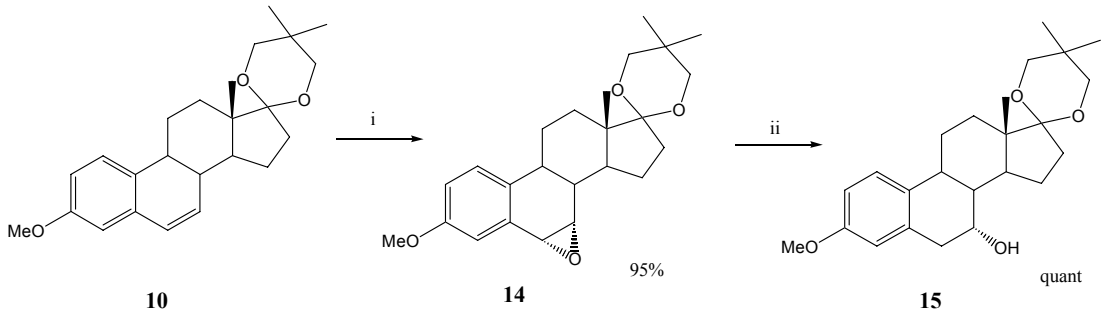


7 **9**

i. a) LiDAKOR, THF -78^{o}C; b) $B(OMe)_3$, 0^{o}C; c) H_2O_2, rt, 1h [ref. 19,20]

Scheme 2

10 was reacted with *m*-chloroperbenzoic acid in a phosphate buffer. The reaction is stereoselective and gives the 6α,7α-epoxyestra-1,3,5(10)-trien-3-ol-17-one derivative **14**. Again, the stereochemistry at C6/C7 was determined by a NOE experiments. In order to better attribute the proton signals, a ^{1}H-^{1}H COSY experiment was carried out beforehand.



10 **14** **15**

i. *m*-CPBA, Na_2HPO_4, NaH_2PO_4, CH_2Cl_2, ii. $LiAlH_4$, THF

Scheme 3.

Benzocycloalkene 1,2-oxides are known to undergo regioselective reductive ring opening with complex hydrides.[21] While reactions of **14** with carbon nucleophiles such as with (*n*-Bu)$_2$Cu(CN)Li$_2$ were found to be not completely regioselective,[22] the reaction of **14** with $LiAlH_4$ led exclusively to estra-1,3,5(10)-trien-3,7-diol-17-one **15**.

Again, the stereochemistry of **15** at C7 was determined by NOE experiments, and the compound was confirmed to be the 7α-hydroxy derivative.[23] Additionally, the coupling constants ^{3}J of H(C7) at δ 4.13 (in $CDCl_3$) with Hα/Hβ(C6) and H(C8) are very small, indicative of H(C7) at an equatorial position as one would expect larger coupling constants between neighboring axially positioned protons.[24]

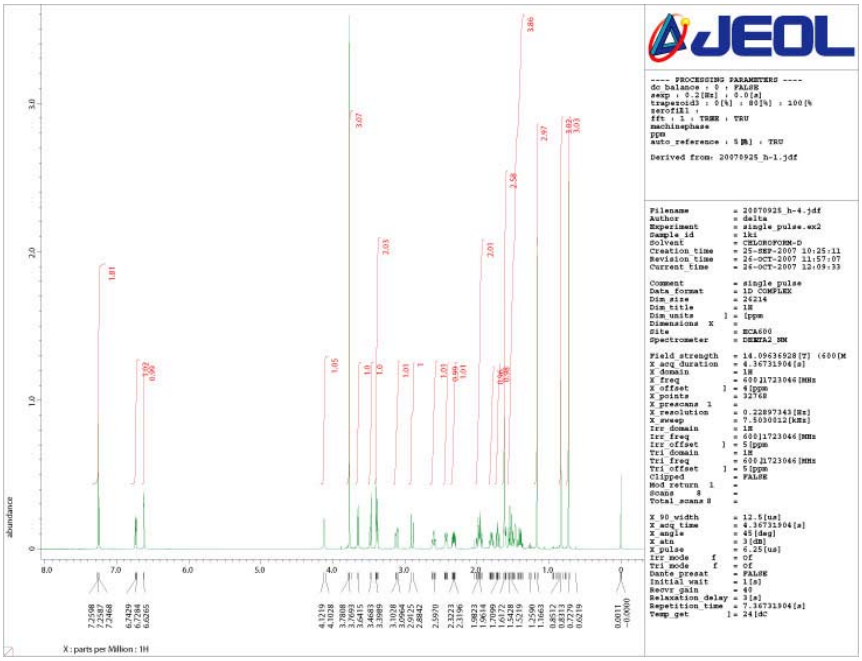


Figure 4. ^{1}H NMR of 3-*O*-Methyl-estra-1,3,5(10)-trien-3,7α-diol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) **15**

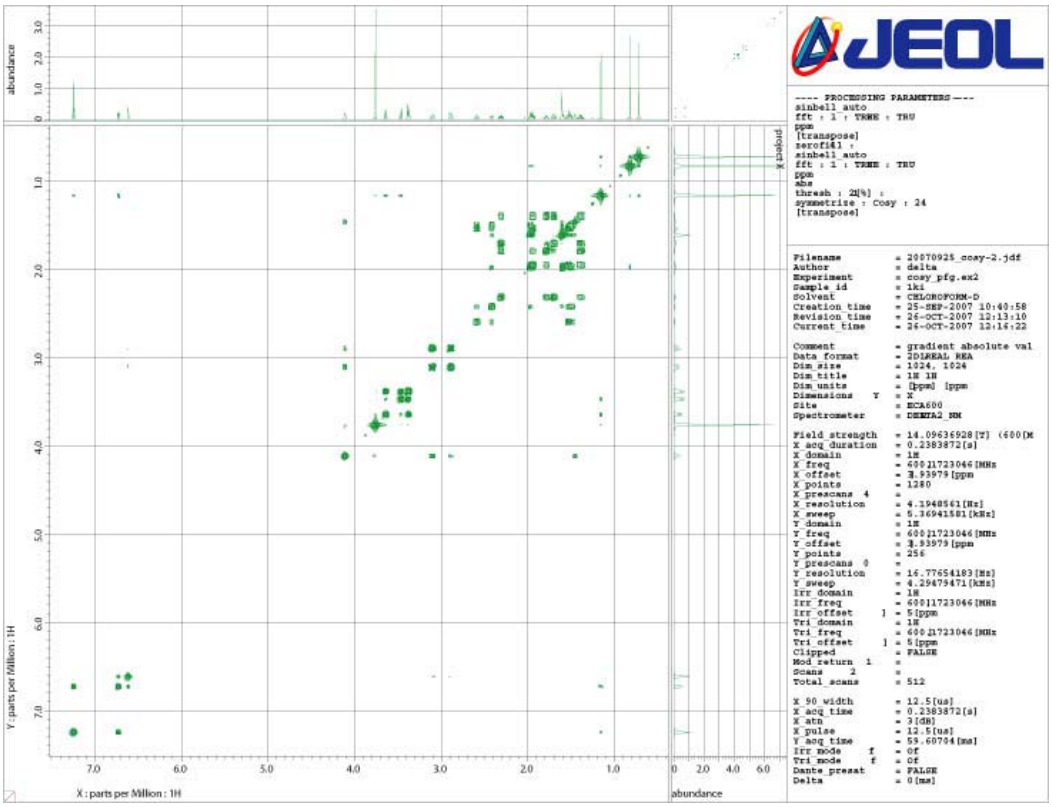
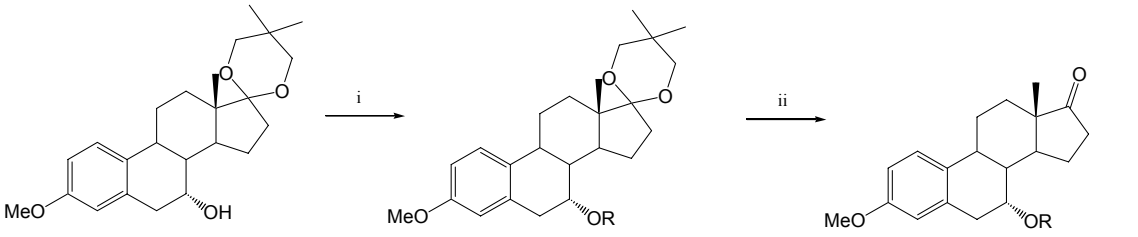


Figure 5. ^{1}H-^{1}H COSY of 3-*O*-methyl-estra-1,3,5(10)-trien-3,7α-diol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) **15**

Etherification of **15** was carried out using NaH as base and alkyl halides such as methyl iodide or benzyl bromide as alkylating agents (Scheme 4). The use of the reaction system NaOH/DMSO/RI failed to give ethers as did the use of Ag_2O, MeI.[25] As of yet, the reactions have not been optimized. Due to the axial position of the ether function, steric constraints may influence the reactivity of the 7α-hydroxy group.



15

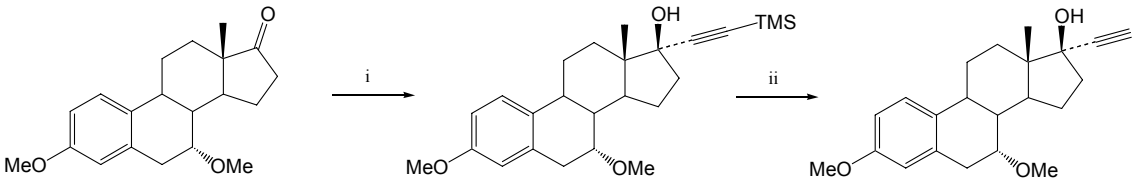
16: R = Me (56%); **17**: R = Bn (25%)
18: R = Am (22%)

19: R = Me (quant); **20**: R = Bn (96%)
21: R = Am (96%)

i. NaH, THF, RX; ii. *p*-TsOH, acetone, rt

Scheme 4

Steroidal ethers **16** – **18** were deprotected at C17 by transacetalisation (acetone, *p*-TsOH, rt) (Scheme 4). In order to utilize derivatives of the steroidal ethers as potential radioligands for the estrogen receptor ERα, the estrones **19** - **21** were converted to estradiols. In the present case, an ethynyl group was chosen as the 17α-substituent in the desired estradiols, ie. in **23**. The ethynyl group can enhance the binding affinity of the steroid to the receptor, but more importantly, the 17α-ethynyl group can be used as a precursor of a 17α-halovinyl group. A radiohalide such as ^{125}I or ^{123}I can be incorporated in such a halovinyl function. An exemplary ethynylation was carried out with **19** and trimethylsilylacetylene and led to desired **23** after F^- induced desilylation of the ethynyl function in **22** (Scheme 5).



19 **22** **23**

i. LDA, THF, TMS-acetylene; ii.Bu_4NF, THF

Scheme 5

It is planned to carry out further experiments with derivatives of **23**. Currently, 7α-alkoxyestranes are being synthesized with the tetrahydropyranyl function as a removable protective group at (C3-O). These compounds will be tested as to their binding affinity to the estrogen receptor ERα and *in vivo* biodistribution assays will be carried out.

Experimental

General. - Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. Infrared spectra were measured with JASCO IR-700, Nippon Denshi JIR-AQ2OM, Perkin Elmer 257 and Perkin Elmer 581 machines. ^{1}H- and ^{13}C-NMR spectra were recorded with a JEOL EX-270 spectrometer (^{1}H at 270 MHz, ^{13}C at 67.8 MHz), and a Bruker WP-300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75.4 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer (EI, 70 eV) and a Finnigan MAT 312 mass spectrometer. Column chromatography was carried out on Wakogel 300 (Wako) and on silica gel 60N (spherical neutral, Kanto). Estrone was obtained commercially from Wako and from Aldrich. Sodium hydride (NaH) was washed with

hexane before use.

3-*O*-Methylestra-1,3,5(10)-trien-3-ol-17-one (**6**). – To DMSO (40 mL) was added powdered KOH (4.15 g, 74 mmol). After the mixture was stirred for 30 min, estrone (**2**, 5.0 g, 18.5 mmol) was added, followed by methyl iodide (5.25 g, 37 mmol). After 30 min, the mixture was poured into water and extracted with CH_2Cl_2 (200 mL). The organic phase was washed with water and dried over anhydrous $MgSO_4$. Then, the solution was concentrated *in vacuo*. To the solid was added hexane (10 mL) and the precipitate formed was collected by filtration to give 3-*O*-methylestra-1,3,5(10)-trien-3-ol-17-one (**6**, 3.85 g, 73%) as a colorless solid; IR (KBr) ν 2924, 2852, 1713, 1639, 1574, 1498, 1455, 1395, 1372, 1305, 1278, 1257, 1246, 1202, 1155, 1128, 1101, 1052, 1019, 989, 965, 899, 871, 847, 813, 785, 755, 728, 708, 640 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.40 – 2.60 (m, 11H), 2.89 (m, 2H), 3.78 (s, 3H, OCH_3), 6.65 (d, 1H, ^4J 2.6 Hz), 6.72 (dd, 1H, ^3J 7.6 Hz, ^4J 2.6 Hz), 7.21 (d, 1H, ^3J 7.6 Hz).

3-*O*-Methyl-estra-1,3,5(10)-trien-3-ol-17-one

17,17-(2'-[5'5'-dimethyl-1',3'-dioxane]) (**7**) – A solution of **6** (4.5 g, 15.8 mmol), 2,2-dimethylpropane-1,3-diol (neopentylglycol, NPG, 2.5 g, 23.7 mmol) and *p*-TsOH (330 mg, 1.6 mmol) in benzene (60 mL) was stirred for 3h under reflux with continuous azeotropic removal of water (Dean-Stark condenser). Thereafter, the cooled reaction mixture was poured into a 10w% aq. solution of $NaHCO_3$ (100 mL) and the resulting mixture was extracted with ether (2 X 100 mL). The organic phase was washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was

subjected to column chromatography on silica gel (ether/$CHCl_3$/hexane 1:1:2) to give **7** (4.4 g, 76%) as a colorless solid; IR (KBr) ν 2940, 2850, 1600, 1570, 1500, 1460, 1270, 1250, 1100, 1030, 960, 900 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.73 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.35 – 1.90 (m, 11H), 2.23 – 2.32 (m, 2H), 2.81 – 2.85 (m, 2H), 3.36 – 3.40 (m, 2H), 3.48 (d, 1H, ^2J 11.2 Hz), 3.66 (d, 1H, ^2J 11.2 Hz), 3.77 (s, 3H, OCH_3), 6.62 (d, 1H, ^4J 2.7 Hz), 6.70 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.21 (d, 1H, ^3J 8.6 Hz).

3-*O*-Methoxy-estra-1,3,5(10)-triene-6,17-dione 17,17-(2'-[5'5'-dimethyl-1',3'-dioxane]) (**8**). – A mixture of **7** (1.98 g, 5.3 mmol), potassium permanganate (3.13 g, 19.8 mmol) and Adogen 464 (0.15 g) in a mixture of benzene (55 mL) and water (55 mL) was heated at 50 ºC for 12h. After the mixture was cooled to rt, it was filtered through a sufficient amount of celite and organic and aqueous phases were separated from each other. The aqueous phase was extracted with ether (3 X 100 mL) and the collected organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was subjected to column chromatography on silica gel to give **8** (650 mg, 32%) and **7** (509 mg, 25% recovery); ^1H NMR (270 MHz, CD_2Cl_2) δ 0.63 (s, 3H, CH_3), 0.73 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.23 – 2.40 (m, 11H), 2.60 (dd, 1H, ^2J 16.6 Hz, ^3J 3.0 Hz), 3.27 – 3.59 (m, 4H), 3.73 (s, 3H, OCH_3), 7.00 (dd, 1H, ^3J 8.6 Hz, ^4J 3.0 Hz), 7.28 (d, 1H, ^3J 8.6 Hz), 7.41 (d, 1H, ^4J 3.0 Hz); MS (EI, 70 eV) *m/z* (%) 384 (M^+, 43), 368 (6), 298 (9), 265 (8), 241 (5), 187 (9), 141 (100), 128 (6).

3-O-Methyl-estra-1,3,5(10)-triene-3,6-diol-17-one

17,17-(2'-[5'5'-dimethyl-1',3'-dioxane]) (**9**). – A solution of **8** (1.52 g, 4.0 mmol) in a mixture of methanol (20 mL) and ether (20 mL) was cooled to 0 ºC and $NaBH_4$ (450 mg, 11.9 mmol) was added in small portions. After the addition, the ice bath was removed, and the mixture was stirred for 1h at ambient temperature. The solvent was removed in vacuo and water (30 mL) was added slowly to the residue. The resulting mixture was extracted with ether (3 X 50 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give **9** (1.53 g, quant); IR (KBr) ν 3592 (bs, OH), 1608, 1572, 1496 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.73 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 3.37 – 3.69 (m, 4H), 3.80 (s, 3H, OCH_3), 4.81 – 4.84 (t, 1H), 6.79 (dd, 1H, ^3J 8.6 Hz, ^4J 2.6 Hz), 7.14 (dd, 1H, ^4J 2.6 Hz), 7.21 (d, 1H, ^3J 8.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.98 (C18), 21.03 (CH_3 [dioxane]), 22.53 (CH_3 [dioxane]), 23.02, 26.11, 27.03, 29.43 (C16, C12, C11, C15), 30.39 (C_{quat} [dioxane]), 32.22, 38.35, 44.18, 47.02 (C7, C14, C9, C8), 47.25 (C13), 55.33 (OCH_3), 70.15, 70.67 (both OCH_2 [dioxane]), 72.60 (C6), 108.57 (C17), 111.61 (C4), 113.71 (C2), 126.45 (C1), 132.65 (C10), 140.81 (C5), 158.02 (C3); MS (EI, 70 eV) *m/z* (%) = 386 (M^+, 7), 299 (11), 282 (35), 171 (13), 141 (100), 69 (21). HRMS Found: 386.2460. Calcd. for $C_{24}H_{34}O_4$: 386.2457.

3-*O*-Methyl-estra-1,3,5(10),6(7)-tetraen-3-ol-17-one

17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**10**). – To a solution of **9** (1.7 g, 4.35 mmol) in benzene (50 mL) was added neopentylglycol (NPG, 2.0 g, 19.2 mmol) and *p*-toluenesulfonic acid monohydrate (*p*-TsOH, 112 mg). The resulting mixture was heated for 4h under reflux with continuous azeotropic removal of water (Dean-Stark condenser). The pale yellow solution was cooled to rt, poured into a 5w% aq. Na_2CO_3

solution, and the organic phase was separated. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford a residue from which **10** (1.3 g, 82%) was obtained after flash column chromatography on silica gel (petroleum ether / ethyl acetate 5:2) as a colorless solid; IR (KBr) ν 2952, 1600, 1568, 1492 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.63 (s, 3H, CH_3), 0.74 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.17 – 2.33 (m, 11H), 3.28 – 3.66 (m, 4H), 3.68 (s, 3H, OCH_3), 5.88 (dd, 1H, ^3J 9.6 Hz, ^4J 1.6 Hz), ^{13}C NMR (75.4 MHz, $CDCl_3$) d 14.40 (CH_3, C18), 22.69 (CH_3 [dioxane]), 23.21 (CH_3 [dioxane]), 23.62, 24.62, 27.60, 29.67 (C11, C12, C15, C16), 31.02 (C_{quat} [dioxane]), 39.48, 42.35, 46.50 (C8, C9, C14), 48.52 (C13), 55.92 (OCH_3), 71.29 (OCH_2 [dioxane]), 73.29 (OCH_2 [dioxane]), 109.13 (C17), 112.26, 112.41 (C2, C4), 124.94 (C6), 128.30 (C1), 132.52 (C10), 133.91 (C7), 136.16 (C5), 158.70 (C3); MS (EI, 70 eV) *m/z* (%) 386 (M+, 29), 282 (21), 238 (22), 225 (19), 184 (11), 167 (34), 149 (100), 141 (27). HRMS Found: 386.2353. Calcd. for $C_{24}H_{32}O_3$: 368.2351.

3-*O*-Methyl-6α,7α-epoxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5'5'-dimethyl-1',3'-dioxane]) 14. – To a mixture of 3-*O*-methylestra-1,3,5(10),6-tetraene-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) **10** (355 mg, 1.0 mmol) in a mixture of CH_2Cl_2 (20 mL) and phosphate buffer (the buffer was prepared by adding sufficient aqueous 0.1 M Na_2HPO_4 to 0.1 M NaH_2PO_4 until pH 8 was reached) was added *m*-chloroperbenzoic acid (173 mg, 1.0 mmol) in small portions at 0 ºC. The reaction mixture was stirred at rt for 5 h and the organic layer was separated, washed with saturated sodium thiosulfate and water and dried over anhydrous $MgSO_4$. Concentration of the solution *in vacuo* and column chromatography

gave **14** (365 mg, 95%) as a colorless solid, mp. 93 ºC; IR (KBr) ν 2946, 1616, 1504, 1470, 1395, 1311, 1257, 1147, 1104, 1040, 860, 839, 749, 687, 643, 603, 557 cm^{-1}; ^1H NMR (270 MHz, CD_2Cl_2) δ 0.64 (s, 3H, CH_3), 0.74 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.42 – 2.03 (m, 7H), 3.27 – 3.63 (m, 7H), 3.71 (s, 1H), 6.73 (dd, 1H, ^3J 8.4 Hz, ^4J 2.4 Hz), ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 13.75 (+, CH_3), 22.07 (+, CH_3), 23.65 (+, CH_3), 24.47 (-), 27.42 (-), 29.36 (C_{quat}), 30.60 (-), 36.55 (+, CH), 38.13 (+, CH), 45.32 (+, CH), 48.36 (C_{quat}), 53.80 (+, CH), 55.65 (+, OCH_3), 56.30 (+, CH), 70.91 (-), 72.97 (-), 108.51 (C_{quat}), 113.35 (+, CH), 115.65 (+, CH), 125.53 (+, CH), 132.75 (C_{quat}), 134.10 (C_{quat}), 158.40 (C_{quat}); MS (EI, 70 eV) *m/z* (%) 384 (M^+, 55), 368 (14), 141 (100). HRMS Found: 384.2298. Calcd. for $C_{24}H_{32}O_4$: 384.2301.

3-*O*-Methyl-estra-1,3,5(10)-trien-3,7α-diol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) 15. – To a suspension of $LiAlH_4$ (98 mg, 2.6 mmol) in dry THF (3 mL) was added **14** (500 mg, 1.3 mmol) in THF (1 mL) at 0 ºC and under an Ar atmosphere. After the addition, the solution was stirred for 3h. Ethyl acetate (1 mL) was added to quench the remaining $LiAlH_4$. Aqueous NH_4Cl was added until a pH of 3 was reached, and the mixture was extracted with ether. The organic phase was washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give **15** (510 mg, quant); IR (KBr) ν 3350 (bs, OH), 1609, 1501, 1467, 1285, 1238, 1104, 1037, 961, 927, 880, 849, 817, 755 cm^{-1}; ^1H NMR (270 MHz, CD_2Cl_2) δ 0.72 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.18 – 1.98 (m, 9H), 2.27 – 2.58 (m, 3H), 2.83 (d, ^2J 16.8 Hz), 3.05 – 3.12 (m, 1H), 3.34 – 3.50 (m, 3H), 3.65 – 3.78 (m, 4H), 6.60 (d, 1H, ^4J 2.6 Hz), 6.70 (dd, 1H, ^3J 8.6 Hz, ^4J 2.6 Hz), 7.23 (d, 1H, ^3J 8.6 Hz); ^1H NMR (270 MHz, $CDCl_3$) δ 0.73 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3),

6.62 (d, 1H, ^4J 2.7 Hz), 6.73 (d, 1H, ^3J 8.6 Hz), 7.24 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.87, 22.02, 22.54 (2C), 26.19, 27.01, 29.37, 30.36, 35.56, 38.62, 42.64, 43.21, 47.45, 55.21, 66.04, 70.61, 72.66, 108.44, 112.13, 114.46, 126.63, 131.72, 134.43, 157.70; MS (EI, 70 eV) *m/z* (%) 386 (M^+, 32), 282 (33), 243 (27), 141 (100). HRMS Found: 386.2459. Calcd. for $C_{24}H_{34}O_4$: 386.2457.

3-*O*-Methyl-7α-methoxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**16**). – To a solution of **15** (100 mg, 0.26 mmol) in dry THF (1.5 mL) was added NaH (19 mg, 0.78 mmol) and thereafter MeI (50 μL, 0.78 mmol). The resulting reaction mixture was stirred at ambient temperature for 20h. Thereafter, the mixture was poured into cold water and extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 5:1:1) to give **16** (58 mg, 56%) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.73 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.34 – 2.43 (m, 10H), 2.67 (m, 1H), 2.82 (dd, 1H, ^2J 18.1 Hz, ^3J 4.1 Hz), 3.09 (d, 1H, ^2J 18.1 Hz), 3.35 (s, 3H, OCH_3), 3.35 – 3.43 (2H), 3.48 (d, 1H, ^2J 10.8 Hz), 3.50 (m, 1H), 3.65 (d, 1H, ^2J 11.1 Hz), 3.77 (s, 3H, OCH_3), 6.61 (d, 1H, ^4J 2.7 Hz), 6.71 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.23 (d, 1H, ^3J 8.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.73, 22.06, 22.56, 22.98, 26.39, 27.10, 29.40, 30.37, 33.41, 36.14, 42.72, 43.04, 47.38, 55.20, 56.95, 70.64, 72.66, 75.04, 108.59, 111.77, 114.43, 126.65, 132.65, 135.00, 157.48; MS (EI, 70 eV) *m/z* (%) 400 (M^+, 22), 385 (M^+-CH_3, 28), 368 (27), 141 (100). HRMS Found: 400.2617. Calcd. for $C_{25}H_{36}O_4$: 400.2614.

3-*O*-Methyl-7α-benzyloxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**17**). – To a solution of **15** (100 mg, 0.26 mmol) in dry THF (3.0 mL) was added NaH (31 mg, 1.3 mmol) and thereafter benzyl bromide (445 mg, 2.6 mmol). The resulting reaction mixture was stirred at reflux temperature for 20h. Thereafter, the mixture was poured into cold water and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 10:1:1) to give **17** (27 mg, 22%) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.72 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.24 – 2.43 (10H), 2.80 (m, 1H), 2.85 (dd, 1H, ^2J 17.0 Hz, ^3J 3.2 Hz), 3.10 (d, 1H, ^2J 17.0 Hz), 3.43 (m, 3H), 3.65 (d, 1H, ^2J 11.3 Hz), 3.75 (m, 1H), 3.76 (s, 3H, OCH_3), 4.44 (d, 1H, ^2J 12.4 Hz), 4.67 (d, 1H, ^2J 12.4 Hz), 6.60 (d, 1H, ^4J 2.4 Hz), 6.72 (dd, 1H, ^3J 8.9 Hz, ^4J 2.4 Hz), 7.23 – 7.33 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.76, 22.04, 22.53, 22.70, 26.27, 27.06, 29.35, 30.35, 34.20, 36.00, 42.80 (2C), 47.30, 55.17, 70.50, 70.56, 72.42, 72.64, 108.58, 111.64, 114.37, 126.56, 127.21, 127.65 (2C), 128.06 (2C), 132.87, 135.13, 139.31, 157.52; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 477 (MH^+, 5.6), 385 (25), 369 (8.4). HRMS Found: 477.3000. Calcd. for $C_{31}H_{41}O_4$: 477.3005.

3-*O*-Methyl-7α-pentoxyestra-1,3,5(10)-trien-3-ol-17-one 17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**18**). – To a solution of **15** (100 mg, 0.26 mmol) in dry THF (1.5 mL) was added NaH (31 mg, 1.3 mmol) and thereafter iodopentane (515 mg, 2.6 mmol). The resulting reaction mixture was stirred at reflux temperature for 20h. Thereafter, the mixture was poured into cold water and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in*

vacuo. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 8:1:1) to give **18** (30 mg, 25%) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.72 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.85 (t, 3H, ^3J 6.7 Hz, CH_3), 1.16 (s, 3H, CH_3), 1.23 – 2.42 (m, 17H), 2.71 (m, 1H), 2.82 (dd, 1H, ^2J 18.6 Hz, ^3J 4.1 Hz), 3.03 (d, 1H, ^2J 18.6 Hz), 3.25 – 3.68 (m, 7H), 3.76 (s, 3H, OCH_3), 6.60 (d, 1H, ^4J 2.7 Hz), 6.70 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.23 (d, 1H, ^3J 8.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.76, 14.11, 22.05, 22.46, 22.53, 23.00, 26.28, 27.08, 28.44, 29.36, 29.72, 30.36, 34.25, 35.92, 42.83, 42.87, 47.33, 55.16, 69.08, 70.60, 72.66, 73.16, 108.65, 111.50, 114.36, 126.46, 133.01, 135.45, 157.37; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 457 (MH^+, 1.9), 385 (1.9), 369 (3.1), 345 (1.7). HRMS Found: 457.3314. Calcd. for $C_{29}H_{45}O_4$: 457.3318 (MH^+, FAB)

3-*O*-Methyl 7α-methoxyestra-1,3,5(10)-trien-3-ol-17-one (**19**). – A solution of **16** (49 mg, 0.12 mmol) and *p*-TsOH (10 mg, 0.052 mmol) in acetone (10 mL) was stirred at rt for 15h. Thereafter, the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) gave **19** (38 mg, quant) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (s, 3H, CH_3), 1.48 – 2.52 (m, 10H), 2.69 (m, 1H), 2.87 (dd, 1H, ^2J 17.8 Hz, ^3J 3.2 Hz), 3.17 (d, 1H, ^2J 17.8 Hz), 3.39 (s, 3H, OCH_3), 3.69 (m, 1H), 3.78 (s, 3H, OCH_3), 6.65 (d, 1H, ^4J 2.4 Hz), 6.74 (d, 1H, ^3J 8.6 Hz), 7.23 (dd, 1H, ^3J 8.6 Hz, ^4J 2.4 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.57, 21.40, 26.03, 31.43, 32.88, 35.79, 36.31, 41.99, 45.79, 47.80, 55.21, 56.76, 74.23, 111.89, 114.50, 126.52, 131.61, 134.72, 157.70, 220.74 (CO); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 314 (M^+, 40.8), 282 (74).

HRMS Found: 314.1879. Calcd. for $C_{20}H_{26}O_3$: 314.1882.

3-*O*-Methyl 7α-benzyloxyestra-1,3,5(10)-trien-3-ol-17-one (**20**). - A solution of **17** (23 mg, 0.048 mmol) and *p*-TsOH (3.6 mg, 0.019 mmol) in acetone (3.6 mL) was stirred at rt for 15h. Thereafter, the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) gave **20** (18 mg, 96%) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.85 (s, 3H, CH_3), 1.45 – 2.48 (m, 10H), 2.82 (m, 1H), 2.91 (dd, 1H, ^2J 18.1 Hz, ^3J 3.2 Hz), 3.20 (d, 1H, ^2J 18.1 Hz), 3.78 (s, 3H, OCH_3), 3.88 (m, 1H), 4.43 (d, 1H, ^2J 11.9 Hz), 4.73 (d, 1H, ^2J 11.9 Hz), 6.65 (d, 1H, ^4J 2.7 Hz), 6.74 (dd, 1H, ^3J 8.9 Hz, ^4J 2.7 Hz), 7.22 – 7.32 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.56, 21.06, 25.90, 31.38, 36.62, 35.80, 36.16, 42.05, 45.67, 47.80, 55.20, 70.34, 71.41, 111.79, 114.50, 126.46, 127.59, 127.80 (2C), 128.26 (2C), 131.84, 134.85, 138.82, 157.65, 220.86 (CO); MS (EI, 70 eV) *m/z* (%) 390 (M^+, 12), 370 (11), 299 (30), 282 (100). HRMS Found: 390.2195. Calcd. for $C_{26}H_{30}O_3$: 390.2195.

3-*O*-Methyl 7α-pentoxyestra-1,3,5(10)-trien-3-ol-17-one (**21**). - A solution of **18** (27 mg, 0.059 mmol) and *p*-TsOH (4.5 mg, 0.024 mmol) in acetone (4.5 mL) was stirred at rt for 15h. Thereafter, the reaction mixture was poured into aq. Na_2CO_3. The mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) gave **21** (21 mg, 96%) as a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.78 (t, 3H, ^3J 6.5 Hz, CH_3), 0.81 (s, 3H, CH_3), 1.17 – 2.48 (m, 16H),

2.67 (m, 1H), 2.80 (dd, 1H, ^{2}J 17.8 Hz, ^{3}J 3.8 Hz), 3.05 (d, 1H, ^{2}J 17.8 Hz), 3.24 (dt, 1H, ^{2}J 8.9 Hz, ^{3}J 7.0 Hz), 3.58 (dt, 1H, ^{2}J 8.9 Hz, ^{3}J 6.2 Hz), 3.69 (m, 1H), 3.71 (s, 3H, OCH_3), 6.56 (d, 1H, ^{4}J 2.7 Hz), 6.66 (dd, 1H, ^{3}J 8.6 Hz, ^{4}J 2.7 Hz), 7.15 (d, 1H, ^{3}J 8.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.59, 14.09, 21.48, 22.46, 25.95, 28.45, 29.71, 31.45, 33.70, 35.86, 36.16, 42.09, 45.83, 47.83, 55.20, 69.02, 72.42, 111.67, 114.46, 126.38, 131.94, 135.16, 157.61, 220.99 (CO); MS (EI, 70 eV) *m/z* (%) 370 (M^+, 22), 282 (100). HRMS Found: 370.2504. Calcd. for $C_{24}H_{34}O_3$: 370.2508.

3-*O*-Methyl 7α-methoxy-17α-trimethylsilylethynylestra-1,3,5(10)-trien-3,17β-diol (**22**). – To a solution of trimethylsilylacetylene (32 mg, 0.33 mmol) in dry THF (1 mL) was added at -78 ºC lithium diisopropylamide (solution in THF/ethylbenzene/heptanes, 2 M, 0.17 mL, 0.34 mmol), and the resulting mixture was stirred at -78 ºC for 30 min, thereafter 30 min at 0 ºC. Then, the reaction mixture was cooled again to -78 ºC and a solution of **19** (35 mg, 0.11 mmol) in dry THF (1 mL) was added. The mixture was allowed to warm overnight (15h). Then, NH_4Cl (2N, 10 mL) was added and the mixture was extracted with ether (3X 50 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) to give **22** (41 mg, 90%) as a slowly crystallizing, colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.19 (s, 9H, $SiMe_3$), 0.85 (s, 3H, CH_3), 1.37 – 2.47 (m, 11H), 2.64 (m, 1H), 2.85 (dd, 1H, ^{2}J 17.3 Hz, ^{3}J 3.0 Hz), 3.10 (d, 1H, ^{2}J 17.3 Hz), 3.39 (s, 3H, OCH_3), 3.55 (m, 1H), 3.78 (s, 3H, OCH_3), 6.64 (d, 1H, ^{3}J 8.6 Hz, ^{4}J 1.8 Hz), 6.73 (dd, 1H, ^{4}J 1.8 Hz), 7.24 (d, 1H, ^{3}J 8.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 0.00, 12.50, 22.66, 26.56, 32.68, 33.58, 36.10, 38.87, 43.13, 44.82, 47.26, 55.20, 57.21, 74.98, 80.09, 90.28, 109.49, 111.83, 114.43,

126.63, 132.01, 134.95, 157.55; MS (EI, 70 eV) m/z (%) 412 (M+, 35), 380 (100), 365 (36), 240 (80). HRMS Found: 412.2429. Calcd. for $C_{25}H_{36}O_3Si$: 412.2434.

3-*O*-Methyl 7α-methoxy-17α-ethynylestra-1,3,5(10)-trien-3,17β-diol (**23**). – To **22** (24 mg, 00.58 mmol) in THF (1 mL) was added tetrabutylammonium fluoride (TBAF, 30 mg, 0.115 mmol) at -10 ºC. The reaction mixture was stirred at rt for 2h. Then ether (10 mL) was added, and the mixture was extracted with H_2O. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel 60N (hexane/ether/$CHCl_3$ 4:1:1) to give **23** (20 mg, quant) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ0.86 (s, 3H, CH_3), 1.26 – 2.48 (m, 11H), 2.62 (s, 1H), 2.66 (m, 1H), 2.84 (dd, 1H, ^2J 17.6 Hz, ^3J 3.5 Hz), 3.11 (d, 1H, ^2J 17.6 Hz), 3.36 (s, 3H, OCH_3), 3.55 (m, 1H), 3.77 (s, 3H, OCH_3), 6.63 (d, 1H, ^4J 2.7 Hz), 6.72 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.23 (d, 1H, ^3J 8.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.44, 22.63, 26.57, 32.60, 33.28, 35.89, 38.90, 43.11, 44.82, 47.16, 55.19, 56.97, 74.26, 74.90, 79.84, 87.34, 111.81, 114.40, 126.60, 132.11, 134.91, 157.53; MS (EI, 70 eV) *m/z* (%) 340 (M^+, 37), 308 (100). HRMS Found: 340.2036. Calcd. for $C_{22}H_{28}O_3$: 340.2038.

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